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Function of Thrombomodulin in Epithelial Cell Shape Changes and Differentiation of Human HaCaT Keratinocytes

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Thrombomodulin (TM) exhibits a range of physiologically important anti-inflammatory, anti-coagulant, and anti-fibrinolytic properties. TM has been detected in the spinous layer of epidermal keratinocytes although the role of TM in epidermis is still under investigation. In this present study, we showed that downregulation of TM delayed the epithelial differentition, while the control cells presented closely normal epidermal morphology by using organotypic skin cultures constructed from HaCaT cells. A shape change appeared in the TM depletion HaCaT cells, wherein they exhibited a more fibroblastic-like morphology with broad lamellipodia which diverged from the epithelial shape of the wild type cells. We observed the redistribution of E-cadherin from the membrane to the cytoplasm but did not affect E-cadherin abundance in TM-knockdown cells. Proteomic analysis identified the interacting partners of TM included α- and β-tubulin, actin and intersectin 1. Since intersectin plays roles in regulation the formation of clathrin-coated endocytotic vesicles and in the regulation of actin assembly. Our data showed that endocytosis of E-cadherin by depletion of TM would result in disruption of cell-cell contacts. This interplay between TM and intersectin components provides an important mechanism for dynamic regulation of E-cadherin in cell morphology.