Antioxidants and Redox Signaling

DOI: 10.1089/ars.2017.7147

Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective

Pietro Ghezzi[1], Luciano Floridi[2], Diana Boraschi[3], Antonio Cuadrado[4], Gina Manda[5], Snezana Levic[1], Fulvio D'Acquisto[6], Alice Hamilton[6], Toby J Athersuch[7], Liza Selley[7]

[1]Brighton & Sussex Medical School, Brighton, United Kingdom

[2]Oxford Internet Institute, University of Oxford, United Kingdom, and Alan Turing Institute, London, United Kingdom.

[3]Institute of Protein Biochemistry, National Research Council, Napoli, Italy.

[4]Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Instituto de Investigación Sanitaria La Paz (IdiPaz), Instituto de Investigaciones Biomédicas Alberto Sols UAM-CSIC , Madrid, Spain , and Department of Biochemistry, Faculty of Medicine, Autonomous University of Madrid , Madrid, Spain .

[5]"Victor Babes" National Institute of Pathology, Bucharest, Romania

[6]William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK

[7]Department of Surgery and Cancer, Faculty of Medicine, and MRC-PHE Centre for Environment and Health, School of Public Health, Imperial College London, London, United Kingdom

Running title: Biomarkers of oxidative stress and inflammation

Note: All authors contributed equally. Contributors to each section: first section on biomarkers and the conclusions, PG and LF; nanomaterials, DB; NRF2, AC and GM; noise, SL; brain-body interactions, FDA, AH and PG; exposome, TA and LS. PG edited and coordinated the text.

Corresponding author: Pietro Ghezzi, Brighton & Sussex Medical School, Falmer, UK, Tel: +44-(0)1273-873112, Fax: +44-01273-876721, Email: p.ghezzi@bsms.ac.uk

Word count of main manuscript: 7900

Number of references: 179

Number of BW illustrations:8

Number of tables:2

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

ABSTRACT

Significance. The environment can elicit biological responses such as oxidative stress (OS) and inflammation as consequence of chemical, physical or psychological changes. As population studies are essential for establishing these environment-organism interactions, biomarkers of oxidative stress or inflammation are critical in formulating mechanistic hypotheses. **Recent advances.** By using examples of stress induced by various mechanisms, we focus on the biomarkers that have been used to assess oxidative stress and inflammation in these conditions. We discuss the difference between biomarkers that are the result of a chemical reaction (such as lipid peroxides or oxidized proteins that are a result of the reaction of molecules with reactive oxygen species, ROS) and those that represent the biological response to stress, such as the transcription factor NRF2 or inflammation and inflammatory cytokines. **Critical issues.** The high-throughput and holistic approaches to biomarker discovery used extensively in large-scale molecular epidemiological exposome are also discussed in the context of human exposure to environmental stressors. **Future directions.** We propose to consider the role of biomarkers as signs and distinguish between signs that are just indicators of biological processes and proxies that one can interact with and modify the disease process.

KEY WORDS

Exposome; nanomaterials; cytokines; proteomics; genomics; NRF2, xenobiotics; emotions; neuroendocrinology

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

BIOMARKERS OF INFLAMMATION AND OXIDATIVE STRESS (OS).

The theory that OS - an unbalance between production of toxic oxygen species, reactive oxygen species (ROS) and endogenous antioxidants (164) -may be at the basis of a disease has been first put forward by Harman in 1956 with the "free radical theory of aging", in which he concluded "This theory is suggestive of chemical means of prolonging effective life "(64). Despite this, there are no antioxidants currently approved by regulatory agencies for any disease (59)

, with the possible exception of edaravone, an antioxidant approved in Japan and India for aiding neuroprotection in stroke patients (96).

Inflammation is also postulated as a pathogenic mechanism in most diseases or as a major risk factor (44). Its oldest definition is by Aulus Cornelius Celsus in the first century AD, who defined the four hallmarks of inflammation: "*rubor, et tumor, cum calore, et dolore*", redness, swelling, heat and pain (29). These are, for Celsus, "*notae vero inflammationis*". "*Notae*" is usually translated in English with "signs" ("the cardinal signs of inflammation"). This is our first encounter, in our review, of the concept of biomarker. In a way, biomarkers are "signs". The father of semiotic, Charles Sanders Peirce, described a semiotic triad where he defines the relationship between a sign, the object it stands for and the interpretant (9). This concept is shown in Figure 1 where when the interpretant sees smoke, she knows that that sign indicates that somewhere there is a wildfire.

From Celsus' perspective, the signs of inflammation were viewed mainly with a diagnostic or classification purpose. However, in clinical and preclinical studies, as well as in epidemiological studies, biomarkers are also used to gain insights into the causal mechanisms underlying diseases. Biomarkers have been classified in biomarkers for the aetiology of the disease (risk factors; including biomarkers of exposure), and biomarkers of disease used in the screening or diagnosis, or to monitor disease progression (prognosis) (116). Even if not implicit in their definition, one desirable criterion for a biomarker is to be accessible - i.e. measurable in biological fluids that can be obtained in a minimally-invasive manner (such as urine, blood or synovial fluid). In animal models, biomarkers can also be measured in tissues and organs, possible only in human patients in the few cases where biopsy samples are obtained for diagnostic purposes.

The study of diseases can, in its turn, lead to the definition of new biomarkers and to the refinement of the criteria for disease classification. For instance, an inflammatory response often results in tissue damage (*e.g.* joint damage in arthritis) and loss of function, the "*functio laesa*" described by Galen (145). The study of the molecular mechanisms of inflammation led to

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

infiltration of white blood cells, their recruitment in the tissues as a result of inflammatory mediators known as chemokines (197), being considered as additional criterion of inflammation, more than the classical cardinal signs. Cytokines and chemokines, inflammatory mediators causative of many features of inflammatory diseases, including the old five cardinal signs, are now used as biomarkers of inflammation.

The identification of cytokines as mediators of inflammation in the mid 1980s led to what Tracey called the "cytokine theory of disease" (176). Contrary to the OS theory of disease, this led to major advances in the treatment of chronic inflammatory diseases, and less than 15 years after the identification of the cytokine tumor necrosis factor-α (TNF-α), anti-TNF-α antibodies were approved in the therapy of chronic inflammatory diseases and are now the top-selling biologicals.

Here we review both biomarkers of OS and inflammation; not a random choice, as the two fields are tightly linked. ROS can activate the transcription factor NF-κB (156), which has many inflammatory cytokines among its target genes. Conversely, inflammation can induce OS (147), as for instance in the case of ROS production by polymorphonuclear neutrophils (125).

Although the two pathways are so intertwined, they present entirely different challenges in terms of biomarkers. When studying disease mechanisms, we want to be able to measure the effectors of inflammation. The development of anti-TNF-α drugs was possible as researchers could measure TNF-α levels in patient with commercially available immunoassays that detect TNF-α in stored blood samples.

All this is very difficult when studying OS in disease. Here the effector molecules are ROS, which have short half-lives, ranging from nanoseconds to milliseconds (85). This makes it impossible to measure ROS in biological samples and we must rely on signs, chemicals that are produced by the interaction of ROS with various cellular molecules (57).

Another important aspect to consider is the difference between biomarkers that are measuring the formation of the effector molecule and those that measure the response of the organism to an inflammatory stimulus; inflammation is a defence/repair reaction of the organism to an infection or injury. The process is complex, as the effector cytokines in inflammation are produced after a series of steps. As we mentioned above, there are several biomarkers of OS that indicate the exposure of the organism to ROS by measuring oxidative breakdown products of cellular molecules. However, exposure to OS can be inferred by measuring the cellular defence response to it and, in this review, we will give the example of the transcription factor nrf2/antioxidant response element (ARE) transcription factor that is activated by ROS and other electrophiles. There are many

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

ways environmental stressors induce disease by common pathways (39,123). The sections in this review will deal with psychological, environmental or noise-induced stress, trying to focus on how their effects on inflammation or OS were detected.

ENGINEERED NANOMATERIALS AS ENVIRONMENTALLY-BORNE AGENTS INDUCING INFLAMMATION AND OS

Engineered nanomaterials (ENM) are manufactured materials in which at least one dimension is in the nanometer-range (< 100 nm). The higher surface area increases the material's reactivity (126). Redox interactions of ENM is a major mechanism of toxicity, particularly for metal and metal oxide nanomaterials, quantum dots and carbon nanotubes (CNT).

Typically, OS is induced by ENM in a three-tiered hierarchical sequence (Figure 2) (126,131). A mild production of ROS induced by ENM (Tier 1) lowers the reduced glutathione (GSH) / oxidized GSH (GSSG) ratio and upregulates genes encoding type II anti-oxidant enzymes, thus re-establishing homeostasis. In Tier 2, the defensive reaction is more complex, ENM induce the production of ROS triggering the production of inflammatory cytokines and chemokines. However, the inflammatory response is transient, as the elimination of the triggering event (*e.g.*, the phagocytosed ENM) and inflammation-damping feedback mechanisms re-establish homeostasis. In Tier 3, the GSH/GSSG ratio is completely unbalanced and essential components of cells are damaged, causing genotoxicity and cytotoxicity.

This sequence does not distinguish between the capacity of ENM to generate ROS in cell-free systems (131) and ROS generation consequent to nano-bio interaction. In a complex system (tissue, organ) a different three-pronged model can be proposed for the inflammatory response to ENM (Figure 3). In this model, Prong 1 represents the lack of response, due to either "ignorance" or "tolerance", in which the living system eliminates ENM immediately, *e.g.* by excretion with urine. Prong 2 is the classical protective inflammatory response, in which a tissue reacts to ENM sending alarm signals, with recruitment of blood immune cells to eliminate the ENM. The reaction is, however, limited in time and circumscribed; after eliminating the ENM, inflammation resolves. Prong 3 is the pathological situation of an inflammatory reaction that cannot resolve, as in the case of persistent materials (*e.g.*, fiber-like particles). This may result in persistent inflammation with tissue destruction and development of non-functional neo-tissue (granuloma, scarring tissue,

pannus, fibrotic tissue). Only Prong 3 can be eventually harmful for the organism and cause irreparable damage.

The three-tiered model of ENM-induced OS does not reflect the three-pronged model of ENM-induced inflammation because the entire organism considers the death of single cells as an acceptable event that may be important in the "cleaning" and healing reaction.

ROS production by nanomaterials

Unstable ENM can undergo oxidation, reduction and dissolution in biological media, releasing reactive free ions (in the case of metal ENM such as silver), or excitation of electrons and generation of ROS (as in the case of titania ENM and fullerenes upon UV irradiation). In addition, the reactive surface of ENM may absorb transition metals that catalyze ROS-generating reactions (Fenton, Fenton-like, Haber-Weiss) and produce cytotoxic and genotoxic hydroxyl radicals (126,131,137). Production of ROS resulting from the interaction of ENM with living systems is mainly indirect, due to damage or alterations caused by ENM to membranes, which trigger an alarm inflammatory reaction. The production of ROS is one of the defensive mechanisms initiated by innate defense cells such as phagocytes, aiming at killing microorganisms. Silica and polycationic particles can interact with plasma membrane phospholipids leading to membrane destabilization and ROS production (3,103). Urate crystals can also bind plasma membrane cholesterol and lead to aggregation of receptors and other molecules within lipid rafts, thus activating Syk-dependent inflammatory signaling and ROS generation (128,202). ROS induction can also be indirect, as for instance in the case of crystalline silica particles that can induce TNF-α production that stimulates ROS generation (15). Once internalized, ENM can destabilize and rupture the membranes of organelles such as phagolysosomes and mitochondria, causing ROS production and inflammation.

High-aspect ratio ENM (rigid fiber-like or needle-like ENM) are particularly challenging for phagocytes and generate a phenomenon known as "frustrated phagocytosis", with waves of phagocytes attempting to take up the material, and persistent inflammation, including ROS production. ROS production induced by ENM is in most cases associated with Akt/mTOR pathway, autophagy and apoptosis (5). This can evolve into a Tier 3 reaction, with ROS production inducing lipid peroxidation, membrane destabilization, DNA and protein damage. Rigid needle-like ENM can also cause phagocyte death by literally perforating the cell membrane (121).

Unlike apoptosis, necrotic cell death implies membrane damage and release of intracellular components, which perpetuates the inflammatory reaction (187). This may lead to tissue damage

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

or, in a "pathological" attempt to contain the danger, can result in fibrotic or granulomatous reactions (Prong 3). In some cases, leukocytes can successfully degrade high-aspect ratio EMN without phagocytosing them, as in the case of multi-walled CNT, which are sensitive to several leukocytic enzymes, and can therefore be eliminated rapidly without causing excessive ROS-mediated tissue damage (183). This would therefore be a classical Prong 2 inflammatory reaction that resolves without causing permanent damages.

Inflammatory reactions induced by nanomaterials

Inflammation (Prong 2) is therefore a central event in ENM-induced OS (24). At the organism level, inflammation is a defensive mechanism, which succeeds in tagging and eliminating potentially dangerous agents (including ENM). Inflammation however always induces some collateral damage, *i.e*. the death of some cells (including both the effector cells and innocent bystanders). In terms of ENM cytotoxicity, at the single-cell level inflammation can be in Tier 2 (resolves without cell death) or in Tier 3 (ending with cell death). Both events can be included in Prong 2, an inflammatory reaction at the tissue/organ/organism level that succeeds in eliminating the danger despite some cell death and tissue damage, and succeeds in repairing the collateral damage and restore functionality. Tier 2 and Tier 3 cellular reactions, on the other hand, are also included in Prong 3, the unresolving inflammation that fails in re-establishing tissue homeostasis, so that organ function is eventually compromised.

One aspect of ENM-induced inflammation is the capacity of activating the inflammasome, in particular NLRP3, which is the main inflammasome complex. This is a complex of proteins that assembles in the cytoplasm in response to inflammatory stimuli and leads to the activation of the enzyme caspase-1, responsible for cleavage and activation of the precursor forms of two important inflammatory cytokines, IL-1β and IL-18 (82). Caspase-1 can also auto-activate and mediate cell death (172). Several studies have shown that ENM can activate the NLRP3 inflammasome (reviewed in (171)), similarly to other particulate agents (*e.g.* hydroxyapatite crystals, cholesterol crystals, and aluminum hydroxide particles) (52,74,83). Inflammasome activation by ENM can occur through different mechanisms, including generation of ROS, which participate in inflammasome activation (63,190). Another mechanism is the destabilization of phagolysosomal membranes with consequent release of lysosomal enzymes, in particular cathepsin B, that activate the inflammasome either directly or via ROS (82). Other putative mechanisms of ENM-induced inflammasome activation include activation of the NADPH oxidases, K^+ efflux, purinergic receptor

P2X7 (P2X7R)-mediated ATP depletion, decrease of mitochondria membrane potential, and thioredoxin-interacting protein (TXNIP)-induced NALP3 activation (82,148). A summary of typical data of ENM-induced NLRP3 inflammasome activation is presented in Table 1. The general conclusion is that crystals and high-aspect particles (such as fibers) are excellent activators of the inflammasome. However, since inflammasome activation is not *per se* a sign of toxicity or pathological inflammation, it is a reaction that can be included both in Prong 2 and in Prong 3, and only a deeper kinetic analysis may allow us to discriminate between protective and pathological activation.

A final note of caution, when studying OS and inflammation induced by RNM, regards the possibility that ENM are inadvertently contaminated with endotoxin. This is a very common event when ENM synthesis and handling are not carried out in endotoxin-free conditions (180). The presence of endotoxin can cause *per se* inflammation that may be erroneously attributed to ENM (106).

Induction of oxidative stress and inflammation by particulate matter

All that has been said above for engineered nanomaterials applies as well to particulate matter (PM) collected from the environment. Indeed, studies on the capacity of PM to induce OS and inflammation are extensive and date back many years. Diesel exhaust particles (DEP), concentrated ambient particles (CAP) and ultrafine particles (UFP) are some of the many types of PM that have been extensively studied in this direction (see for instance Li et al. (105)). Although many studies show that PM can induce significant pulmonary inflammation upon inhalation *in vivo*, still we are unable to associate PM characteristics with the ability to induce OS and inflammation. In fact, ambient PM is typically morphologically and chemically heterogeneous, very much depending on the specific environmental conditions (such as temperature and humidity) and concomitant emissions. In addition, the presence of biologically active molecules such as bacterial LPS (see above for ENM) is practically never tested in the many studies published so far (see for instance Ying et al. (204)), leaving open the possibility that several of the effects caused by PM can be attributed to the presence of bacterial moieties, which typically trigger the same OS and inflammatory effects. Thus, the PM ability of inducing OS and inflammation is most likely the result of intrinsic toxicity of the chemicals present in the PM, of its state of aggregation and consequent changes in morphology (which may cause mechanical stress to cells) and of the presence of bystander biological substances (such as pollens, animal allergens, bacterial fragments of whole

micro-organisms). In this context, although we can list many biomarkers of both OS and inflammation induced by inhalation of PM, it is impossible to associate any of them to particle-specific effects.

NRF2 AS AN INDICATOR OF RESPONSE TO OS

One approach to monitoring OS as well as environmental electrophilic chemicals is to use biomarkers based on the response of the organism, as opposed to measuring oxidized products of cellular components. NRF2 is the main transcriptional regulator of cellular homeostasis and protects against multiple stress conditions. Upon dimerization with small MAF proteins, it recognizes an enhancer in the promoter region of target genes, termed Antioxidant Response Element/Electrophile Responsive Element (ARE/EpRE) genes. These account for about 1% of human genome and encode phase I, II and III detoxification enzymes, GSH, peroxiredoxin (PRDX) and thioredoxin (TXN) metabolism, intermediary metabolism related to pentose phosphate pathway, etc. (67).

The main mechanism of regulation is protein stability by the ubiquitin/proteasome system (UPS) illustrated in Figure 4. Under non-stress conditions, the E3 ubiquitin ligase adapter Kelch-like ECH-associated protein 1(KEAP1) drives NRF2 to ubiquitination by the Cul3/RBX complex and rapid proteasomal degradation. However, KEAP1 contains several cysteine residues which have a low pKa value, making highly suited for acting as a sensor for oxidative and electrophilic stress (112). Oxidant or electrophilic modification of critical cysteines in KEAP1, mainly C155, C273 and C288, prevent the protein from connecting NRF2 to the UPS, thus resulting in the accumulation of nuclear NRF2 and transcriptional activation of ARE genes. Another crucial mechanism for control of NRF2 stability is by phosphorylation. Several kinases phosphorylate NRF2 with different outcomes. Activating phosphorylation by MAP kinases, PKC or PERK at Ser40 and other residues appears to free NRF2 from KEAP1 control. On the other hand, the Ser/Thr protein kinase GSK-3 phosphorylates at least Ser 335 and 338 in murine NRF2 thereby creating a recognition site for the E3 ubiquitin ligase adapter β-TrCP, leading to ubiquitination by Cul1/RBX and proteasome degradation of NRF2 (40,141,142). Importantly, several phosphatases, such as phosphatase and tensin homolog (PTEN), contain thiol reactive cysteines in their catalytic centre, which become inactive upon oxidation or reaction with electrophiles (139,149). In this case, PTEN inhibition leads

to sustained activation of AKT and inhibition of GSK-3. As a result, NRF2 escapes Glycogen synthase kinase 3 (GSK-3)/β-TrCP mediated degradation (40). Below we will discuss advances on its role for protection against several environmental forms of stress.

Heavy metals

Occupational or environmental exposure to heavy metals generate OS that, depending of the route of entrance and clearance, may produce liver, kidney or lung damage among others. Chromium, arsenic, cadmium, mercury, and lead can interact with nucleophilic thiol groups, e.g. cysteines residues in proteins. Cells have a thiol buffering capacity represented by the GSH and PRDX/TXN systems. Exposure to heavy metals will compromise these systems and alter a significant fraction of thiols in critical enzymes. Formation of sulfur-metal bonds in redox-sensitive cysteines of KEAP1 will result in its stabilization. Also, signaling pathways are altered, with phosphatases such as PTEN being inhibited resulting in increased activation of AKT, inhibition of GSK-3 and further stabilization of NRF2. The result is up-regulation of genes involved in GSH synthesis and maintenance of reduced TRX and GSH, both important to tolerate metal exposure.

Furthermore, as reported for cadmium, chromium, arsenic and others, low-level chronic exposure to metals may induce cancer. Somatic mutations in the interface of interaction between KEAP1 and NRF2 have been correlated with several types of tumors (162), and NRF2 levels are elevated in cancer cells, resulting in a metabolic reprogramming that allows to withstand OS and adverse growth conditions. It is therefore possible that part of the tumorigenic activity associated with exposure to heavy metals might be due to dysregulation of NRF2 (165).

Most of the exposure to heavy metals is in the form or reactive molecules. For example, intracellular reduction of hexavalent chromium generates highly reactive pro-oxidant intermediates, together with superoxide, hydrogen peroxide, and hydroxyl radical. These compounds irreversibly inhibit TXN reductase and deplete TXN and PRDX (124). While this situation is typical of KEAP1 inhibition, it is also recognized that TXN depletion has additional effects on signalling pathways such as activation of ASK1, leading to up-regulation of NRF2 by MAPK kinases by yet unknown mechanisms.

Noise injury

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

As expected, noise-induced oxidative stress also results in the activation of NRF2 and induction of some of its target genes including SOD and heme oxygenase (54,73). These studies also show that NRF2 deficiency increases noise-induced injury and hearing loss, while its induction has protective effects (54,73).

Exposure to particulate matter (PM)

Like other forms of environmental stress, exposure to PM results in activation of NRF2 and increased transcription of its target genes (48,77). Not only NRF2 induces transcription of antioxidant genes but also in phase 2 enzymes of xenobiotic metabolism. As a consequence, NRF2 deficiency increases the genotoxic actions of diesel exhaust (6). This has led to the suggestion that the levels of expression of NRF2 target genes could represent markers of exposure to PM (196). Because NRF2 also regulates secondary effects of environmental pollutants, such as inflammation and allergy, the NRF2 response to PM could also be used to predict those at risk of developing asthma (104), cardiovascular disease and atherosclerosis (99).

Mental stress

Recent studies have correlated depression, typically caused by mental stress and social defeat, with low grade chronic inflammation that affects critical regions of the brain (14). NRF2 modulates inflammation by down-regulating the NF-κB pathway (41,78). Additionally, NRF2 inhibits expression of IL-6 and IL-1β by directly binding the proximal promoter of these genes (90). *Nrf2*-knockout mice exhibit a depressive-like behaviour, with reduced levels of dopamine and serotonin and increased levels of glutamate in the prefrontal cortex, altered levels of proteins associated to depression such as VEGF and synaptophysin, as well as microgliosis. Importantly, depressive-like behaviour elicited by endotoxin in wild-type mice could be attenuated with the NRF2 activator sulforaphane (114).

Ionizing and UV-radiation

Exposure to cosmic, ionising radiations and UV radiation, either from natural sources of from devices, represents a significant challenge to homeostatic redox mechanisms and nucleic acids integrity. Recent studies have demonstrated that NRF2 promotes DNA repair and drives

detoxification of superoxide that is generated after irradiation (158). In particular, NRF2 regulates the expression of RAD51, many DNA repair genes, including those of homologous recombination repair pathway, and have putative antioxidant response elements (80).

NOISE INDUCED HEARING LOSS

Noise-induced hearing loss (NIHL) can be induced by exposure to loud sound. Affected individuals may have inability to hear certain frequencies of sound, cognitive impairment of sound perception, including sensitivity to sound and ringing in the ears (tinnitus) (1). The association between noise exposure and hearing loss was first recognized by Sir Francis Bacon (1561-1626) (65).

NIHL is caused by acute (*e.g.* sudden exposure to loud noise, explosion) or chronic acoustic trauma (*e.g.* loud music). NIHL is the most common occupational disease and its severity differs amongst individuals, and increases with age, compromising the quality of life that extend beyond hear loss. Unfortunately, unlike birds and amphibians, ability to regenerate hearing is lost in mammals. Thus, in human beings any damage to the hearing organ from any sound source over time leads to permanent hearing loss.

Cochlea is located within the inner ear and houses the specialized peripheral end organ of the auditory system, which mediates the transduction of sound waves into electrical nerve impulses that travel to the brain for central processing of auditory information. Acoustic insults to the cochlea cause mechanical and metabolic changes affecting almost all cell types, but particularly the sensory hair cells and neurons. Temporary and permanent threshold shifts occur from mechanical and metabolic changes caused by the exposure to different noise levels (34,70,92,95,100). Mechanical damages occur with exposure to the noise levels of 115-125 dB sound pressure level (SPL), while metabolic damages occur with exposure to the noise level of less than 115 dB SPL. These changes in threshold shifts are related to noise-induced neural degeneration, which begins shortly after noise exposure and can progress for several years post exposure (94,119) Importantly, early noise exposure can intensify age-related hearing loss (94).

Beginning at 85 dB (~300 times the energy level of 60 dB), long or repeated exposures may result in a notable loss of hearing. This level of 85 dB and above includes some everyday sounds, for example, music on personal listening devices or emanating from small machinery such as lawnmowers. Noise coming from urban traffic, household appliances, personal listening devices or occupational noise can also elicit hearing loss. Importantly, long or repeated exposure to moderate

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

noise levels is often associated with alterations in behavior, as well as changes in neuroendocrine, cardiovascular and immune systems (45,189). Cochlear damage and hearing loss associated with chronic environmental noise exposure may be linked to an increase in ROS levels as well as inflammatory processes in the cochlea.

Noise induced hearing loss - pathology

Early studies of NIHL demonstrated mechanical damages of the cochlear structures including the disruption of Reissner's and basilar membranes, damage and loss of stereocilia bundles, damage of the inner and outer hair cells (IHCs, OHCs), *stria vascularis*, spiral ganglion cells, and lateral wall of the OHCs (23,92,100,168). OS and inflammation are major contributors to NIHL.

Cell death induced by acoustic overexposure occurs primarily through apoptosis and necrosis. Apoptosis is a programmed cell death, with no inflammatory response (70). As discussed below, the apoptosis can be mediated by the activity of enzymes, induced by increased production of ROS (ROS) and Reactive Nitrogen Species (RNS) (92,129,188). The second cell death pathway is necrosis, a passive unprogrammed cell death which is identified by swollen and pale-staining cytoplasm resulting in rupture of the cell, spillage of the cell contents, damage to surrounding tissue, and evocation of an inflammatory response (70). Both apoptotic and necrotic pathways have been observed in the cochlea immediately after noise exposure (76), as discussed below and illustrated in Figure 5.

OS induced apoptosis in hearing loss

The cochlea is a highly metabolically active sensory organ, which receives 0.5 mL per minute of blood flow in normal conditions (92). Metabolically, noise exposure can decrease cochlear blood flow leading to cochlear ischemia-reperfusion injury, induce cell death by producing ROS, and contribute to injury and death of hair cells and spiral ganglion cells (33,70,92). Noise-induced OS causes lipid peroxidation in the spiral ganglion, organ of Corti, and *stria vascularis*, leads to oxidation of actin filaments of stereocilia and cell membrane lipids, protein oxidation, damage to nuclear and mitochondrial DNA, swelling and degeneration of afferent nerve endings, and release of toxic lipid peroxidation products such as 4-hydroxy 2, 3-nonenal (HNE) (51,92).

OS biomarkers in hearing loss

OS occurs immediately and is present up to 30 days following noise exposure (70,200). In the first 10 days, the formation of ROS reaches its peak (200). OS has been identified by a variety of biomarkers of ROS and RNS activity in the cochlea and the brain (51). These biomarkers include HNE, nitrotyrosine (NT), malondialdehyde (MDA), inducible nitric oxide synthase (iNOS), cytochrome-C, caspase-3, 8, 9, and p66shc. Formation of HNE was observed after noise exposure in the lateral wall and Claudius cells, the Deiter's cells and the outer hair cell bodies (33,51,200). Formation of NT, a biomarker of NO production formed by nitration of a tyrosine residue in proteins, occurs in the hair cells after noise exposure (33,51,200). MDA was observed in cochlea immediately after noise exposure (33). The expression of iNOS in the hair cells, wall of the blood vessels of *stria vascularis* and marginal cells was observed immediately after noise exposure (160). Noise exposure induces cytochrome-C release from mitochondria and caspase-3, -8, or -9 activation in both apoptotic and necrotic OHCs, while caspase activation occurred only in apoptotic OHCs (129). Another important issue is the cause of ROS production in NIHL. Animal studies have shown that local application of NADPH oxidase (NOX) inhibitors has protective effects (21) and a genome-wide association study (98) showed that NOX3 is critical in the development of NIHL. These studies led to the suggestion of a potential therapeutic approach to inner ear pathologies (150).

Inflammatory biomarkers in hearing loss

Acoustic trauma can also initiate inflammation in the *stria vascularis*, compromising blood supply to the cochlea, causing hypoxia and injury to HCs (166). Injuries to the *stria vascularis* and spiral ligament occur following noise trauma, damaging type II and IV fibrocytes leading to permanent hearing loss (71).

As a response to acoustic trauma, the cochlear cells express cytokines, such as TNF-α and IL-1β, and chemokines, which cause leukocyte migration (86). These inflammatory cells, producing cytokines, chemokines, ROS and RNS, then propagate the inflammatory process to the inner ear.

Following acoustic trauma, an influx of inflammatory cells occurs (71,173,174,186). These cells are mostly found in the spiral ligament (type I, III and type IV fibrocytes), and in the perilymph of the *scala tympani* and *scala vestibule* (71,173,174,186).). IL-6 immunoreactive cells were observed initially in the cytoplasm of type III and IV fIbrocytes, then throughout the spiral ligament and the *stria vascularis* (58). Double labelling with the neuronal marker NeuN showed IL-6 expression in

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

the spiral ganglion neurons after noise exposure. Chemokines (such as MCP-1/CCL2, MCP-5/CCL12, and MIP-1β/CCL4) are upregulated by acoustic trauma (174). ICAM-1/CD54, a vascular adhesion molecule that mediates leukocyte extravasation, as well as other adhesion molecules including P-selectin, PECAM-1 and VCAM-1, are also increased after noise exposure (161,174,199).

The measurement of cytokines as biomarkers on inflammation in hearing loss may have translational implication. For instance, the IL-1 receptor antagonist drug anakingra improves hearing loss associated with autoinflammatory diseases (120) and autoimmune diseases, including in glucocorticoid-resistant patients (181).

BRAIN-BODY INTERACTIONS OF STRESS, OS AND INFLAMMATION

While stress and inflammation are often implicated in disease, there is a bidirectional regulation between the two. Figure 6 outlines the main regulatory pathways. The classical pathway is mediated by glucocorticoids (GC). The fact that stress activates the hypothalamus pituitary adrenal axis (HPAA) to increase GC has been known for a long time, and GC are probably the oldest anti-inflammatory drugs. The finding that GC inhibit the expression of inflammatory cytokines provided an important mechanism of action (20). It soon became clear that inflammatory cytokines activate the HPAA and thus increase GC that not only inhibit cytokine synthesis but also protect from their toxicity, in a classical feedback (18,19,35,179). This raises an important point in the interpretation of the scheme in Figure 6: inflammatory cytokines and inflammation are also stressors themselves, sometime defined as “immune stressors”.

It comes therefore as no surprise that corticosteroids are used as biomarkers of stress. Because their level in the blood vary with time, the measurement of hair cortisol, which accumulates over weeks and months, has been proposed as a biomarker of stress (117) and has been successfully used in the study of post-traumatic stress disorder (PTSD) (111). More recent studies have identified in the cholinergic response mediated by vagus nerve stimulation another mechanism of regulation of peripheral inflammation by the brain, which also led to development of novel therapeutic options (133,177).

The fact that infection induces a sickness behaviour (lethargy, anorexia, social isolation) is an old observation, but findings by Dantzer (reviewed in (47)) that this is mediated by cytokines has provided a molecular mechanism for what is thought to be an adaptive response of the organism to better survive an infection (46). Similar to their effect on IL-1-induced lethality (19), GC inhibit

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

the anorexigenic response to IL-1 (140), indicating that they act not only by inhibiting cytokine production but also their action.

As we mentioned earlier, OS can induce inflammation and, vice-versa, inflammation induces OS. This has been hypothesized to be the case in PTSD, where a study measuring levels of inflammatory cytokines and markers of OS suggests that inflammatory cytokines induce ROS production, which then amplifies the inflammatory response (194).

Fitting GC and the HPAA in this bi-directional autostimulatory loop between inflammation and OS is more difficult. Clearly GC, by blocking production of inflammatory cytokines, could remove a major stimulus of OS. On the other hand, activation of the HPAA, by increasing metabolic rate and glucose availability, can result in increased OS (167) and, in agreement with this hypothesis, administration of corticosterone to rats causes an increase in biomarkers of OS, lipid peroxides and protein carbonyls (153).

It should be pointed out, however, that the latter study, as well as the study on PTSD cited earlier (194) were performed measuring, among other biomarkers, superoxide levels in plasma and blood. Because, as mentioned above, superoxide has a half-life in milliseconds, some aspects of the methodological approach might be questioned.

Effect of emotional states on OS and inflammation

Emotions, inflammation and OS share three fundamental features: 1- they help the host to adjust to different environmental challenges and maintain a status of homeostasis; 2- they can have both protective or deleterious effects for the host; 3- they are deeply intertwined in ways that we have only started to appreciate and are not fully explored. The few examples below should be sufficient to support these statements.

There is evidence that basic emotions, like laughter and joy, improve immunological competence of host through NK cells, important in cancer surveillance (60). It is possible that the negative emotional state often experienced following a diagnosis of cancer might contribute to the development of this disorder, and that 'laughing therapy' (60) and patient support groups might have a biological therapeutic value for cancer patients undergoing chemotherapy.

Negative emotions (anger and rage) can be protective as they represent an immediate reaction to real or imaginative dangers but also contribute to the exacerbation of chronic inflammatory

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

diseases (25,88). Anger, rage and aggressive behaviour cause a significant increase in the serum levels of IL-1 (136).

Several studies (11,26,32,42,43,113,138) have highlighted the link between emotion and immunity.

Studies have shown how external conditions (massage-like stroking or enriched environment) can improve the host resilience to immunosuppression (107,138).

We think that the implications of these studies go beyond the simple duality of emotions and immunity as an example of body-mind continuum. Indeed, the “mirroring effect” that we have proposed to explain how emotions influence immune response and vice-versa (26,42,43) might as well work for another system.

There is increasing evidence that emotional state and personality affects inflammation and OS. Interestingly, several risk factors for cardiovascular disease (CVD) (high fat diet, sedentary lifestyle and smoking) are associated with elevated OS, and are lifestyle choices associated with depression (7,97).

Many recent studies highlighted links between outlook on life and outcome in disease. For example, people who have Type D personality, a pessimistic and socially inhibited outlook, do worse during CVD. Heart failure patients with this personality type have elevated levels of xanthine oxidase (XO) and reduced heat shock protein 70. These factors combined might increase OS and inflammation, leading to a worse prognosis (89). On the other hand, higher optimism correlates with lower levels of inflammation, IL-6, and markers of endothelial dysfunction. Similarly, there is a positive correlation between higher optimism scores and increased carotenoid and antioxidant levels, suggestive that optimists may have lower OS (22).

These studies might help with the stratification of patients based on their personality traits. People who practice meditation have lower levels of lipid peroxidation in serum but higher levels of NO, which is indicative of normalized endothelial function (69). The risk of all-cause mortality, stroke and myocardial infarction can be lowered by as much as 45%, due to a reduction in psychosocial stress and in blood pressure which are both linked to OS (151). Similarly, yoga seems to attenuate OS possibly increasing glutathione reductase (GR) and glutathione peroxidase (GPx) and decreasing serum lipid peroxides and F2-isoprostane. Yoga practice in type 2 diabetics decreases MDA, increase GSH and vitamin C and improve glycaemic control (66). However, studies done in this area are small and therefore should be interpreted with caution until larger randomised clinical trials are done.

Social isolation is an increasingly worrying threat, as socially isolated people are at increased risk of several diseases including atherosclerosis and dementia (56,157). Social isolation downregulates the genes required for the glucocorticoid response, which could impair ability to dampen immune responses, and inflammation is exacerbated by increased expression of NF-κB (38). Similarly, in rats who have been chronically isolated OS is observed, accompanied by decreased GPx and GR (49).

Opposed to social isolation, environmental enrichment normalises levels of TNF-α, CCL3 and CCL4 by preventing changes in microglial expression in Alzheimer's Disease models (184), and lowers hippocampal damage and OS during chronic cerebral hypoperfusion (113).

Most animal models of environmental enrichment use physical exercise. Depressed patients who exercise have lower markers of OS (155). In rats, GSH depletion causes anxiety-like behaviour, while moderate exercise on a treadmill prevents OS-induced anxiety and decreasing OS markers in the hippocampus, amygdala and the *locus coeruleus* (146).

Biomarkers of OS and inflammation in mental disorders

There is a lot of clinical evidence to support a role of oxidative stress and inflammation in mental disorders. Depression causes elevated total oxidative stress in plasma and serum with increased plasma NO levels associated with suicidal thoughts (88,101). Depressive patients are found to have lower total antioxidant activity (TAA) with scores being indicative of poor response to pharmacological treatments (13). A meta-analysis study looking at CRP, IL-1, IL-6 found that these factors were positively correlated with depression (75). Serum TNF-α and CRP are elevated during depression and treatment with SSRIs returned levels to that seen in non-depressed patients and this was associated with decreased clinical scores of depression (178). In social phobia patients, studies have shown that alongside having increased MDA there was increased SOD, GSH-Px and catalase and lipid peroxidation. Interestingly, a positive correlation was seen between anxiety levels and MDA, SOD and GSH-Px as well as a positive correlation between MDA, SOD and CAT and the duration of illness (10).CRP levels are elevated in men who have anxiety disorders and are higher in those who have late onset anxiety disorders (>50 years) but no difference in TNF-α and IL-6 (184).

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

THE HUMAN EXPOSOME

Proposed by Wild in 2005 as an environmental counterpart to the human genome, the human exposome represents the totality of environmental (*i.e.* non-genetic) exposure individual experiences between conception and death (191). As a "comprehensive description of lifelong exposure history" (192) the exposome effectively provides a new framework for bringing together interdisciplinary teams to understand the environmental determinants of chronic disease risk, the influence of which are estimated to exceed those relating to genetic predisposition (144). Wild subsequently elaborated on his definition of the exposome, emphasising the dynamic nature of exposures over a lifetime and categorising components of the exposome into three domains; internal, specific external and general external (192). Specific reference was made to factors that influence the internal or cellular environment (*e.g.* metabolism, ageing, gut microflora activity), vary at the individual level (*e.g.* occupation, lifestyle components, mental stress, noise, air pollutants) or influence populations (*e.g.* climate, education, urban/rural surroundings) (192). The definition was also expanded to include behavioural interactions and products of endogenous exposure (*e.g.* epigenetic changes), and to account for the cumulative nature of exposures and their corresponding biological adaptations (118). While there have been several proposed revisions of this original definition, the practical implementation of this general concept has led researchers to embrace more holistic and integrated methods for assessing the external and internal environments. Central to the implementation of this idea is the application of data-dense omics techniques that report on various aspects of the internal chemical milieu (in most cases focused on the blood) to provide complementary datasets relating to biochemical status in individual biosamples. Combined with access to mature biobanking resources, the recent radical advances in molecular biology approaches, multivariate data analysis tools, biomonitoring technology, and the proliferation of inexpensive mobile devices have enabled exposome studies to become a reality. The exposome proposal came in response to the limitations in epidemiological studies attempting to link environmental exposure assessments with disease endpoints – effectively 'bottom-up' approaches, focused on a small number of priority exposures. By contrast, exposome studies seek to benefit from 'top-down', data-driven, agnostic approaches that can uncover previously unknown and/or complex relationships, as well as guide subsequent hypothesis-based investigations to provide mechanistic insight about disease aetiology. Complete characterisation of the exposome - which would require high-resolution, real time monitoring of all exposures throughout life - is clearly unfeasible for multiple obvious reasons (8). However, it is proposed that

understanding the status of the exposome, particularly that of the internal chemical environment, at the individual level during critical periods of life may help delineate the contributions of various genetic and environmental factors.

Studying the exposome

An improved ability to characterise the external chemical environment can enhance exposure models both spatially and temporally, but it is the extensive characterisation of *internal chemical environment* that represents the most significant advance in recent years, and an opportunity to delineate the contributions made by multiple, interacting factors, to the biological changes observed at an individual level. High-throughput platforms now exist for profiling the metabolome (metabolites), proteome (proteins), transcriptome (gene transcripts) and adductome (typically endogenous-xenobiotic conjugates) and provide collectively a wealth of information about the status of a biological samples (reviewed in the context of the human exposome by (193), summarised briefly in Table 2). These platforms (mostly, now) provide broad coverage of their biomolecular target classes, and therefore permit the application of data-driven approaches that mirror those used in the genome-wide association studies (GWAS). The techniques may be performed on cells, tissues or biofluids, making novel biomarker selection possible for *in vitro, in vivo* and human studies and integrated analyses may be performed across the omics platforms to cross-validate or integrate findings. Initial studies have indicated that suitably collected/stored biobanked samples are amenable to analysis by multiple omics platforms (68), and large scale initiatives to conduct exposome studies are now underway (including the EXPOsOMICS (182), HELIX (185), and HEALS (http://www.heals-eu.eu) projects in the EU).

Unpicking the exposome: cellular inflammatory responses to diesel exhaust particles

While there is considerable activity in molecular epidemiological analysis to characterise biological samples archived in biobanks, the validation and mechanistic understanding that accompanies these largely correlative analyses is both complementary and vital; tying together evidence from multiple levels of analysis is required to corroborate the correlative analyses that are conducted on these omics readouts (144,182). For example, while many of the ongoing exposome studies include aspects concerning air pollutants, validation of these studies requires a coherent molecular context, while conversely targeted analyses need to be directed appropriately. For example, diesel exhaust particles (DEP) are considered important environmental causes of OS and pulmonary

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

inflammation due to their ubiquitous presence in air (84), their concentration in populated areas (206) and the breadth of sub-populations that are susceptible to their inflammatory and oxidative effects (12,17,27,37,53). Adverse responses to DEP exposure have traditionally been assessed by quantifying specific inflammatory cells, cytokines or cell adhesion molecules (CAM) following exposures (2,93,127,152,175). These targets are well characterised mediators of inflammation that provide strong evidence of DEP induction of inflammatory cellular response, but are limited in their potential to expand our mechanistic knowledge of the observed toxicity. In contrast, agnostic approaches for omics screening report on both characterised and uncharacterised markers, offering chances to explore a wider range of associations with DEP toxicity. Xiao *et al* used a proteomic screening approach, showing that DEP induced OS in RAW 264.7 macrophages; the response was accompanied by > 8-fold increases in new protein expression. Furthermore, the biological functions of the proteins reflected a hierarchical response to OS with the macrophages expressing antioxidant enzymes after low dose exposures (≤ 10 μg/ml), pro-inflammatory signalling proteins after mid dose exposures (10-50 μg/ml) and regulators of mitochondrial function at cytotoxic doses (≥ 50 μg/ml) (198). Although many of these proteomic changes validated existing hypotheses of how macrophages respond to DEP, others (including the induction of receptor-induced apoptosis) were previously uncharacterised (198). These changes revealed novel pathways that are triggered by DEP-induced OS, advancing our understanding of the response.

Metabolomic, transcriptomic, and proteomic profiles are strongly dependent on the expression and behaviour of the other molecular species as well as experiencing a dynamic interaction with the external chemical environment (Figure 7). Proteomic response to DEP-induced OS (198) are mirrored by transcriptomic studies showing changed expression of oxidative response genes after DEP exposure (91,134) as well as micro RNA (miRNA) (79).

Supporting the hypothesis that surface bound metals and polycyclic aromatic hydrocarbons (PAHs) contribute to particulate toxicity (87,135), metal and PAH-rich heavy fuel oil (HFO) particles induce inflammatory and OS pathways more than carbonaceous DEP (130).

Redox status, inflammation and ROS are all intricately linked with biotransformation of compounds across this continuum. For example, dietary components have been linked with modulation of cytokine levels, with concomitant impact on the metabolome (36), with other recent examples including herbal medicine (205), involvement in arthritis (reviewed by Chimenti et al. (31)), and broader implication in pathways identified by cross-omics analysis (16,163). Additionally, a comprehensive survey focused on the role of metabolome studies in characterising oxidative studies was previously published by Liu et al (108).

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Exposome and Adverse Outcome Pathways: inflammation and ROS are key integrators of complex exposure-response relationships

One exemplar that elegantly illustrates the interplay of inflammatory mediators and ROS with other components of the internal chemical milieu, is the analgesic/antipyretic compound paracetamol (a.k.a. acetaminophen), one of the most commonly used over-the-counter drugs worldwide. Self-administration is the main cause for personal exposure (exposure in the wider environment is negligible), and large-scale, cross-sectional metabolic phenotyping studies of humans have shown a high prevalence of significant (*e.g.* therapeutic dose) exposure (109,110). Characterising population-level use of therapeutics (*e.g.* anti-inflammatory agents) provides an overall profile of the exposome, and help contextualise and validate observed responses at the individual level (*e.g.* when addressing research questions relating to chronic inflammation that may be confounded by unreported pharmaceutical use). Intense scrutiny has allowed many of the toxicological consequences of paracetamol exposure and metabolism be elucidated (including depletion of cellular antioxidants, increased ROS formation, formation of reactive intermediates). However, despite such widespread, long-term and consistent use, the complexities of the exposure-response relationship continue to be uncovered (including metabolite conjugation to arachidonic acid to produce an active metabolite AM404 (72) and metabolite modulation of the nociceptive response (4). This also illustrates the challenge that is faced when considering how to dissect the complex, multicomponent exposures that occur throughout life; considerations of additive or non-linear effects arising from co-exposures all add up.

Attempts to bring together the diverse pieces of evidence that relate to exposure-response-disease relationships, and address the challenge of this inherent complexity have resulted in the formulation of systems toxicology tools such as adverse outcome pathways (AOPs), as summarised by Burden et al. (28). By establishing a series of causal steps from an initial molecular initiating event (MIE) onwards, the AOP approach may help integrate knowledge about multiple environmental exposures that share common pathways, described using an agreed ontology. The combination of the exposome and AOP frameworks is likely to be particularly useful when the complexity of exposure-response relationships is considered; exposures do not occur in isolation, but in a context that encodes previous exposures and responses, and mediates the dynamic relationship between co-exposures.

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

In the context of oxidative stress, several redox proteomics techniques and their application to the field of inflammation and neuroinflammation have led to the identification of specific oxidized proteins undergoing carbonylation (170) or glutathionylation (30,122). The extension of omics to oxidative post-translational modifications may add a dimension to the information obtained and eventually provide a more precise way of identifying exposure to agents that cause oxidative stress.

The strong underlying biological network connections between certain sets of pathologies - particularly those relating to systemic inflammatory status that underpin multiple chronic disease conditions - may mean we move away from attempts to find correspondence between individual exposures and outcomes, and towards using biological networks to link and explain complex exposure patterns with (multi)morbidities defined by detailed molecular phenotyping (102,169).

CONCLUSIONS

The use of biomarkers of inflammation or OS has been instrumental to formulating causal hypotheses on disease mechanisms (such as the effect of environmental stressors).

We mentioned above that, in a way, biomarkers are signs. However, there are different types of signs and so, if biomarkers really are signs in a non-metaphorical sense, there must be different types of biomarkers as well, depending on the relation they have with their referent. In fact, we don't just measure biomarkers, in some cases we can measure the "real thing". For instance, to quantify exposure to heavy metals we can measure their level in the organism. When this is not possible, we can measure signs that are indicators of the exposure of the body to heavy metals. Some of them have a direct relationship to the object, for example a product of lipid peroxidation is directly formed by a chemical reaction between a ROS and a lipid. Others can be an indicator of the response of the organism to the object we want to measure, and this is the case of NRF2 or the markers of exposure described in the section on the exposome; all these will have various degrees of separation from the object we want to measure and this needs to be considered as some may require just transcription (if we measure a mRNA), others transcription and translation (if we measure a protein). This is particularly important if we are measuring exposure to a physical stressor, such as noise, or a psychological stressor, that is not present at the time of the examination.

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Interestingly, even if not obvious, inflammation itself is a response to a foreign body or to an endogenous of exogenous stressor. It is important to note that measuring biomarkers is not always a second, imperfect choice when we cannot measure what we need (like in the case of short-lived radicals). Often measuring a biological response adds a second dimension, that of biological relevance. But in the case of inflammatory biomarkers, we observe a further level of relevance.

Let us consider inflammatory cytokines. As we wrote earlier, they are easily measurable biomarkers of inflammation, many of which measurable in plasma or serum. However, some of them are not simple signs but proxies. A proxy of something is a sign that has a vicarious relation with that something: it both "stands for" its referent and "stands *in* for" it. This means that not only there is a link between proxy and referent; one can also interact with the referent by operating on the proxy and, as a result, affect the object (or process, in this case) it stands for (55). In short, they have a bidirectional relationship with the referent. If MDA is elevated in a disease because of increased lipid peroxidation, you cannot improve the disease by administering an anti-MDA antibody, because it is just a sign of OS. However, in inflammatory diseases IL-6 and TNF-α are not only signs of the inflammatory process but proxies, and so their inhibition, for instance with antibodies, improves the disease in patients with chronic inflammation. This concept is exemplified in Figure 8 where the mediators and processes described in this paper are assigned a value of biomarker (considering their ease of measurement) or proxies. Researchers often classify biomarkers differently. For instance, MDA, IL-6 and TNF would be considered mechanism-based biomarkers because they reflect a potential disease mechanism. On the other hand, IL-6 and TNF are also defined as "pharmacological targets", although not all pharmacological targets are biomarkers as some of them are not measurable. The definition of biomarkers as signs and their value, whether they are proxies or just signs, will need to be considered when considering their role in disease.

Acknowledgements. LS is supported by an Integrative Toxicology Training Partnership (ITTP) PhD studentship from the Medical Research Council (MRC). AH is recipient of a PhD studentship from the BHF. AC and GM are funded by SAF2013-43271-R of the Spanish Ministry of Economy and Competitiveness and European Regional Development Fund, Competitiveness Operational Program 2014-2020, grant P_37_732/2016 REDBRAIN. DB is supported by the H2020 MSCA project PANDORA (GA 671881) and by the Cluster project *Medintech* granted by the Italian MIUR. AH is a recipient of a BHF PhD studentship.

REFERENCES

1. Alberti PW. Noise induced hearing loss. *BMJ* 304: 522, 1992.

2. Alexeeff SE, Coull BA, Gryparis A, Suh H, Sparrow D, Vokonas PS, Schwartz J. Medium-term exposure to traffic-related air pollution and markers of inflammation and endothelial function. *Environ Health Perspect* 119: 481-6, 2011.

3. Allison AC. Lysosomes and the toxicity of particulate pollutants. *Arch Intern Med* 128: 131-9, 1971.

4. Andersson DA, Gentry C, Alenmyr L, Killander D, Lewis SE, Andersson A, Bucher B, Galzi JL, Sterner O, Bevan S, Hogestatt ED, Zygmunt PM. TRPA1 mediates spinal antinociception induced by acetaminophen and the cannabinoid Delta(9)-tetrahydrocannabiorcol. *Nat Commun* 2: 551, 2011.

5. Anozie UC, Dalhaimer P. Molecular links among non-biodegradable nanoparticles, reactive oxygen species, and autophagy. *Adv Drug Deliv Rev*, 2017.

6. Aoki Y, Sato H, Nishimura N, Takahashi S, Itoh K, Yamamoto M. Accelerated DNA adduct formation in the lung of the Nrf2 knockout mouse exposed to diesel exhaust. *Toxicol Appl Pharmacol* 173: 154-60, 2001.

7. Ariyo AA, Haan M, Tangen CM, Rutledge JC, Cushman M, Dobs A, Furberg CD. Depressive symptoms and risks of coronary heart disease and mortality in elderly Americans. Cardiovascular Health Study Collaborative Research Group. *Circulation* 102: 1773-9, 2000.

8. Athersuch TJ. The role of metabolomics in characterizing the human exposome. *Bioanalysis* 4: 2207-12, 2012.

9. Atkin A. Peirce's Theory of Signs. In: *The Stanford Encyclopedia of Philosophy*. edited by Zalta EN. 2013.

10. Atmaca M, Kuloglu M, Tezcan E, Ustundag B. Antioxidant enzyme and malondialdehyde levels in patients with social phobia. *Psychiatry Res* 159: 95-100, 2008.

11. Aubert A. Psychosocial stress, emotions and cytokine-related disorders. *Recent Pat Inflamm Allergy Drug Discov* 2: 139-48, 2008.

12. Autrup H. Ambient air pollution and adverse health effects. *Procedia-Social and Behavioral Sciences* 2: 7333-7338, 2010.

13. Baek SE, Lee GJ, Rhee CK, Rho DY, Kim DH, Huh S, Lee SK. Decreased Total Antioxidant Activity in Major Depressive Disorder Patients Non-Responsive to Antidepressant Treatment. *Psychiatry Investig* 13: 222-6, 2016.

14. Bakunina N, Pariante CM, Zunszain PA. Immune mechanisms linked to depression via oxidative stress and neuroprogression. *Immunology*, 2015.

15. Barrett EG, Johnston C, Oberdorster G, Finkelstein JN. Silica-induced chemokine expression in alveolar type II cells is mediated by TNF-alpha-induced oxidant stress. *Am J Physiol* 276: L979-88, 1999.

16. Bartel J, Krumsiek J, Schramm K, Adamski J, Gieger C, Herder C, Carstensen M, Peters A, Rathmann W, Roden M, Strauch K, Suhre K, Kastenmuller G, Prokisch H, Theis FJ. The Human Blood Metabolome-Transcriptome Interface. *PLoS Genet* 11: e1005274, 2015.

17. Bell ML, Zanobetti A, Dominici F. Evidence on vulnerability and susceptibility to health risks associated with short-term exposure to particulate matter: a systematic review and meta-analysis. *Am J Epidemiol* 178: 865-76, 2013.

18. Benigni F, Fantuzzi G, Sacco S, Sironi M, Pozzi P, Dinarello CA, Sipe JD, Poli V, Cappelletti M, Paonessa G, Pennica D, Panayotatos N, Ghezzi P. Six different cytokines that share GP130 as a receptor subunit, induce serum amyloid A and potentiate the induction of interleukin-6 and the activation of the hypothalamus-pituitary-adrenal axis by interleukin-1. *Blood* 87: 1851-4, 1996.

19. Bertini R, Bianchi M, Ghezzi P. Adrenalectomy sensitizes mice to the lethal effects of interleukin 1 and tumor necrosis factor. *J Exp Med* 167: 1708-12, 1988.

20. Beutler B, Krochin N, Milsark IW, Luedke C, Cerami A. Control of cachectin (tumor necrosis factor) synthesis: mechanisms of endotoxin resistance. *Science* 232: 977-80, 1986.

21. Bielefeld EC. Reduction in impulse noise-induced permanent threshold shift with intracochlear application of an NADPH oxidase inhibitor. *J Am Acad Audiol* 24: 461-73, 2013.

22. Boehm JK, Williams DR, Rimm EB, Ryff C, Kubzansky LD. Association between optimism and serum antioxidants in the midlife in the United States study. *Psychosom Med* 75: 2-10, 2013.

23. Bohne BA, Harding GW, Lee SC. Death pathways in noise-damaged outer hair cells. *Hear Res* 223: 61-70, 2007.

24. Boraschi D, Duschl A. *Nanoparticles and the immune system: safety and effects*: Academic Press; 2013.

25. Boylan JM, Lewis TT, Coe CL, Ryff CD. Educational Status, Anger, and Inflammation in the MIDUS National Sample: Does Race Matter? *Ann Behav Med* 49: 570-8, 2015.

26. Brod S, Rattazzi L, Piras G, D'Acquisto F. 'As above, so below' examining the interplay between emotion and the immune system. *Immunology* 143: 311-8, 2014.

27. Bui DS, Burgess JA, Matheson MC, Erbas B, Perret J, Morrison S, Giles GG, Hopper JL, Thomas PS, Markos J, Abramson MJ, Walters EH, Dharmage SC. Ambient wood smoke, traffic pollution and adult asthma prevalence and severity. *Respirology* 18: 1101-7, 2013.

28. Burden N, Sewell F, Andersen ME, Boobis A, Chipman JK, Cronin MT, Hutchinson TH, Kimber I, Whelan M. Adverse Outcome Pathways can drive non-animal approaches for safety assessment. *J Appl Toxicol* 35: 971-5, 2015.

29. Celsus A. De Medicina. Loeb Classical Library (trans. WG Spencer). Cambridge, MA: Harvard University Press; 1935.

30. Checconi P, Salzano S, Bowler L, Mullen L, Mengozzi M, Hanschmann EM, Lillig CH, Sgarbanti R, Panella S, Nencioni L, Palamara AT, Ghezzi P. Redox proteomics of the inflammatory secretome identifies a common set of redoxins and other glutathionylated proteins released in inflammation, influenza virus infection and oxidative stress. *PLoS One* 10: e0127086, 2015.

31. Chimenti MS, Triggianese P, Conigliaro P, Candi E, Melino G, Perricone R. The interplay between inflammation and metabolism in rheumatoid arthritis. *Cell Death Dis* 6: e1887, 2015.

32. Chiurchiu V, Maccarrone M. Bioactive lipids as modulators of immunity, inflammation and emotions. *Curr Opin Pharmacol* 29: 54-62, 2016.

33. Choi CH, Chen K, Du X, Floyd RA, Kopke RD. Effects of delayed and extended antioxidant treatment on acute acoustic trauma. *Free Radic Res* 45: 1162-72, 2011.

34. Choi CH, Chen K, Vasquez-Weldon A, Jackson RL, Floyd RA, Kopke RD. Effectiveness of 4-hydroxy phenyl N-tert-butylnitrone (4-OHPBN) alone and in combination with other antioxidant drugs in the treatment of acute acoustic trauma in chinchilla. *Free Radic Biol Med* 44: 1772-84, 2008.

35. Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N Engl J Med* 332: 1351-62, 1995.

36. Chuang SC, Vermeulen R, Sharabiani MT, Sacerdote C, Fatemeh SH, Berrino F, Krogh V, Palli D, Panico S, Tumino R, Athersuch TJ, Vineis P. The intake of grain fibers modulates cytokine levels in blood. *Biomarkers* 16: 504-10, 2011.

37. Clougherty JE, Rossi CA, Lawrence J, Long MS, Diaz EA, Lim RH, McEwen B, Koutrakis P, Godleski JJ. Chronic social stress and susceptibility to concentrated ambient fine particles in rats. *Environ Health Perspect* 118: 769-75, 2010.

38. Cole SW. Social regulation of leukocyte homeostasis: the role of glucocorticoid sensitivity. *Brain Behav Immun* 22: 1049-55, 2008.

39. Cosselman KE, Navas-Acien A, Kaufman JD. Environmental factors in cardiovascular disease. *Nat Rev Cardiol* 12: 627-42, 2015.

40. Cuadrado A. Structural and functional characterization of Nrf2 degradation by glycogen synthase kinase 3/beta-TrCP. *Free Radic Biol Med* 88: 147-57, 2015.

41. Cuadrado A, Martin-Moldes Z, Ye J, Lastres-Becker I. Transcription factors NRF2 and NF-kappaB are coordinated effectors of the Rho family, GTP-binding protein RAC1 during inflammation. *J Biol Chem* 289: 15244-58, 2014.

42. D'Acquisto F. Editorial overview: Immunomodulation: Exploiting the circle between emotions and immunity: impact on pharmacological treatments. *Curr Opin Pharmacol* 29: viii-xii, 2016.

43. D'Acquisto F, Rattazzi L, Piras G. Smile--It's in your blood! *Biochem Pharmacol* 91: 287-92, 2014.

44. Daiber A, Steven S, Weber A, Shuvaev VV, Muzykantov VR, Laher I, Li H, Lamas S, Munzel T. Targeting vascular (endothelial) dysfunction. *Br J Pharmacol*, 2016.

45. Danielsson A, Landstrom U. Blood pressure changes in man during infrasonic exposure. An experimental study. *Acta Med Scand* 217: 531-5, 1985.

46. Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. *Brain Behav Immun* 21: 153-60, 2007.

47. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci* 9: 46-56, 2008.

48. Deng X, Rui W, Zhang F, Ding W. PM2.5 induces Nrf2-mediated defense mechanisms against oxidative stress by activating PIK3/AKT signaling pathway in human lung alveolar epithelial A549 cells. *Cell Biol Toxicol* 29: 143-57, 2013.

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

49. Djordjevic A, Adzic M, Djordjevic J, Radojcic MB. Chronic social isolation suppresses proplastic response and promotes proapoptotic signalling in prefrontal cortex of Wistar rats. *J Neurosci Res* 88: 2524-33, 2010.

50. Dostert C, Petrilli V, Van Bruggen R, Steele C, Mossman BT, Tschopp J. Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica. *Science* 320: 674-7, 2008.

51. Du X, Choi CH, Chen K, Cheng W, Floyd RA, Kopke RD. Reduced formation of oxidative stress biomarkers and migration of mononuclear phagocytes in the cochleae of chinchilla after antioxidant treatment in acute acoustic trauma. *Int J Otolaryngol* 2011: 612690, 2011.

52. Duewell P, Kono H, Rayner KJ, Sirois CM, Vladimer G, Bauernfeind FG, Abela GS, Franchi L, Nunez G, Schnurr M, Espevik T, Lien E, Fitzgerald KA, Rock KL, Moore KJ, Wright SD, Hornung V, Latz E. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. *Nature* 464: 1357-61, 2010.

53. Estevez-Garcia JA, Rojas-Roa NY, Rodriguez-Pulido AI. Occupational exposure to air pollutants: particulate matter and respiratory symptoms affecting traffic-police in Bogota. *Rev Salud Publica (Bogota)* 15: 889-902, 2013.

54. Fetoni AR, Paciello F, Rolesi R, Eramo SL, Mancuso C, Troiani D, Paludetti G. Rosmarinic acid up-regulates the noise-activated Nrf2/HO-1 pathway and protects against noise-induced injury in rat cochlea. *Free Radic Biol Med* 85: 269-81, 2015.

55. Floridi L. A proxy culture. *Philosophy & Technology* 28: 487-490, 2015.

56. Fratiglioni L, Wang HX, Ericsson K, Maytan M, Winblad B. Influence of social network on occurrence of dementia: a community-based longitudinal study. *Lancet* 355: 1315-9, 2000.

57. Frijhoff J, Winyard PG, Zarkovic N, Davies SS, Stocker R, Cheng D, Knight AR, Taylor EL, Oettrich J, Ruskovska T, Gasparovic AC, Cuadrado A, Weber D, Poulsen HE, Grune T, Schmidt HH, Ghezzi P. Clinical Relevance of Biomarkers of Oxidative Stress.

Antioxid Redox Signal 23: 1144-70, 2015.

58. Fujioka M, Kanzaki S, Okano HJ, Masuda M, Ogawa K, Okano H. Proinflammatory cytokines expression in noise-induced damaged cochlea. *J Neurosci Res* 83: 575-83, 2006.

59. Ghezzi P, Jaquet V, Marcucci F, Schmidt HH. The oxidative stress theory of disease: levels of evidence and epistemological aspects. *Br J Pharmacol*, 2016.

60. Giangrego E. Laughing fits. Laugh your way to good health. *CDS Rev* 97: 22-4, 2004.

61. Halle A, Hornung V, Petzold GC, Stewart CR, Monks BG, Reinheckel T, Fitzgerald KA, Latz E, Moore KJ, Golenbock DT. The NALP3 inflammasome is involved in the innate immune response to amyloid-beta. *Nat Immunol* 9: 857-65, 2008.

62. Hamilton RF, Wu N, Xiang C, Li M, Yang F, Wolfarth M, Porter DW, Holian A. Synthesis, characterization, and bioactivity of carboxylic acid-functionalized titanium dioxide nanobelts. *Part Fibre Toxicol* 11: 43, 2014.

63. Harijith A, Ebenezer DL, Natarajan V. Reactive oxygen species at the crossroads of inflammasome and inflammation. *Front Physiol* 5: 352, 2014.

64. Harman D. Aging: a theory based on free radical and radiation chemistry. *J Gerontol* 11: 298-300, 1956.

65. Hawkins JE. Sketches of otohistory. Part 1: otoprehistory: how it all began. *Audiol Neurootol* 9: 66-71, 2004.

66. Hayashi T, Tsujii S, Iburi T, Tamanaha T, Yamagami K, Ishibashi R, Hori M, Sakamoto S, Ishii H, Murakami K. Laughter up-regulates the genes related to NK cell activity in diabetes. *Biomed Res* 28: 281-5, 2007.

67. Hayes JD, Dinkova-Kostova AT. The Nrf2 regulatory network provides an interface between redox and intermediary metabolism. *Trends Biochem Sci* 39: 199-218, 2014.

68. Hebels DG, Georgiadis P, Keun HC, Athersuch TJ, Vineis P, Vermeulen R, Portengen L,

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Bergdahl IA, Hallmans G, Palli D, Bendinelli B, Krogh V, Tumino R, Sacerdote C, Panico S, Kleinjans JC, de Kok TM, Smith MT, Kyrtopoulos SA, EnviroGenomarkers Project C. Performance in omics analyses of blood samples in long-term storage: opportunities for the exploitation of existing biobanks in environmental health research. *Environ Health Perspect* 121: 480-7, 2013.

69. Hegde SV, Adhikari P, Kotian S, Pinto VJ, D'Souza S, D'Souza V. Effect of 3-month yoga on oxidative stress in type 2 diabetes with or without complications: a controlled clinical trial. *Diabetes Care* 34: 2208-10, 2011.

70. Henderson D, Bielefeld EC, Harris KC, Hu BH. The role of oxidative stress in noise-induced hearing loss. *Ear Hear* 27: 1-19, 2006.

71. Hirose K, Liberman MC. Lateral wall histopathology and endocochlear potential in the noise-damaged mouse cochlea. *J Assoc Res Otolaryngol* 4: 339-52, 2003.

72. Hogestatt ED, Jonsson BA, Ermund A, Andersson DA, Bjork H, Alexander JP, Cravatt BF, Basbaum AI, Zygmunt PM. Conversion of acetaminophen to the bioactive N-acylphenolamine AM404 via fatty acid amide hydrolase-dependent arachidonic acid conjugation in the nervous system. *J Biol Chem* 280: 31405-12, 2005.

73. Honkura Y, Matsuo H, Murakami S, Sakiyama M, Mizutari K, Shiotani A, Yamamoto M, Morita I, Shinomiya N, Kawase T, Katori Y, Motohashi H. NRF2 Is a Key Target for Prevention of Noise-Induced Hearing Loss by Reducing Oxidative Damage of Cochlea. *Sci Rep* 6: 19329, 2016.

74. Hornung V, Bauernfeind F, Halle A, Samstad EO, Kono H, Rock KL, Fitzgerald KA, Latz E. Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization. *Nat Immunol* 9: 847-56, 2008.

75. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med* 71: 171-86, 2009.

76. Hu BH, Henderson D, Nicotera TM. Involvement of apoptosis in progression of cochlear lesion following exposure to intense noise. *Hear Res* 166: 62-71, 2002.

77. Huang YC, Karoly ED, Dailey LA, Schmitt MT, Silbajoris R, Graff DW, Devlin RB. Comparison of gene expression profiles induced by coarse, fine, and ultrafine particulate matter. *J Toxicol Environ Health A* 74: 296-312, 2011.

78. Innamorato NG, Rojo AI, Garcia-Yague AJ, Yamamoto M, de Ceballos ML, Cuadrado A. The transcription factor Nrf2 is a therapeutic target against brain inflammation. *J Immunol* 181: 680-9, 2008.

79. Jardim MJ, Fry RC, Jaspers I, Dailey L, Diaz-Sanchez D. Disruption of microRNA expression in human airway cells by diesel exhaust particles is linked to tumorigenesis-associated pathways. *Environ Health Perspect* 117: 1745-51, 2009.

80. Jayakumar S, Pal D, Sandur SK. Nrf2 facilitates repair of radiation induced DNA damage through homologous recombination repair pathway in a ROS independent manner in cancer cells. *Mutat Res* 779: 33-45, 2015.

81. Ji Z, Wang X, Zhang H, Lin S, Meng H, Sun B, George S, Xia T, Nel AE, Zink JI. Designed synthesis of CeO2 nanorods and nanowires for studying toxicological effects of high aspect ratio nanomaterials. *ACS Nano* 6: 5366-80, 2012.

82. Jin C, Flavell RA. Molecular mechanism of NLRP3 inflammasome activation. *J Clin Immunol* 30: 628-31, 2010.

83. Jin C, Frayssinet P, Pelker R, Cwirka D, Hu B, Vignery A, Eisenbarth SC, Flavell RA. NLRP3 inflammasome plays a critical role in the pathogenesis of hydroxyapatite-associated arthropathy. *Proc Natl Acad Sci U S A* 108: 14867-72, 2011.

84. Karagulian F, Belis CA, Dora CFC, Prüss-Ustün AM, Bonjour S, Adair-Rohani H, Amann M. Contributions to cities' ambient particulate matter (PM): A systematic review of local source contributions at global level. *Atmospheric Environment* 120: 475-483, 2015.

85. Kehrer JP. The Haber-Weiss reaction and mechanisms of toxicity. *Toxicology* 149: 43-50, 2000.

86. Keithley EM, Wang X, Barkdull GC. Tumor necrosis factor alpha can induce

recruitment of inflammatory cells to the cochlea. *Otol Neurotol* 29: 854-9, 2008.

87. Kelly FJ. Oxidative stress: its role in air pollution and adverse health effects. *Occup Environ Med* 60: 612-6, 2003.

88. Kim YK, Paik JW, Lee SW, Yoon D, Han C, Lee BH. Increased plasma nitric oxide level associated with suicide attempt in depressive patients. *Prog Neuropsychopharmacol Biol Psychiatry* 30: 1091-6, 2006.

89. Kitayama S, Park J, Boylan JM, Miyamoto Y, Levine CS, Markus HR, Karasawa M, Coe CL, Kawakami N, Love GD, Ryff CD. Expression of anger and ill health in two cultures: an examination of inflammation and cardiovascular risk. *Psychol Sci* 26: 211-20, 2015.

90. Kobayashi EH, Suzuki T, Funayama R, Nagashima T, Hayashi M, Sekine H, Tanaka N, Moriguchi T, Motohashi H, Nakayama K, Yamamoto M. Nrf2 suppresses macrophage inflammatory response by blocking proinflammatory cytokine transcription. *Nat Commun* 7: 11624, 2016.

91. Koike E, Hirano S, Shimojo N, Kobayashi T. cDNA microarray analysis of gene expression in rat alveolar macrophages in response to organic extract of diesel exhaust particles. *Toxicol Sci* 67: 241-6, 2002.

92. Kopke R, Coleman J, Liu J, Jackson R, Van De Water T. Mechanism of noise-induced hearing loss and otoprotective strategies. *Otolaryngology, Basic science and clinical review. 1st ed. New York: Thieme Medical Publishers*: 395-408, 2006.

93. Krishnan RM, Sullivan JH, Carlsten C, Wilkerson HW, Beyer RP, Bammler T, Farin F, Peretz A, Kaufman JD. A randomized cross-over study of inhalation of diesel exhaust, hematological indices, and endothelial markers in humans. *Part Fibre Toxicol* 10: 7, 2013.

94. Kujawa SG, Liberman MC. Acceleration of age-related hearing loss by early noise exposure: evidence of a misspent youth. *J Neurosci* 26: 2115-23, 2006.

95. Kujawa SG, Liberman MC. Adding insult to injury: cochlear nerve degeneration after

"temporary" noise-induced hearing loss. *J Neurosci* 29: 14077-85, 2009.

96. Lapchak PA. A critical assessment of edaravone acute ischemic stroke efficacy trials: is edaravone an effective neuroprotective therapy? *Expert Opin Pharmacother* 11: 1753-63, 2010.

97. Lasselin J, Alvarez-Salas E, Grigoleit JS. Well-being and immune response: a multi-system perspective. *Curr Opin Pharmacol* 29: 34-41, 2016.

98. Lavinsky J, Crow AL, Pan C, Wang J, Aaron KA, Ho MK, Li Q, Salehide P, Myint A, Monges-Hernadez M, Eskin E, Allayee H, Lusis AJ, Friedman RA. Genome-wide association study identifies nox3 as a critical gene for susceptibility to noise-induced hearing loss. *PLoS Genet* 11: e1005094, 2015.

99. Lawal AO. Air particulate matter induced oxidative stress and inflammation in cardiovascular disease and atherosclerosis: The role of Nrf2 and AhR-mediated pathways. *Toxicol Lett* 270: 88-95, 2017.

100. Le Prell CG, Yamashita D, Minami SB, Yamasoba T, Miller JM. Mechanisms of noise-induced hearing loss indicate multiple methods of prevention. *Hear Res* 226: 22-43, 2007.

101. Lee BH, Lee SW, Yoon D, Lee HJ, Yang JC, Shim SH, Kim DH, Ryu SH, Han C, Kim YK. Increased plasma nitric oxide metabolites in suicide attempters. *Neuropsychobiology* 53: 127-32, 2006.

102. Lee DS, Park J, Kay KA, Christakis NA, Oltvai ZN, Barabasi AL. The implications of human metabolic network topology for disease comorbidity. *Proc Natl Acad Sci U S A* 105: 9880-5, 2008.

103. Leroueil PR, Hong S, Mecke A, Baker JR, Jr., Orr BG, Banaszak Holl MM. Nanoparticle interaction with biological membranes: does nanotechnology present a Janus face? *Acc Chem Res* 40: 335-42, 2007.

104. Li N, Nel AE. Role of the Nrf2-mediated signaling pathway as a negative regulator of inflammation: implications for the impact of particulate pollutants on asthma.

Antioxid Redox Signal 8: 88-98, 2006.

105. Li N, Xia T, Nel AE. The role of oxidative stress in ambient particulate matter-induced lung diseases and its implications in the toxicity of engineered nanoparticles. *Free Radic Biol Med* 44: 1689-99, 2008.

106. Li Y, Boraschi D. Endotoxin contamination: a key element in the interpretation of nanosafety studies. *Nanomedicine (Lond)* 11: 269-87, 2016.

107. Lichtman JH, Froelicher ES, Blumenthal JA, Carney RM, Doering LV, Frasure-Smith N, Freedland KE, Jaffe AS, Leifheit-Limson EC, Sheps DS, Vaccarino V, Wulsin L, American Heart Association Statistics Committee of the Council on E, Prevention, the Council on C, Stroke N. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from the American Heart Association. *Circulation* 129: 1350-69, 2014.

108. Liu J, Litt L, Segal MR, Kelly MJ, Pelton JG, Kim M. Metabolomics of oxidative stress in recent studies of endogenous and exogenously administered intermediate metabolites. *Int J Mol Sci* 12: 6469-501, 2011.

109. Loo RL, Chan Q, Brown IJ, Robertson CE, Stamler J, Nicholson JK, Holmes E, Elliott P, Group IR. A comparison of self-reported analgesic use and detection of urinary ibuprofen and acetaminophen metabolites by means of metabonomics: the INTERMAP Study. *Am J Epidemiol* 175: 348-58, 2012.

110. Loo RL, Coen M, Ebbels T, Cloarec O, Maibaum E, Bictash M, Yap I, Elliott P, Stamler J, Nicholson JK, Holmes E, Group IR. Metabolic profiling and population screening of analgesic usage in nuclear magnetic resonance spectroscopy-based large-scale epidemiologic studies. *Anal Chem* 81: 5119-29, 2009.

111. Luo H, Hu X, Liu X, Ma X, Guo W, Qiu C, Wang Y, Wang Q, Zhang X, Zhang W, Hannum G, Zhang K, Liu X, Li T. Hair cortisol level as a biomarker for altered hypothalamic-pituitary-adrenal activity in female adolescents with posttraumatic stress disorder after the 2008 Wenchuan earthquake. *Biol Psychiatry* 72: 65-9,

2012.

112. Ma Q. Role of nrf2 in oxidative stress and toxicity. *Annu Rev Pharmacol Toxicol* 53: 401-26, 2013.

113. Major B, Rattazzi L, Brod S, Pilipovic I, Leposavic G, D'Acquisto F. Massage-like stroking boosts the immune system in mice. *Sci Rep* 5: 10913, 2015.

114. Martin-de-Saavedra MD, Budni J, Cunha MP, Gomez-Rangel V, Lorrio S, Del Barrio L, Lastres-Becker I, Parada E, Tordera RM, Rodrigues AL, Cuadrado A, Lopez MG. Nrf2 participates in depressive disorders through an anti-inflammatory mechanism. *Psychoneuroendocrinology* 38: 2010-22, 2013.

115. Martinon F, Petrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature* 440: 237-41, 2006.

116. Mayeux R. Biomarkers: potential uses and limitations. *NeuroRx* 1: 182-188, 2004.

117. Meyer JS, Novak MA. Minireview: Hair cortisol: a novel biomarker of hypothalamic-pituitary-adrenocortical activity. *Endocrinology* 153: 4120-7, 2012.

118. Miller GW, Jones DP. The nature of nurture: refining the definition of the exposome. *Toxicol Sci* 137: 1-2, 2014.

119. Miller J, Watson CS, Covell WP. Deafencing Effects of Noise on the Cat. *Journal of Occupational and Environmental Medicine* 5: 555, 1963.

120. Mirault T, Launay D, Cuisset L, Hachulla E, Lambert M, Queyrel V, Quemeneur T, Morell-Dubois S, Hatron PY. Recovery from deafness in a patient with Muckle-Wells syndrome treated with anakinra. *Arthritis Rheum* 54: 1697-700, 2006.

121. Moller P, Christophersen DV, Jensen DM, Kermanizadeh A, Roursgaard M, Jacobsen NR, Hemmingsen JG, Danielsen PH, Cao Y, Jantzen K, Klingberg H, Hersoug LG, Loft S. Role of oxidative stress in carbon nanotube-generated health effects. *Arch Toxicol* 88: 1939-64, 2014.

122. Mullen L, Seavill M, Hammouz R, Bottazzi B, Chan P, Vaudry D, Ghezzi P.

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Development of 'Redox Arrays' for identifying novel glutathionylated proteins in the secretome. *Sci Rep* 5: 14630, 2015.

123. Munzel T, Knorr M, Schmidt F, von Bardeleben S, Gori T, Schulz E. Airborne disease: a case of a Takotsubo cardiomyopathie as a consequence of nighttime aircraft noise exposure. *Eur Heart J* 37: 2844, 2016.

124. Myers CR. The effects of chromium(VI) on the thioredoxin system: implications for redox regulation. *Free Radic Biol Med* 52: 2091-107, 2012.

125. Nathan C. Neutrophils and immunity: challenges and opportunities. *Nat Rev Immunol* 6: 173-82, 2006.

126. Nel A, Xia T, Madler L, Li N. Toxic potential of materials at the nanolevel. *Science* 311: 622-7, 2006.

127. Neophytou AM, Hart JE, Cavallari JM, Smith TJ, Dockery DW, Coull BA, Garshick E, Laden F. Traffic-related exposures and biomarkers of systemic inflammation, endothelial activation and oxidative stress: a panel study in the US trucking industry. *Environ Health* 12: 105, 2013.

128. Ng G, Sharma K, Ward SM, Desrosiers MD, Stephens LA, Schoel WM, Li T, Lowell CA, Ling CC, Amrein MW, Shi Y. Receptor-independent, direct membrane binding leads to cell-surface lipid sorting and Syk kinase activation in dendritic cells. *Immunity* 29: 807-18, 2008.

129. Nicotera TM, Hu BH, Henderson D. The caspase pathway in noise-induced apoptosis of the chinchilla cochlea. *J Assoc Res Otolaryngol* 4: 466-77, 2003.

130. Oeder S, Kanashova T, Sippula O, Sapcariu SC, Streibel T, Arteaga-Salas JM, Passig J, Dilger M, Paur HR, Schlager C, Mulhopt S, Diabate S, Weiss C, Stengel B, Rabe R, Harndorf H, Torvela T, Jokiniemi JK, Hirvonen MR, Schmidt-Weber C, Traidl-Hoffmann C, BeruBe KA, Wlodarczyk AJ, Prytherch Z, Michalke B, Krebs T, Prevot AS, Kelbg M, Tiggesbaumker J, Karg E, Jakobi G, Scholtes S, Schnelle-Kreis J, Lintelmann J, Matuschek G, Sklorz M, Klingbeil S, Orasche J, Richthammer P, Muller L, Elsasser

M, Reda A, Groger T, Weggler B, Schwemer T, Czech H, Ruger CP, Abbaszade G, Radischat C, Hiller K, Buters JT, Dittmar G, Zimmermann R. Particulate matter from both heavy fuel oil and diesel fuel shipping emissions show strong biological effects on human lung cells at realistic and comparable in vitro exposure conditions. *PLoS One* 10: e0126536, 2015.

131. Ovrevik J, Refsnes M, Lag M, Holme JA, Schwarze PE. Activation of Proinflammatory Responses in Cells of the Airway Mucosa by Particulate Matter: Oxidant- and Non-Oxidant-Mediated Triggering Mechanisms. *Biomolecules* 5: 1399-440, 2015.

132. Palomaki J, Valimaki E, Sund J, Vippola M, Clausen PA, Jensen KA, Savolainen K, Matikainen S, Alenius H. Long, needle-like carbon nanotubes and asbestos activate the NLRP3 inflammasome through a similar mechanism. *ACS Nano* 5: 6861-70, 2011.

133. Pavlov VA, Tracey KJ. The vagus nerve and the inflammatory reflex--linking immunity and metabolism. *Nat Rev Endocrinol* 8: 743-54, 2012.

134. Peretz A, Peck EC, Bammler TK, Beyer RP, Sullivan JH, Trenga CA, Srinouanprachnah S, Farin FM, Kaufman JD. Diesel exhaust inhalation and assessment of peripheral blood mononuclear cell gene transcription effects: an exploratory study of healthy human volunteers. *Inhal Toxicol* 19: 1107-19, 2007.

135. Perrone MG, Zhou J, Malandrino M, Sangiorgi G, Rizzi C, Ferrero L, Dommen J, Bolzacchini E. PM chemical composition and oxidative potential of the soluble fraction of particles at two sites in the urban area of Milan, Northern Italy. *Atmospheric Environment* 128: 104-113, 2016.

136. Pesce M, Fratta IL, Ialenti V, Patruno A, Ferrone A, Franceschelli S, Rizzuto A, Tatangelo R, Campagna G, Speranza L, Felaco M, Grilli A. Emotions, immunity and sport: Winner and loser athlete's profile of fighting sport. *Brain Behav Immun* 46: 261-9, 2015.

137. Petersen EJ, Nelson BC. Mechanisms and measurements of nanomaterial-induced oxidative damage to DNA. *Anal Bioanal Chem* 398: 613-50, 2010.

138. Piras G, Rattazzi L, McDermott A, Deacon R, D'Acquisto F. Emotional change-associated T cell mobilization at the early stage of a mouse model of multiple sclerosis. *Front Immunol* 4: 400, 2013.

139. Pitha-Rowe I, Liby K, Royce D, Sporn M. Synthetic triterpenoids attenuate cytotoxic retinal injury: cross-talk between Nrf2 and PI3K/AKT signaling through inhibition of the lipid phosphatase PTEN. *Invest Ophthalmol Vis Sci* 50: 5339-47, 2009.

140. Plata-Salaman CR. Dexamethasone inhibits food intake suppression induced by low doses of interleukin-1 beta administered intracerebroventricularly. *Brain Res Bull* 27: 737-8, 1991.

141. Rada P, Rojo AI, Chowdhry S, McMahon M, Hayes JD, Cuadrado A. SCF/{beta}-TrCP promotes glycogen synthase kinase 3-dependent degradation of the Nrf2 transcription factor in a Keap1-independent manner. *Mol Cell Biol* 31: 1121-33, 2011.

142. Rada P, Rojo AI, Evrard-Todeschi N, Innamorato NG, Cotte A, Jaworski T, Tobon-Velasco JC, Devijver H, Garcia-Mayoral MF, Van Leuven F, Hayes JD, Bertho G, Cuadrado A. Structural and functional characterization of Nrf2 degradation by the glycogen synthase kinase 3/beta-TrCP axis. *Mol Cell Biol* 32: 3486-99, 2012.

143. Rajamaki K, Lappalainen J, Oorni K, Valimaki E, Matikainen S, Kovanen PT, Eklund KK. Cholesterol crystals activate the NLRP3 inflammasome in human macrophages: a novel link between cholesterol metabolism and inflammation. *PLoS One* 5: e11765, 2010.

144. Rappaport SM. Genetic Factors Are Not the Major Causes of Chronic Diseases. *PLoS One* 11: e0154387, 2016.

145. Rather LJ. Disturbance of function (functio laesa): the legendary fifth cardinal sign of inflammation, added by Galen to the four cardinal signs of Celsus. *Bull N Y Acad Med* 47: 303-22, 1971.

146. Rattazzi L, Piras G, Ono M, Deacon R, Pariante CM, D'Acquisto F. CD4(+) but not

CD8(+) T cells revert the impaired emotional behavior of immunocompromised RAG-1-deficient mice. *Transl Psychiatry* 3: e280, 2013.

147. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: how are they linked? *Free Radic Biol Med* 49: 1603-16, 2010.

148. Riteau N, Baron L, Villeret B, Guillou N, Savigny F, Ryffel B, Rassendren F, Le Bert M, Gombault A, Couillin I. ATP release and purinergic signaling: a common pathway for particle-mediated inflammasome activation. *Cell Death Dis* 3: e403, 2012.

149. Rojo AI, Rada P, Mendiola M, Ortega-Molina A, Wojdyla K, Rogowska-Wrzesinska A, Hardisson D, Serrano M, Cuadrado A. The PTEN/NRF2 axis promotes human carcinogenesis. *Antioxid Redox Signal* 21: 2498-514, 2014.

150. Rousset F, Carnesecchi S, Senn P, Krause KH. Nox3-Targeted Therapies for Inner Ear Pathologies. *Curr Pharm Des* 21: 5977-87, 2015.

151. Salim S, Sarraj N, Taneja M, Saha K, Tejada-Simon MV, Chugh G. Moderate treadmill exercise prevents oxidative stress-induced anxiety-like behavior in rats. *Behav Brain Res* 208: 545-52, 2010.

152. Salvi S, Blomberg A, Rudell B, Kelly F, Sandstrom T, Holgate ST, Frew A. Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers. *Am J Respir Crit Care Med* 159: 702-9, 1999.

153. Sato H, Takahashi T, Sumitani K, Takatsu H, Urano S. Glucocorticoid Generates ROS to Induce Oxidative Injury in the Hippocampus, Leading to Impairment of Cognitive Function of Rats. *J Clin Biochem Nutr* 47: 224-32, 2010.

154. Schmidt HH, Stocker R, Vollbracht C, Paulsen G, Riley D, Daiber A, Cuadrado A. Antioxidants in Translational Medicine. *Antioxid Redox Signal* 23: 1130-43, 2015.

155. Schneider RH, Grim CE, Rainforth MV, Kotchen T, Nidich SI, Gaylord-King C, Salerno JW, Kotchen JM, Alexander CN. Stress reduction in the secondary prevention of cardiovascular disease: randomized, controlled trial of transcendental meditation

and health education in Blacks. *Circ Cardiovasc Qual Outcomes* 5: 750-8, 2012.

156. Schreck R, Rieber P, Baeuerle PA. Reactive oxygen intermediates as apparently widely used messengers in the activation of the NF-kappa B transcription factor and HIV-1. *Embo J* 10: 2247-58, 1991.

157. Schuch FB, Vasconcelos-Moreno MP, Borowsky C, Zimmermann AB, Wollenhaupt-Aguiar B, Ferrari P, de Almeida Fleck MP. The effects of exercise on oxidative stress (TBARS) and BDNF in severely depressed inpatients. *Eur Arch Psychiatry Clin Neurosci* 264: 605-13, 2014.

158. Sekhar KR, Freeman ML. Nrf2 promotes survival following exposure to ionizing radiation. *Free Radic Biol Med* 88: 268-74, 2015.

159. Sharp FA, Ruane D, Claass B, Creagh E, Harris J, Malyala P, Singh M, O'Hagan DT, Petrilli V, Tschopp J, O'Neill LA, Lavelle EC. Uptake of particulate vaccine adjuvants by dendritic cells activates the NALP3 inflammasome. *Proc Natl Acad Sci U S A* 106: 870-5, 2009.

160. Shi X, Dai C, Nuttall AL. Altered expression of inducible nitric oxide synthase (iNOS) in the cochlea. *Hear Res* 177: 43-52, 2003.

161. Shi X, Nuttall AL. Expression of adhesion molecular proteins in the cochlear lateral wall of normal and PARP-1 mutant mice. *Hear Res* 224: 1-14, 2007.

162. Shibata T, Ohta T, Tong KI, Kokubu A, Odogawa R, Tsuta K, Asamura H, Yamamoto M, Hirohashi S. Cancer related mutations in NRF2 impair its recognition by Keap1-Cul3 E3 ligase and promote malignancy. *Proc Natl Acad Sci U S A* 105: 13568-73, 2008.

163. Shin SY, Fauman EB, Petersen AK, Krumsiek J, Santos R, Huang J, Arnold M, Erte I, Forgetta V, Yang TP, Walter K, Menni C, Chen L, Vasquez L, Valdes AM, Hyde CL, Wang V, Ziemek D, Roberts P, Xi L, Grundberg E, Multiple Tissue Human Expression Resource C, Waldenberger M, Richards JB, Mohney RP, Milburn MV, John SL, Trimmer J, Theis FJ, Overington JP, Suhre K, Brosnan MJ, Gieger C, Kastenmuller G, Spector TD, Soranzo N. An atlas of genetic influences on human blood metabolites.

Nat Genet 46: 543-50, 2014.

164. Sies H. Oxidative stress: a concept in redox biology and medicine. *Redox Biol* 4: 180-3, 2015.

165. Simmons SO, Fan CY, Yeoman K, Wakefield J, Ramabhadran R. NRF2 Oxidative Stress Induced by Heavy Metals is Cell Type Dependent. *Curr Chem Genomics* 5: 1-12, 2011.

166. Smith DI, Lawrence M, Hawkins JE, Jr. Effects of noise and quinine on the vessels of the stria vascularis: an image analysis study. *Am J Otolaryngol* 6: 280-9, 1985.

167. Spiers JG, Chen HJ, Sernia C, Lavidis NA. Activation of the hypothalamic-pituitary-adrenal stress axis induces cellular oxidative stress. *Front Neurosci* 8: 456, 2014.

168. Spoendlin H. Primary structural changes in the organ of Corti after acoustic overstimulation. *Acta Otolaryngol* 71: 166-76, 1971.

169. Sturmberg JP, Bennett JM, Martin CM, Picard M. 'Multimorbidity' as the manifestation of network disturbances. *J Eval Clin Pract*, 2016.

170. Sultana R, Perluigi M, Allan Butterfield D. Lipid peroxidation triggers neurodegeneration: a redox proteomics view into the Alzheimer disease brain. *Free Radic Biol Med* 62: 157-69, 2013.

171. Sun B, Wang X, Ji Z, Li R, Xia T. NLRP3 inflammasome activation induced by engineered nanomaterials. *Small* 9: 1595-1607, 2013.

172. Sun Q, Scott MJ. Caspase-1 as a multifunctional inflammatory mediator: noncytokine maturation roles. *J Leukoc Biol* 100: 961-967, 2016.

173. Tan WJ, Thorne PR, Vlajkovic SM. WJO. 2013.

174. Tornabene SV, Sato K, Pham L, Billings P, Keithley EM. Immune cell recruitment following acoustic trauma. *Hear Res* 222: 115-24, 2006.

175. Tornqvist H, Mills NL, Gonzalez M, Miller MR, Robinson SD, Megson IL, Macnee W,

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Donaldson K, Soderberg S, Newby DE, Sandstrom T, Blomberg A. Persistent endothelial dysfunction in humans after diesel exhaust inhalation. *Am J Respir Crit Care Med* 176: 395-400, 2007.

176. Tracey KJ. Physiology and immunology of the cholinergic antiinflammatory pathway. *J Clin Invest* 117: 289-96, 2007.

177. Tracey KJ. Reflex control of immunity. *Nat Rev Immunol* 9: 418-28, 2009.

178. Tuglu C, Kara SH, Caliyurt O, Vardar E, Abay E. Increased serum tumor necrosis factor-alpha levels and treatment response in major depressive disorder. *Psychopharmacology (Berl)* 170: 429-33, 2003.

179. Turnbull AV, Rivier CL. Regulation of the hypothalamic-pituitary-adrenal axis by cytokines: actions and mechanisms of action. *Physiol Rev* 79: 1-71, 1999.

180. Vallhov H, Qin J, Johansson SM, Ahlborg N, Muhammed MA, Scheynius A, Gabrielsson S. The importance of an endotoxin-free environment during the production of nanoparticles used in medical applications. *Nano Lett* 6: 1682-6, 2006.

181. Vambutas A, Lesser M, Mullooly V, Pathak S, Zahtz G, Rosen L, Goldofsky E. Early efficacy trial of anakinra in corticosteroid-resistant autoimmune inner ear disease. *J Clin Invest* 124: 4115-22, 2014.

182. Vineis P, Chadeau-Hyam M, Gmuender H, Gulliver J, Herceg Z, Kleinjans J, Kogevinas M, Kyrtopoulos S, Nieuwenhuijsen M, Phillips DH, Probst-Hensch N, Scalbert A, Vermeulen R, Wild CP, Consortium EX. The exposome in practice: Design of the EXPOsOMICS project. *Int J Hyg Environ Health*, 2016.

183. Vlasova, II, Kapralov AA, Michael ZP, Burkert SC, Shurin MR, Star A, Shvedova AA, Kagan VE. Enzymatic oxidative biodegradation of nanoparticles: Mechanisms, significance and applications. *Toxicol Appl Pharmacol* 299: 58-69, 2016.

184. Vogelzangs N, Beekman AT, de Jonge P, Penninx BW. Anxiety disorders and inflammation in a large adult cohort. *Transl Psychiatry* 3: e249, 2013.

185. Vrijheid M, Slama R, Robinson O, Chatzi L, Coen M, van den Hazel P, Thomsen C, Wright J, Athersuch TJ, Avellana N, Basagana X, Brochot C, Bucchini L, Bustamante M, Carracedo A, Casas M, Estivill X, Fairley L, van Gent D, Gonzalez JR, Granum B, Grazuleviciene R, Gutzkow KB, Julvez J, Keun HC, Kogevinas M, McEachan RR, Meltzer HM, Sabido E, Schwarze PE, Siroux V, Sunyer J, Want EJ, Zeman F, Nieuwenhuijsen MJ. The human early-life exposome (HELIX): project rationale and design. *Environ Health Perspect* 122: 535-44, 2014.

186. Wakabayashi K, Fujioka M, Kanzaki S, Okano HJ, Shibata S, Yamashita D, Masuda M, Mihara M, Ohsugi Y, Ogawa K, Okano H. Blockade of interleukin-6 signaling suppressed cochlear inflammatory response and improved hearing impairment in noise-damaged mice cochlea. *Neurosci Res* 66: 345-52, 2010.

187. Wallach D, Kang TB, Dillon CP, Green DR. Programmed necrosis in inflammation: Toward identification of the effector molecules. *Science* 352: aaf2154, 2016.

188. Wang J, Ruel J, Ladrech S, Bonny C, van de Water TR, Puel JL. Inhibition of the c-Jun N-terminal kinase-mediated mitochondrial cell death pathway restores auditory function in sound-exposed animals. *Mol Pharmacol* 71: 654-66, 2007.

189. Waye KP, Bengtsson J, Rylander R, Hucklebridge F, Evans P, Clow A. Low frequency noise enhances cortisol among noise sensitive subjects during work performance. *Life Sci* 70: 745-58, 2002.

190. Wenzel P, Kossmann S, Munzel T, Daiber A. Redox regulation of cardiovascular inflammation - Immunomodulatory function of mitochondrial and Nox-derived reactive oxygen and nitrogen species. *Free Radic Biol Med*, 2017.

191. Wild CP. Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. *Cancer Epidemiol Biomarkers Prev* 14: 1847-50, 2005.

192. Wild CP. The exposome: from concept to utility. *Int J Epidemiol* 41: 24-32, 2012.

193. Wild CP, Scalbert A, Herceg Z. Measuring the exposome: a powerful basis for

evaluating environmental exposures and cancer risk. *Environ Mol Mutagen* 54: 480-99, 2013.

194. Wilson CB, McLaughlin LD, Nair A, Ebenezer PJ, Dange R, Francis J. Inflammation and oxidative stress are elevated in the brain, blood, and adrenal glands during the progression of post-traumatic stress disorder in a predator exposure animal model. *PLoS One* 8: e76146, 2013.

195. Winter M, Beer HD, Hornung V, Kramer U, Schins RP, Forster I. Activation of the inflammasome by amorphous silica and TiO2 nanoparticles in murine dendritic cells. *Nanotoxicology* 5: 326-40, 2011.

196. Wittkopp S, Staimer N, Tjoa T, Stinchcombe T, Daher N, Schauer JJ, Shafer MM, Sioutas C, Gillen DL, Delfino RJ. Nrf2-related gene expression and exposure to traffic-related air pollution in elderly subjects with cardiovascular disease: An exploratory panel study. *J Expo Sci Environ Epidemiol* 26: 141-9, 2016.

197. Wright HL, Moots RJ, Bucknall RC, Edwards SW. Neutrophil function in inflammation and inflammatory diseases. *Rheumatology (Oxford)* 49: 1618-31, 2010.

198. Xiao GG, Wang M, Li N, Loo JA, Nel AE. Use of proteomics to demonstrate a hierarchical oxidative stress response to diesel exhaust particle chemicals in a macrophage cell line. *J Biol Chem* 278: 50781-90, 2003.

199. Yamamoto H, Omelchenko I, Shi X, Nuttall AL. The influence of NF-kappaB signal-transduction pathways on the murine inner ear by acoustic overstimulation. *J Neurosci Res* 87: 1832-40, 2009.

200. Yamashita D, Jiang HY, Le Prell CG, Schacht J, Miller JM. Post-exposure treatment attenuates noise-induced hearing loss. *Neuroscience* 134: 633-42, 2005.

201. Yang EJ, Kim S, Kim JS, Choi IH. Inflammasome formation and IL-1beta release by human blood monocytes in response to silver nanoparticles. *Biomaterials* 33: 6858-67, 2012.

202. Yasukawa S, Miyazaki Y, Yoshii C, Nakaya M, Ozaki N, Toda S, Kuroda E, Ishibashi K,

Yasuda T, Natsuaki Y, Mi-ichi F, Iizasa E, Nakahara T, Yamazaki M, Kabashima K, Iwakura Y, Takai T, Saito T, Kurosaki T, Malissen B, Ohno N, Furue M, Yoshida H, Hara H. An ITAM-Syk-CARD9 signalling axis triggers contact hypersensitivity by stimulating IL-1 production in dendritic cells. *Nat Commun* 5: 3755, 2014.

203. Yazdi AS, Guarda G, Riteau N, Drexler SK, Tardivel A, Couillin I, Tschopp J. Nanoparticles activate the NLR pyrin domain containing 3 (Nlrp3) inflammasome and cause pulmonary inflammation through release of IL-1alpha and IL-1beta. *Proc Natl Acad Sci U S A* 107: 19449-54, 2010.

204. Ying Z, Xu X, Chen M, Liu D, Zhong M, Chen LC, Sun Q, Rajagopalan S. A synergistic vascular effect of airborne particulate matter and nickel in a mouse model. *Toxicol Sci* 135: 72-80, 2013.

205. Zhao YY, Wang HL, Cheng XL, Wei F, Bai X, Lin RC, Vaziri ND. Metabolomics analysis reveals the association between lipid abnormalities and oxidative stress, inflammation, fibrosis, and Nrf2 dysfunction in aristolochic acid-induced nephropathy. *Sci Rep* 5: 12936, 2015.

206. Zuurbier M, Hoek G, Oldenwening M, Lenters V, Meliefste K, van den Hazel P, Brunekreef B. Commuters' exposure to particulate matter air pollution is affected by mode of transport, fuel type, and route. *Environ Health Perspect* 118: 783-9, 2010.

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

ABBREVIATIONS

AOP, adverse outcome pathway

ARE, antioxidant response element

CAM, cell adhesion molecules

CCL, CC chemokine ligand

CNT, carbon nanotubes

CVD, cardiovascular disease

DEP, diesel exhaust particles

ENM, engineered nanomaterials

EpRE, Electrophile Responsive Element

GC, glucocorticoids

GSH, reduced glutathione

GSK-3, Glycogen synthase kinase 3

GSSG, oxidized glutathione

GWAS, genome-wide association studies

HC, hair cells

HFO, heavy fuel oil

HNE, hydroxy-2-nonenal

HPAA, hypothalamus-pituitary adrenal axis

IHC, inner hair cells

IL-, interleukin

iNOS, inducible nitric oxide synthase

KEAP1, Kelch-like ECH-associated **protein** 1

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

MAF, musculoaponeurotic fibrosarcoma oncogene homolog

MAPK, mitogen-activated protein kinase

MDA, malondialdehyde

MIE, molecular initiating event

NF-kB, nuclear factor kappa B

NIHL, Noise-induced hearing loss

NLP3, NACHT, LRR and PYD domains-containing protein 3

NRF2, nuclear factor (erythroid-derived 2)-like 2

NT, nitrotyrosine

OHC, outer hair cells

OS, oxidative stress

P2X7R, purinergic receptor P2X7

PAH, polycyclic aromatic hydrocarbons

PRDX, peroxiredoxin

PTSD, post-traumatic stress disorder

RNS, reactive nitrogen species

ROS, reactive oxygen species

SPL, sound pressure level

TNF, tumor necrosis factor

TXN, thioredoxin

TXNIP, thioredoxin-interacting protein

UPS, ubiquitin/proteasome system

XO, xanthine oxidase

Table 1. Inflammasome activation induced by particles *vs*. engineered nanomaterials

Material	***Main findings***	***References***
MSU crystals	NLRP3-dependent induction of IL-1β release *in vitro*	(115)
Cholesterol crystals	Cholesterol crystals activate NLRP3 and induce IL-1β production in human macrophages	(52,143)
Hydroxyapatite crystals	Induction of IL-1β and IL-18 production in mouse macrophages is induced by needle-like and clumped nanocrystals, but not spherical and larger crystals, and depends on potassium efflux, generation of ROS, and lysosomal damage/cathepsin B *in vitro*, and on various NLRP3 components *in vivo* (KO mice)	(83)
Crystalline silica	Crystalline silica induces NLRP3 activation and IL-1β production through phagolysosome destabilization	(50,74,195)
Amyloid β	Induction of IL-1β release *in vitro* in LPS-primed primary mouse microglial cells, NLRP3 inflammasome-dependent, ATP-dependent	(61)
Asbestos	Asbestos induces NLRP3 inflammasome activation *in vitro* (human primary macrophages), dependent on ROS production, cathepsin B activity, P2X7 receptors and Src/Syk kinases	(50,132)
Aluminum salts	Aluminum salts induce NLRP3 activation and IL-1β production through phagolysosome destabilization	(74)

CeO_2 nanowires of various size	Correlation between nanowires' length and lysosomal damage, cathepsin B release and IL-1β release *in vitro* (human THP-1)	(81)
Polystyrene and PLG nanospheres	Smaller particles are taken up better by mouse BMDC *in vitro* and induce more IL-1β release, in a NLRP3-, cathepsin B- and phagosomal acidification-dependent manner	(159)
Silver nanospheres	Smaller particles induce IL-1β release in monocytes better than larger ones, dependent on mitochondrial superoxide, cathepsin release and K^+ efflux.	(201)
TiO_2 nanobelts	Induction of IL-1β release *in vitro* by long but not by short or spherical particles (human THP-1, murine alveolar macrophages)	(62)
TiO_2 nanospheres	Phagocytosis-independent induction of IL-1β release *in vitro* (mouse BMDM, human THP-1 and primary keratinocytes). Smaller particles more active than larger ones in murine DC, in an actin-, ROS-, NLRP3-, and caspase-1-dependent fashion.	(195,203)
SiO_2 nanospheres	Phagocytosis-independent induction of IL-1β release *in vitro* (mouse BMDM, human THP-1 and primary keratinocytes). Amorphous silica NPs induce IL-1β production in mouse DC in an actin-, ROS-, NLRP3-, and caspase-1-dependent fashion.	(195,203)
Carbon nanotubes	Long CNT induce NLRP3 inflammasome activation *in vitro* (human primary macrophages), dependent on ROS production, cathepsin B activity, P2X7 receptors and Src/Syk kinases	(132)

Table 2. Summary of common omics approaches in exposome studies

Omics	***Target Molecule***	***Analytical Platform***	***Typical Profile Content (~ # of molecules)***	***Advantages and** limitations **of technique***
Transcriptome	Gene transcripts	Microarray	<50,000	**Custom arrays available** **Suitable for cellular, tissue and biofluid samples** Limited target number Limited detection limit
		Next generation sequencing	Full transcriptome	**High sensitivity (single nucleotide level)** **Low limit of detection** **Qualitative and quantitative** **Suitable for cellular, tissue and biofluid samples** High cost
Proteome	Proteins	Mass spectrometry		**High throughput, specificity and sensitivity** **Qualitative and quantitative** Multiple methods required to cover proteome

				Complex feature annotation
		Protein array	>20,000	**High throughput and sensitivity** **Low sample consumption** **Efficient feature annotation** Limited target number
Metabolome	Small molecule metabolites	Nuclear magnetic resonance spectroscopy (^{1}H NMR)	>100	**Minimal sample preparation** **Suitable for cellular, tissue and biofluid samples** **Metabolite annotation/assignment typically straighforward**
		Liquid chromatography - Mass spectrometry (LC-MS)	>1000	**Suitable for cellular, tissue and biofluid samples** Derivatisation required for polar and high molecular weight metabolites Metabolite annotation/assignment can be time-consuming
Adductome (serum albumin)	Endogenous-xenobiotic conjugates	Mass spectrometry	>100	**Ability to capture information on reactive intermediates and/or short-lived exposures** **Variety of techniques available for targeting with different specificity and resolution**

				Time-consuming annotation

Antioxidants & Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (doi: 10.1089/ars.2017.7147)
This article has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

FIGURE LEGENDS

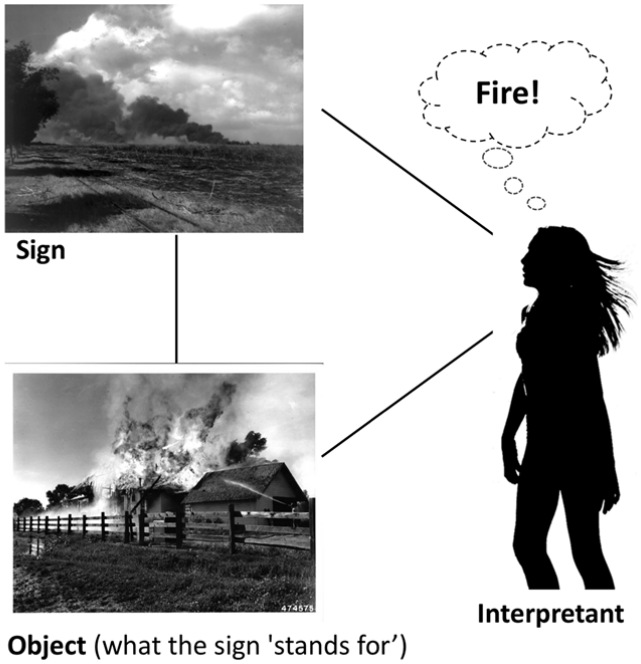

Figure 1. The semiotic triad according to Peirce. Images from Wikimedia Commons.

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

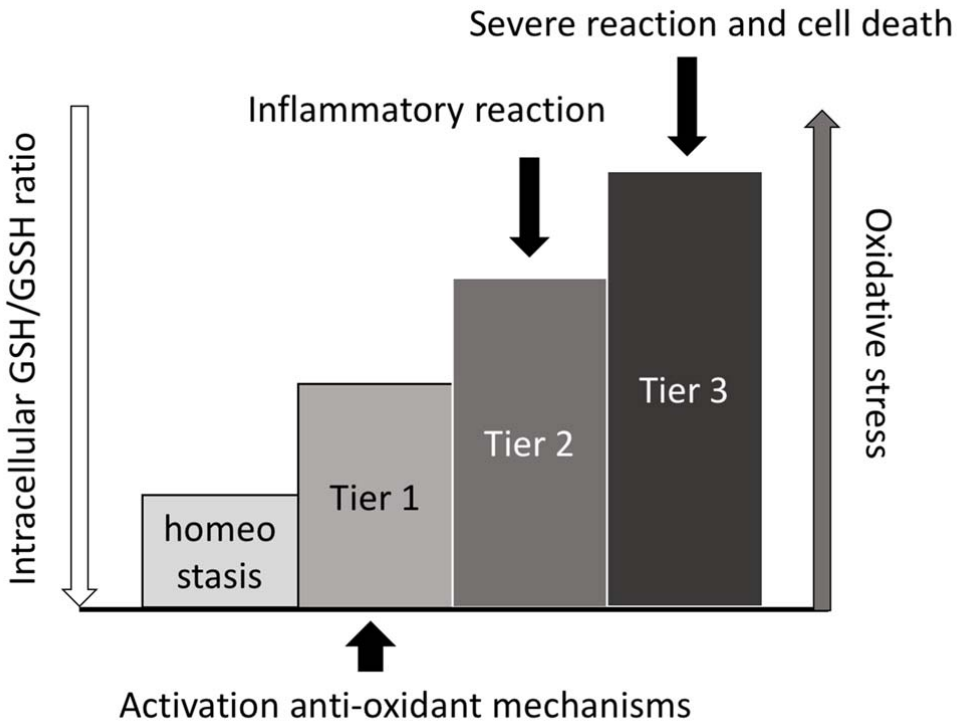

Figure 2. The three-tiered paradigm of OS induced by nanomaterials at the single cell level.

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

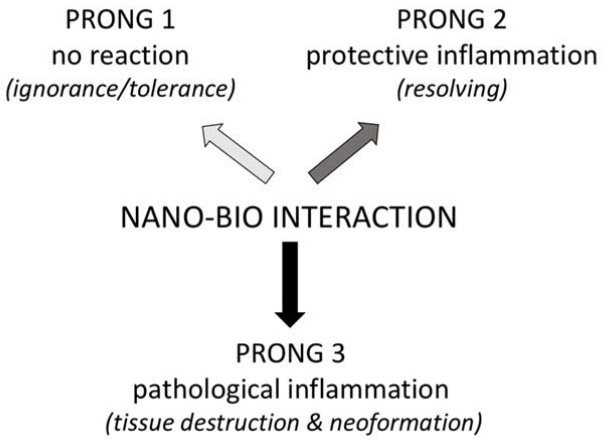

Figure 3. The three-pronged response of complex living systems to nanomaterials.

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

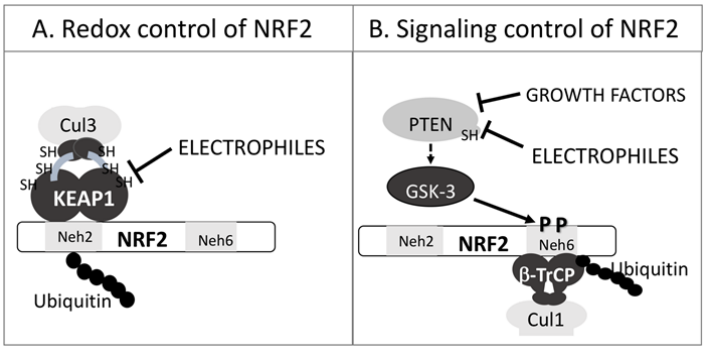

Figure 4. Regulation of NRF2 by protein stability. A, KEAP1/NRF2 interaction. Thiol reactive groups in KEAP1 provide a mechanism for sensing the levels of ROS and electrophiles. B, β-TrCP/GSK-3/NRF2 interaction. Phosphorylation of NRF2 by GSK-3 provides a layer of regulation by signaling pathways and by electrophilic compounds and alter the balance kinase/phosphatase, exemplified here with PTEN (modified from (154)).

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

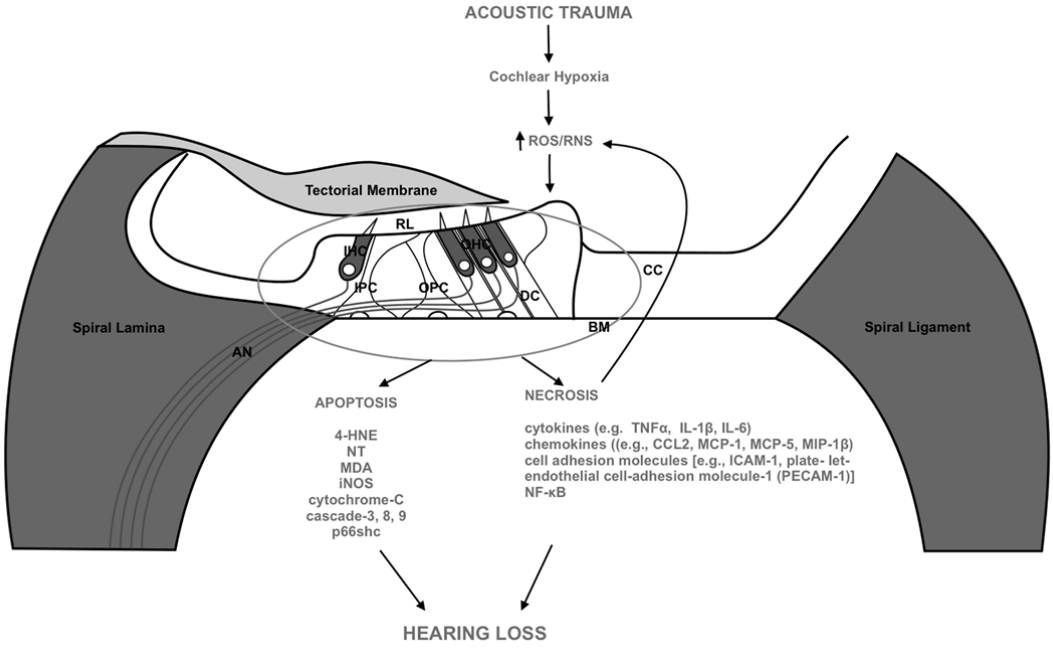

Figure 5. Mechanisms of ototoxicity induced by acoustic trauma.

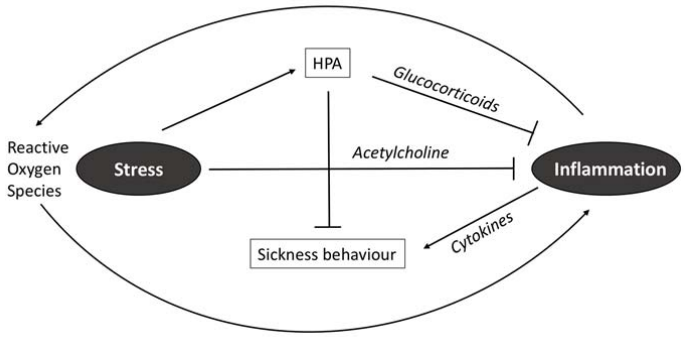

Figure 6. The main neuroendocrine-immune pathways.

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

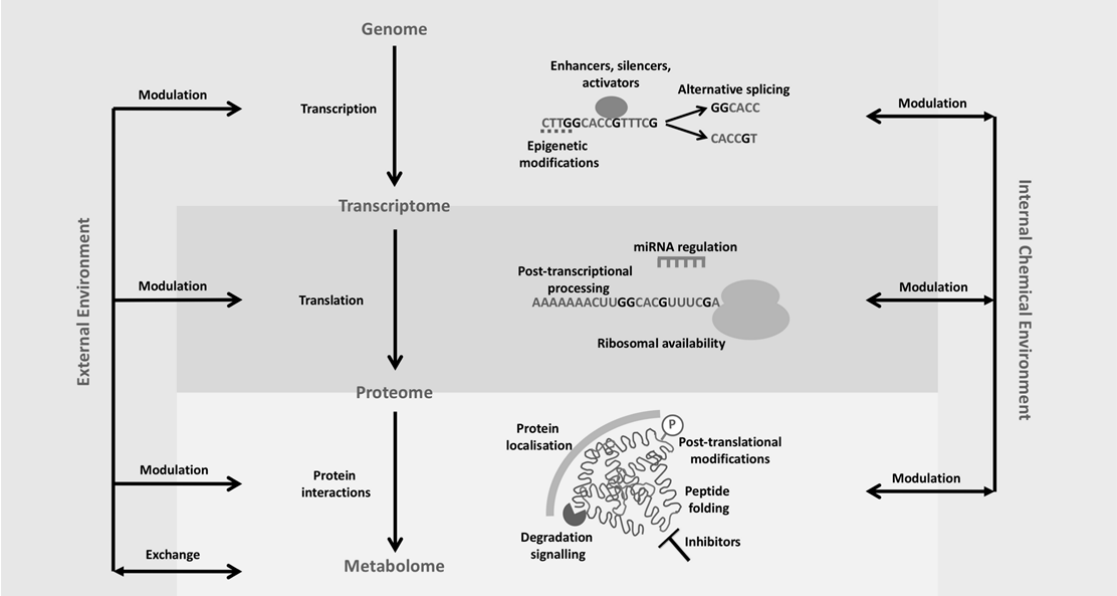

Figure 7. Interactions between genes and the environment are mediated by a complex network of biological entities. Environmental exposures occur in the context of all previous exposures and the multifactorial responses elicited by the biological network. Characterising the biological complexity of the internal chemical milieu during key periods of life (e.g. small molecules that constitute the metabolic phenotype; status of gene expression; etc.) using high-throughput omics platforms provides a window on the human exposome, and an opportunity to start dissecting the contributions of various factors to the etiology of chronic diseases.

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Antioxidants and Redox Signaling
Oxidative stress and inflammation induced by environmental and psychological stressors: a biomarker perspective (DOI: 10.1089/ars.2017.7147)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

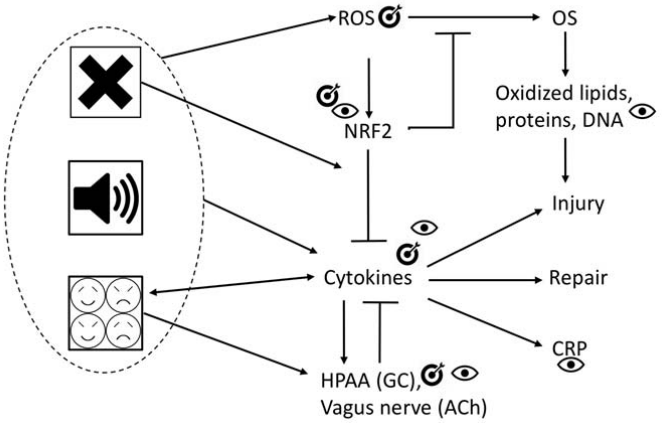

Figure 8. Biomarkers for stress-induced inflammation and OS. The symbols denote whether the biomarker is a sign (that indicates the activation of a process) or a proxy (that are also targets we can interact with to modify the disease process).