Desmoglein 3 Acts as a Potential Oncogene in Promoting Cancer Cell Migration and Invasion through Regulating AP-1 and PKC dependent-Ezrin Activation

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Introduction

Desmoglein 3 (Dsg3) is an adhesion protein in desmosomes that confer strong cell-cell adhesion in epithelia. It is best known as the autoantigen of pemphigus vulgaris, a life threatening blistering disease, caused by autoantibodies targeting Dsg3 which lead to the loss of cell cohesion in the skin and oral mucosa. However, the upregulation of Dsg3 in cancers has been reported recently though the mechanism remains poorly defined. The actin-binding protein Ezrin is an important regulator of membrane cytoskeleton, whereas AP-1 is a dimeric transcription factor composed of proteins including c-Jun/c-Fos. Both Ezrin and AP-1 are implicated in cancers, especially in the invasive phenotype, and can be activated by Protein kinase C (PKC) and Rho kinase (ROCK). The aim of this study was to investigate the hypothesis that Dsg3 plays a role in regulating Ezrin and AP-1 that could be attributed to cancer cell migration and invasion.

Results

Figure 1. Dsg3 colocalises and is physically associated with Ezrin at the plasma membrane.

Figure 2. Dsg3 silencing affects colocalisation of Ezrin with F-actin and CD44 at the plasma membrane.

Figure 3. Overexpression of Dsg3 enhances Ezrin phosphorylation at T567 (activates Ezrin).

Figure 4. Overexpression of Dsg3 activates Ezrin-T567 that could be abrogated by the PKC and ROCK inhibitions.

Figure 5. Overexpression of Dsg3 enhances phosphorylation of c-Jun S63 and activates the AP-1 transcriptional activity.

Figure 6. Overexpression of Dsg3 in cancer cell lines induces membrane protrusion and promotes cell migration and invasion.

Summary and Conclusion

- Dsg3 associates with Ezrin at the plasma membrane and regulates its activity through T567 phosphorylation.
- The Dsg3 mediated Ezrin activation can be abrogated by PKC inhibition, as well as by several other inhibitors, suggesting it is at least PKC-dependent.
- Our data from this study as well as others suggest that Dsg3 acts as a key regulator for several signal pathways that are essential for the actin-based membrane morphology and cell migration and invasion.

Publications: