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Abstract

Prevalence of obesity and related complications such as type 2 diabetes (T2D) has increased dramatically in recent decades. Metabolic complications of obesity arise in part due to subcutaneous adipose tissue (SAT) dysfunction. However, it is currently unclear why some obese individuals develop insulin resistance and T2D and others do not. In this review, we discuss the role of the skin in regulating SAT function, and whether presence of inflammatory skin diseases such as psoriasis represent a novel risk mechanism mediating development of obesity-related complications.

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Highlights

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· Psoriasis is an independent risk-factor for development of T2D

· Skin-specific transgenic mice display altered whole-body glucose and lipid homeostasis

· Subcutaneous adipose tissue function is impaired directly below psoriatic skin lesions

· The skin secretes proteins and peptides which can enhance or impair metabolic control

Can the Skin Make You Fat? A role for the skin in regulating adipose tissue function and whole-body glucose and lipid homeostasis.

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Skin and metabolic health

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Abstract

Prevalence of obesity and related complications such as type 2 diabetes (T2D) has increased dramatically in recent decades. Metabolic complications of obesity arise in part due to subcutaneous adipose tissue (SAT) dysfunction. However, it is currently unclear why some obese individuals develop insulin resistance and T2D and others do not. In this review, we discuss the role of the skin in regulating SAT function, and whether presence of inflammatory skin diseases such as psoriasis represent a novel risk mechanism mediating development of obesity-related complications.

Obesity and Adipose tissue

Obesity and its associated metabolic complications, including type 2 diabetes (T2D) and cardiovascular disease, have increased dramatically in recent decades. Global prevalence of obesity and overweight were estimated at 2.1 billion individuals in 2014[1], whilst the number of people with T2D is predicted to rise from 382 million in 2013 to 592 million by 2035. This increased disease burden has become a major public health issue, with increased morbidity and mortality and associated socioeconomic costs [1], with costs of obesity and related complications estimated at $2 trillion globally. There is a widely-recognised association between obesity-related metabolic diseases and

skin disease[2]. For example, psoriasis is an independent risk factor for development of T2D. Here we discuss the contribution of the skin in driving adipose tissue dysfunction and onset of T2D.

White adipose tissue (AT) plays an essential role in metabolic homeostasis, via its role in storage and release of lipids and fatty acids, respectively; through its role as an endocrine organ, and as a location of beige adipogenesis. Conversely, dysfunction of white AT function is a central aspect of obesity related pathophysiology [1]. White AT is present as two major distinct depots; visceral AT (VAT) which is mainly located in intra-abdominal (mesenteric), pericardial and peri-renal regions, and subcutaneous adipose tissue (SAT) located in the hypodermic regions below the skin [1].

SAT and metabolic homeostasis

SAT is the largest adipose tissue depot and as a result plays a key role in regulating whole-body glucose and lipid homeostasis via its endocrine and lipid storage and release functions as well as a major site of beige adipocyte formation[3]. Consequently, dysregulation of SAT function is a central factor in the pathophysiology of obesity-induced insulin resistance and T2D [4, 5]. SAT is regarded as the primary adipose tissue depot for safe storage of lipids, in the form of triacylglycerols (TAG) [3]. However, the ability of SAT to expand in response to chronic over-nutrition is limited and when energy supply exceeds the capacity of SAT to store lipids, fat is instead stored in non-adipose tissue such as liver and skeletal muscle and also in VAT depots, a process referred to as ectopic lipid deposition [4]. Studies have demonstrated that the limited potential of SAT to expand is a key mediating factor in the dysfunction of SAT and the development of obesity associated insulin resistance and T2D[6]. Healthy adipogenesis occurs largely via adipocyte hyperplasia – i.e. the formation of new adipocytes from adipocyte precursor cells. In contrast, in obesity adipocyte hyperplasia can become impaired leading SAT expansion to occur primarily through adipocyte hypertrophy, i.e. expansion of existing adipocytes [7, 8]. This can lead directly to impaired SAT function, characterised by angiogenesis, hypoxia and adipocyte cell death. As a result, lipid storage capacity declines, immune cell infiltration and SAT inflammation develop and insulin sensitivity and adipocytokine secretion become impaired [7, 9, 10]. The importance of dysregulation of SAT expansion in obesity pathophysiology is emphasised by the fact that presence of hypertrophic adipocytes is a strong, early predictor of developing insulin resistance and T2D in first degree relatives of individuals with T2D, as well being a major phenotype in non-obese individuals with T2D[11, 12].

SAT dysfunction and ectopic lipid deposition

Loss of SAT storage capacity results in in ectopic lipid deposition in VAT, liver, skeletal muscle and pancreas [3, 7, 8, 13]. In liver and muscle, this can lead to build-up of toxic lipid metabolites such as diacylglycerols (DAG) and ceramides, which directly promote tissue insulin resistance. Specifically, DAGs induce serine phosphorylation of IRS1/2[14, 15], whilst ceramides promote de-phosphorylation of AKT [16], resulting in decreased insulin signalling transduction. In the pancreas, excess lipid levels can impair insulin secretion and beta-cell proliferation [17, 18]. Deposition of excess lipid into VAT depots results in VAT expansion and consequent dysfunction. In addition, in all these tissues, saturated fatty acids released from SAT can directly induce inflammatory signalling pathways [18, 19]. These include induction of TLR4 signalling together with increased reactive oxygen species production, which can both directly inhibit insulin signalling.

Obesity also leads to impaired SAT endocrine function. SAT secretes bioactive proteins and peptides (adipocytokines) including adiponectin, retinol binding protein (RBP4), resistin and various pro-inflammatory cytokines and chemokines (MCP1, TNF□, IL6) [20-22]. In addition, SAT can also secrete insulin sensitising anti-inflammatory bioactive lipids, including palmitoleate[23] and the recently identified fatty-acid esters of hydroxyl fatty acids (FAHFAs)[24]. Dysfunction of SAT leads to altered expression and endocrine profile, broadly characterised by reductions in anti-inflammatory, insulin sensitisers (adiponectin, FAHFAs, palmitoleate) and increases in RBP4, resistin and pro-inflammatory cytokines which exert deleterious effects on whole-body insulin sensitivity [22, 25]. Interestingly, dysregulation of SAT endocrine function is related in part to adipocyte insulin sensitivity and levels and activity of insulin-dependent glucose transporter 4 (GLUT4) [3]. Despite AT glucose uptake only accounting for 10 – 15% of total insulin-stimulated glucose uptake, AT GLUT4 levels are an accurate marker of insulin sensitivity, whilst AT-GLUT4 KO mice display the same severity of insulin resistance as skeletal muscle GLUT4 KO mice [26]. This important role of AT-GLUT4 is due to its role in SAT endocrine function. Reduced levels of AT-GLUT4 lead to increased expression and secretion of RBP4 and reductions in ChREBP-mediated synthesis and secretion of FAHFAs [24, 27]. Together, the changes in endocrine function observed in obese dysfunctional SAT are directly related to development of obesity-mediated pathologies including insulin resistance and T2D.

A final mechanism linking SAT dysfunction and insulin resistance involves beige adipogenesis. SAT is the primary site for the formation of beige adipocytes, which are brown adipocyte cells located within classical white AT depots [28]. Beige adipocytes develop from a different lineage to classical brown

adipocytes, but retain many of the same functional characteristics, including induction by thermogenic triggers such as cold/noradrenaline and morphological characteristics, such as expression of uncoupling protein 1 (UCP1), presence of multilocular lipid droplets, numerous mitochondria and abundant vascularisation and innervation[28]. Moreover, induction of beige adipogenesis ('browning' of white adipose tissue) – via mechanisms including non-shivering thermogenesis and exercise [29, 30] - has been demonstrated to exert beneficial effects on insulin sensitivity and glucose tolerance. The fact that these browning effects are lost or reduced in obesity and diabetes further emphasises the importance of beige adipocytes in SAT mediated maintenance of whole-body glucose metabolism[30, 31].

Taken together, the local and systemic functions of SAT play a critical contributory role in the maintenance of whole-body glucose and lipid homeostasis. Conversely, SAT dysfunction plays a crucial role in the pathophysiology of obesity-mediated onset of insulin resistance and T2D. Consequently, elucidating the underlying mechanisms, and specifically the genetic and environmental factors, that lead to dysregulation of SAT is essential in order to fully understand the pathophysiology of T2D and to identify novel prevention and treatment approaches. The understanding of these mechanisms is of particular importance since many obese individuals do not develop insulin resistance – a condition referred to as metabolically healthy obesity – in large part due to insufficient adipocyte hyperplasia enabling excess energy storage. However, the genetic and environmental factors which cause inter-individual differences in response to obesity remain unclear [10, 32].

A role for the skin in regulating SAT function and glycaemic control

The importance of inter-organ cross-talk in the regulation of insulin sensitivity is widely recognised. In addition to the important roles for bioactive adipocytokines and lipokines secreted from adipose tissue, an endocrine function of skeletal muscle (myokines) and liver (hepatokines) is also reported [33-36]. A large number bioactive factors are secreted from these tissues with both beneficial and deleterious effects on glucose metabolism reported, with secretion profiles altered in obesity and diabetes. However, despite being the largest organ in the body with an established secretory function, a potential role for the **skin** in regulating insulin sensitivity and glucose homeostasis has not been examined.

Clinical, epidemiological and experimental evidence supporting a direct role for skin in glycaemic control.

In support of this idea, accumulating evidence suggests a role for the skin in regulating whole-body glucose metabolism. The association between psoriasis and obesity has long been recognised, with the earliest evidence based on a study on prisoners of war during world war II in which psoriasis improved with caloric restriction [2, 37]. Since then, a number of studies have shown a direct link between psoriasis and obesity, and that each condition can drive the other. Clinical and epidemiological studies have demonstrated that the inflammatory skin disease psoriasis is an independent risk factor for development of T2D, as well as related metabolic conditions such as NAFLD and CVD [38-42] . For example, a systematic review and meta-analysis concluded that a nearly 30% increased risk of developing T2D was associated with psoriasis [43]. More recently, a population based study showed that patients with comorbid psoriasis who were diagnosed with T2DM were significantly younger at the age of diagnosis than non-psoriasis patients [44], whilst T2D patients with psoriasis present with increased disease severity compared to T2D patients without psoriasis [44]. Moreover, severity of psoriasis has been shown to correlate with both increased likelihood of developing T2DM and with increased rate of progression to requirement for exogenous insulin [38]. Similar associations have been reported between psoriasis and both non-alcoholic fatty liver disease (NAFLD) and cardiovascular disease (CVD) [41, 42]. Experimental studies also support a specific role for skin in regulating whole-body glucose and lipid homeostasis. Mice with a keratinocyte-specific knockout of SCD1, a key lipogenic gene, showed altered whole-body glucose and lipid metabolism, including altered lipogenic gene expression in liver and skeletal muscle, and altered glucose tolerance and hepatic glycogen content [45]. This implies that specific signalling pathways within the skin can exert systemic effects to regulate whole-body glucose and lipid homeostasis, and have the potential to play an important role in development of T2D.

Thus, associations between skin inflammation, insulin resistance and T2D are well established. Research to date has largely focussed on obesity itself, via altered adipocytokine secretion from dysfunctional adipose tissue, as the primary risk factor linking psoriasis with T2D. However, as detailed above, many studies have demonstrated that psoriasis and skin health are independent risk factors and that associations between psoriasis and T2D are independent of underlying obesity [46]. This suggests that ***impaired skin function itself*** may be an underlying contributory factor in the development of T2D. In addition, other recognised causes of increased T2D risk, such as ageing and

exposure to atmospheric pollution [47, 48], are also characterised by declining skin health and presence of skin inflammation [49, 50].

Mechanisms linking skin health to whole-body metabolism: the skin secretome and SAT?

The underlying mechanisms linking skin function to whole-body metabolism are unclear but potentially relate to skin endocrine function. Analysis using LCMS/MS as well as candidate protein approaches have begun to characterise the skin secretome. Sebocytes, the secretory cells of the sebaceous gland, have been reported to secrete adipokines including IL6, leptin and eNAMPT/visfatin, as well as serpin E1 [51]. Of relevance to skin inflammation, expression and secretion of these proteins was upregulated following TLR2/4 activation. Separately, LCMS/MS analysis has shown sebocytes to secrete lipocalin 2 (LCN2) and complement C3 [52]. Keratinocytes are reported to secrete small molecules and proteins including glucocorticoids, mineralocorticoids, serpins B1 and E1, anti-microbial peptides (e.g. LL37), eNAMPT/visfatin, IL6 and apolipoprotein E [35, 51, 53-56]**.** In addition, a wide range of pro-inflammatory cytokines and chemokines, including TNF-α, IL6, IL8, IL17, and IL1-β, are also secreted from both keratinocytes and immune cells within the skin [39, 40, 55, 57, 58]. Importantly, such cytokines as well as many of the skin-derived proteins described above, have been separately shown to exert well described gluco- and lipo-regulatory effects on metabolic target tissues [35, 46, 59-63]. This, together with the fact that skin expression and secretion of a number of these bioactive mediators are altered in psoriasis and ageing [64-66], provides a plausible link between skin inflammation, poor skin function and development of insulin resistance and T2D. Given that SAT is anatomically adjacent to skin, it is rationale to hypothesise that SAT would be a primary recipient of signalling factors derived from inflamed skin. Exposure of SAT to e.g. inflammatory stimuli is has been shown to impair glucose uptake, lipid storage, adiponectin secretion, promote SAT inflammation and reduce beige adipogenesis. Thus, skin inflammation may directly induce SAT dysfunction with consequent increased risk of development of insulin resistance and T2D. In support of this, a recent study demonstrated that in psoriasis, expression of specific miRNAs are upregulated in SAT located directly below psoriatic skin, leading to impaired regulation of cholesterol efflux [67]. Specifically, miR-26b-5p was upregulated, and found to down regulate the essential cholesterol efflux enzyme neutral cholesterol ester hydrolase 1 various SAT cells including adipocytes, monocytes/macrophages, and vascular endothelial cells. A separate study has also reported increased SAT inflammation in psoriasis patients [68]. Whilst these studies do not directly establish directionality, such altered cholesterol regulation and inflammation provide plausible links between psoriasis and related co-morbidities via direct impairment of SAT function. Separately from

inflammatory effects, some rodent studies have pointed to a potential role for skin in regulating browning of SAT. Defects in the barrier and thermoregulatory functions of skin, as are observed in psoriasis, are noted to lead to cold-induced beige adipogenesis, whilst other mouse studies have indirectly linked skin function with SAT browning [69].

In summary, alterations in the skin secretome linked to inflammatory skin disease and declining skin health may play an important role in mediating SAT dysfunction, resulting in increased predisposition to obesity-associated development of insulin resistance and T2D. Moreover, presence of inflammatory skin disease or poor skin health may partly explain inter-individual differences in SAT responses to over-nutrition and provide insight into the underlying mechanisms of metabolically healthy obesity. We hypothesise that maintaining skin health or treating inflammatory skin disease may represent a novel approach for prevention or treatment of obesity-related metabolic complications.

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References

[1] Gonzalez-Muniesa P, Martinez-Gonzalez MA, Hu FB, et al. (2017) Obesity. Nature reviews Disease primers 3: 17034

[2] Correia B, Torres T (2015) Obesity: a key component of psoriasis. Acta bio-medica : Atenei Parmensis 86: 121-129

[3] Smith U, Kahn BB (2016) Adipose tissue regulates insulin sensitivity: role of adipogenesis, de novo lipogenesis and novel lipids. Journal of internal medicine 280: 465-475

***** Excellent overview of the importance of subcutaneous adipose tissue in metabolic homeostasis***

[4] McMorrow AM, Connaughton RM, Lithander FE, Roche HM (2015) Adipose tissue dysregulation and metabolic consequences in childhood and adolescent obesity: potential impact of dietary fat quality. The Proceedings of the Nutrition Society 74: 67-82

[5] Stout MB, Justice JN, Nicklas BJ, Kirkland JL (2017) Physiological Aging: Links Among Adipose Tissue Dysfunction, Diabetes, and Frailty. Physiology 32: 9-19

[6] Gustafson B, Hedjazifar S, Gogg S, Hammarstedt A, Smith U (2015) Insulin resistance and impaired adipogenesis. Trends in endocrinology and metabolism: TEM 26: 193-200

[7] Sun K, Kusminski CM, Scherer PE (2011) Adipose tissue remodeling and obesity. The Journal of clinical investigation 121: 2094-2101

[8] Pellegrinelli V, Carobbio S, Vidal-Puig A (2016) Adipose tissue plasticity: how fat depots respond differently to pathophysiological cues. Diabetologia 59: 1075-1088

[9] Gustafson B, Gogg S, Hedjazifar S, Jenndahl L, Hammarstedt A, Smith U (2009) Inflammation and impaired adipogenesis in hypertrophic obesity in man. American journal of physiology Endocrinology and metabolism 297: E999-E1003

[10] Choe SS, Huh JY, Hwang IJ, Kim JI, Kim JB (2016) Adipose Tissue Remodeling: Its Role in Energy Metabolism and Metabolic Disorders. Frontiers in endocrinology 7: 30

[11] Acosta JR, Douagi I, Andersson DP, et al. (2016) Increased fat cell size: a major phenotype of subcutaneous white adipose tissue in non-obese individuals with type 2 diabetes. Diabetologia 59:
560-570

[12] Cederberg H, Stancakova A, Kuusisto J, Laakso M, Smith U (2015) Family history of type 2 diabetes increases the risk of both obesity and its complications: is type 2 diabetes a disease of inappropriate lipid storage? Journal of internal medicine 277: 540-551

[13] Jensen MD (2008) Role of body fat distribution and the metabolic complications of obesity. The Journal of clinical endocrinology and metabolism 93: S57-63

[14] Petersen MC, Shulman GI (2017) Roles of Diacylglycerols and Ceramides in Hepatic Insulin Resistance. Trends in pharmacological sciences 38: 649-665

[15] Shulman GI (2014) Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. The New England journal of medicine 371: 2237-2238

[16] Summers SA, Goodpaster BH (2016) CrossTalk proposal: Intramyocellular ceramide accumulation does modulate insulin resistance. The Journal of physiology 594: 3167-3170

[17] Pascoe J, Hollern D, Stamateris R, et al. (2012) Free fatty acids block glucose-induced betacell proliferation in mice by inducing cell cycle inhibitors p16 and p18. Diabetes 61: 632-641 [18] Eguchi K, Manabe I, Oishi-Tanaka Y, et al. (2012) Saturated fatty acid and TLR signaling link beta cell dysfunction and islet inflammation. Cell metabolism 15: 518-533

[19] Glass CK, Olefsky JM (2012) Inflammation and lipid signaling in the etiology of insulin resistance. Cell metabolism 15: 635-645

[20] Hotamisligil GS, Shargill NS, Spiegelman BM (1993) Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science 259: 87-91

[21] Turer AT, Scherer PE (2012) Adiponectin: mechanistic insights and clinical implications. Diabetologia 55: 2319-2326

[22] Ouchi N, Parker JL, Lugus JJ, Walsh K (2011) Adipokines in inflammation and metabolic disease. Nature reviews Immunology 11: 85-97

[23] Cao H, Gerhold K, Mayers JR, Wiest MM, Watkins SM, Hotamisligil GS (2008) Identification of a lipokine, a lipid hormone linking adipose tissue to systemic metabolism. Cell 134: 933-944

[24] Yore MM, Syed I, Moraes-Vieira PM, et al. (2014) Discovery of a class of endogenous mammalian lipids with anti-diabetic and anti-inflammatory effects. Cell 159: 318-332

[25] Yang Q, Graham TE, Mody N, et al. (2005) Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. Nature 436: 356-362

[26] Abel ED, Peroni O, Kim JK, et al. (2001) Adipose-selective targeting of the GLUT4 gene impairs insulin action in muscle and liver. Nature 409: 729-733

[27] Herman MA, Peroni OD, Villoria J, et al. (2012) A novel ChREBP isoform in adipose tissue regulates systemic glucose metabolism. Nature 484: 333-338

[28] Wu J, Bostrom P, Sparks LM, et al. (2012) Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. Cell 150: 366-376

[29] Stanford KI, Middelbeek RJ, Goodyear LJ (2015) Exercise Effects on White Adipose Tissue: Beiging and Metabolic Adaptations. Diabetes 64: 2361-2368

[30] Stanford KI, Middelbeek RJ, Townsend KL, et al. (2015) A novel role for subcutaneous adipose tissue in exercise-induced improvements in glucose homeostasis. Diabetes 64: 2002-2014 [31] Ishibashi J, Seale P (2010) Medicine. Beige can be slimming. Science 328: 1113-1114

[32] Kloting N, Fasshauer M, Dietrich A, et al. (2010) Insulin-sensitive obesity. American journal of physiology Endocrinology and metabolism 299: E506-515
[33] Hussain MA, Akalestou E, Song WJ (2016) Inter-organ communication and regulation of beta cell function. Diabetologia 59: 659-667
[34] Bouzakri K, Plomgaard P, Berney T, Donath MY, Pedersen BK, Halban PA (2011) Bimodal effect on pancreatic beta-cells of secretory products from normal or insulin-resistant human skeletal muscle. Diabetes 60: 1111-1121
[35] El Ouaamari A, Dirice E, Gedeon N, et al. (2016) SerpinB1 Promotes Pancreatic beta Cell Proliferation. Cell metabolism 23: 194-205
[36] Shirakawa J, De Jesus DF, Kulkarni RN (2017) Exploring inter-organ crosstalk to uncover mechanisms that regulate beta-cell function and mass. European journal of clinical nutrition [37] Simons RD (1949) Additional studies on psoriasis in the tropics and in starvation camps. The Journal of investigative dermatology 12: 285-294
[38] Azfar RS, Seminara NM, Shin DB, Troxel AB, Margolis DJ, Gelfand JM (2012) Increased risk of diabetes mellitus and likelihood of receiving diabetes mellitus treatment in patients with psoriasis. Archives of dermatology 148: 995-1000
***The authors show that psoriasis is an indepednent risk-factor for T2D developmen*t
[39] Mantovani A, Gisondi P, Lonardo A, Targher G (2016) Relationship between Non-Alcoholic Fatty Liver Disease and Psoriasis: A Novel Hepato-Dermal Axis? International journal of molecular sciences 17: 217
[40] Ganzetti G, Campanati A, Molinelli E, Offidani A (2016) Psoriasis, non-alcoholic fatty liver disease, and cardiovascular disease: Three different diseases on a unique background. World journal of cardiology 8: 120-131
[41] Armstrong AW, Harskamp CT, Armstrong EJ (2013) Psoriasis and metabolic syndrome: a systematic review and meta-analysis of observational studies. Journal of the American Academy of Dermatology 68: 654-662
[42] Armstrong EJ, Harskamp CT, Armstrong AW (2013) Psoriasis and major adverse cardiovascular events: a systematic review and meta-analysis of observational studies. Journal of the American Heart Association 2: e000062
[43] Armstrong AW, Harskamp CT, Armstrong EJ (2013) Psoriasis and the risk of diabetes mellitus: a systematic review and meta-analysis. JAMA dermatology 149: 84-91
[44] Schwandt A, Bergis D, Dapp A, et al. (2015) Psoriasis and Diabetes: A Multicenter Study in 222078 Type 2 Diabetes Patients Reveals High Levels of Depression. Journal of diabetes research 2015: 792968
*** This study shows that T2D clinical symptoms are worse in patients with psoriasis than those without psoriasis***
[45] Sampath H, Flowers MT, Liu X, et al. (2009) Skin-specific deletion of stearoyl-CoA desaturase-1 alters skin lipid composition and protects mice from high fat diet-induced obesity. The Journal of biological chemistry 284: 19961-19973
*** Proof-of-concept study showing that alterations in skin-specific pathwyas can impact wholebody glucose and lipid metabolism***
[46] Kamble PG, Pereira MJ, Sidibeh CO, et al. (2016) Lipocalin 2 produces insulin resistance and can be upregulated by glucocorticoids in human adipose tissue. Molecular and cellular endocrinology 427: 124-132
[47] Rajagopalan S, Brook RD (2012) Air pollution and type 2 diabetes: mechanistic insights. Diabetes 61: 3037-3045

[48] Barzilai N, Huffman DM, Muzumdar RH, Bartke A (2012) The critical role of metabolic pathways in aging. Diabetes 61: 1315-1322

[49] Kohl E, Steinbauer J, Landthaler M, Szeimies RM (2011) Skin ageing. Journal of the European Academy of Dermatology and Venereology : JEADV 25: 873-884

[50] Mancebo SE, Wang SQ (2015) Recognizing the impact of ambient air pollution on skin health. J Eur Acad Dermatol 29: 2326-2332

[51] Kovacs D, Lovaszi M, Poliska S, et al. (2016) Sebocytes differentially express and secrete adipokines. Experimental dermatology 25: 194-199

Interesting study showing that sebocytes within the skin secrete adipokines

[52] Dahlhoff M, Frohlich T, Arnold GJ, Zouboulis CC, Schneider MR (2016) LC-MS/MS analysis reveals a broad functional spectrum of proteins in the secretome of sebocytes. Experimental dermatology 25: 66-67

[53] Hannen RF, Michael AE, Jaulim A, Bhogal R, Burrin JM, Philpott MP (2011) Steroid synthesis by primary human keratinocytes; implications for skin disease. Biochemical and biophysical research communications 404: 62-67

[54] Gordon DA, Fenjves ES, Williams DL, Taichman LB (1989) Synthesis and secretion of apolipoprotein E by cultured human keratinocytes. The Journal of investigative dermatology 92: 9699

[55] Hau CS, Kanda N, Noda S, et al. (2013) Visfatin enhances the production of cathelicidin antimicrobial peptide, human beta-defensin-2, human beta-defensin-3, and S100A7 in human keratinocytes and their orthologs in murine imiquimod-induced psoriatic skin. The American journal of pathology 182: 1705-1717

[56] Hannen R, Udeh-Momoh C, Upton J, et al. (2017) Dysfunctional Skin-Derived Glucocorticoid Synthesis Is a Pathogenic Mechanism of Psoriasis. The Journal of investigative dermatology

The authors describe the importance of skin-derived glucocorticoids in psoriasis. Changes in secretion of steroids from skin may play a key role in regulating local SAT function

[57] Cho KA, Suh JW, Lee KH, Kang JL, Woo SY (2012) IL-17 and IL-22 enhance skin inflammation by stimulating the secretion of IL-1beta by keratinocytes via the ROS-NLRP3-caspase-1 pathway. International immunology 24: 147-158

[58] Feldmeyer L, Keller M, Niklaus G, Hohl D, Werner S, Beer HD (2007) The inflammasome mediates UVB-induced activation and secretion of interleukin-1beta by keratinocytes. Current biology : CB 17: 1140-1145

[59] Donath MY, Dalmas E, Sauter NS, Boni-Schnetzler M (2013) Inflammation in obesity and diabetes: islet dysfunction and therapeutic opportunity. Cell metabolism 17: 860-872

[60] Olefsky JM, Glass CK (2010) Macrophages, inflammation, and insulin resistance. Annual review of physiology 72: 219-246

[61] Pound LD, Patrick C, Eberhard CE, et al. (2015) Cathelicidin Antimicrobial Peptide: A Novel Regulator of Islet Function, Islet Regeneration, and Selected Gut Bacteria. Diabetes 64: 4135-4147

[62] Kieswich J, Sayers SR, Silvestre MF, Harwood SM, Yaqoob MM, Caton PW (2016) Monomeric eNAMPT in the development of experimental diabetes in mice: a potential target for type 2 diabetes treatment. Diabetologia 59: 2477-2486

[63] Nestle FO, Kaplan DH, Barker J (2009) Psoriasis. The New England journal of medicine 361: 496-509

[64] Waldera Lupa DM, Kalfalah F, Safferling K, et al. (2015) Characterization of Skin AgingAssociated Secreted Proteins (SAASP) Produced by Dermal Fibroblasts Isolated from Intrinsically Aged Human Skin. The Journal of investigative dermatology 135: 1954-1968

[65] Williamson JC, Scheipers P, Schwammle V, Zibert JR, Beck HC, Jensen ON (2013) A proteomics approach to the identification of biomarkers for psoriasis utilising keratome biopsy. Journal of proteomics 94: 176-185

***** A proteomic analysis of the skin secretome in psoriatic skin***

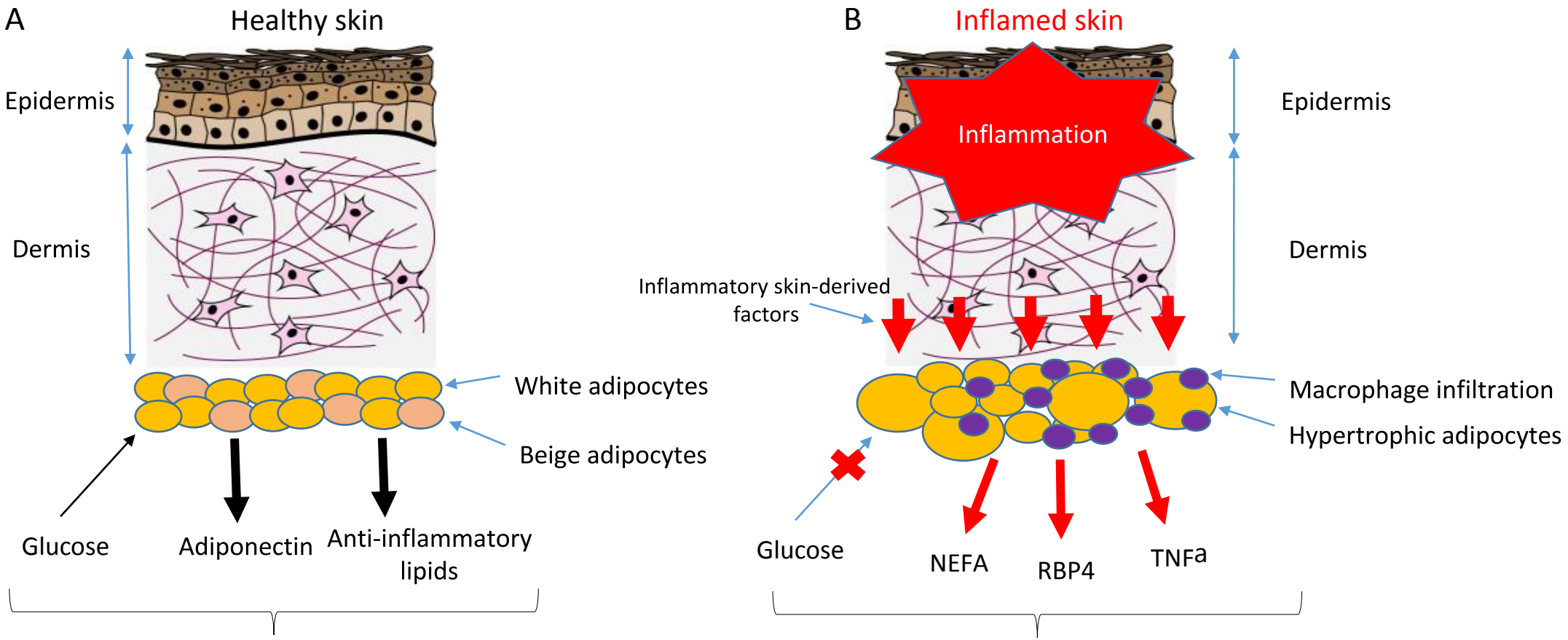
[66] Ali N, Zirak B, Rodriguez RS, et al. (2017) Regulatory T Cells in Skin Facilitate Epithelial Stem Cell Differentiation. Cell

[67] Cheung L, Fisher RM, Kuzmina N, et al. (2016) Psoriasis Skin Inflammation-Induced microRNA26b Targets NCEH1 in Underlying Subcutaneous Adipose Tissue. The Journal of investigative dermatology 136: 640-648 **

The authors describe changes in SAT function directly below psoriatic lesions, providing the fist evidence that secretions from psoriatic skin may influence underlying adipose tissue function

[68] Hjuler KF, Gormsen LC, Vendelbo MH, Egeberg A, Nielsen J, Iversen L (2017) Increased global arterial and subcutaneous adipose tissue inflammation in patients with moderate-to-severe psoriasis. The British journal of dermatology 176: 732-740

[69] Nedergaard J, Cannon B (2014) The browning of white adipose tissue: some burning issues. Cell metabolism 20: 396-407



Tissue and systemic insulin sensitivity and *decreased* T2D risk

Tissue and systemic insulin resistance and *increased* T2D risk#

Figure 1: Diagram demonstrating how skin inflammation may impair whole-body glucose homeostasis via SAT dysfunction. (A) Healthy skin displays limited inflammation and does not secrete pro-inflammatory cytokines or other deleterious skin-derived factors. Underlying SAT is healthy, characterised by small hyperplasic adipocytes, beige adipogenesis, insulin sensitivity and glucose uptake, adequate lipid storage capacity and secretion of insulin sensitising and anti-inflammatory proteins and lipids. (B) Skin is inflamed and the epidermis and dermis are infiltrated by immune cells, resulting in secretion of proinflammatory cytokines, anti-microbial peptides and other components of the skin secretome. Exposure to skin-derived inflammatory proteins leads to dysfunction of underlying SAT, characterised by large hypertrophic adipocytes, impaired insulin sensitivity and glucose uptake, inadequate lipid storage capacity, macrophage infiltration, secretion of inflammatory proteins and fatty acids, ultimately leading to development of systemic insulin resistance and risk of T2D. NEFA – non-esterified fatty acids; RBP4 – retinol binding protein 4; TNFa – tumour necrosis factor alpha

Conflicts of interest: none