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Thrombomodulin (TM) is a type I transmembrane glycoprotein that was formerly identified as an anticoagulant factor in endothelial cells (ECs) in 1982. It can form a complex with thrombin to facilitate the activation of protein C in the blood circulation. The activated protein C will catalyze the cleavage and inactivation of coagulation factors to constrain the blood coagulation cascade. However, TM was also identified in various cell types which do not have direct contact with blood circulation, indicating that TM may have distinct biological functions in different cell types and contexts. In our studies we demonstrated that TM was highly concentrated at the cell-cell contact region in ECs and keratinocytes, where it functions as an adhesion protein, in conjunction with cadherin/occludin, to stabilize cell-cell junctions. Moreover, we also demonstrated that lectin domain of TM is essential for cell-cell adhesion and LeYoligo-saccharide is the ligand of the lectin domain. The cytoplasmic domain of TM can be anchored to F-actin through actin linker protein ezrin. In addition, TM expression is involved in the epithelial/mesenchymal transition in cancer cells. On the other hands, we demonstrated that TM functions as a novel plasminogen (Plg) receptor in migrating cells. The dissociation constant of Plg and TM is about 10-7M as determined by Biacore plasma resonance system. TM, plg and urokinasePlg activator was colocalized at the leading edges in the migrating ECs. It is possible that TM expression can promote Plg activation to facilitate the pericellularproteilysis in front of migrating ECs to facilitate cell migration, invasion and angiogenesis. Keywords: Thrombomodulin, cell-cell adhesion, angiogenesis, inflammation, vascular disease, and wound healing

Because thrombin can affect wound healing by stimulating the proliferation of keratinocytes and fibroblasts, 16 we hypothesized that thrombomodulin can regulate re-epithelialization and / or deposition of collagen during skin wound healing. In a previous study, we investigated the effects of increased keratinocyte thrombomodulin activity on wound healing in transgenic mice that express human thrombomodulin under the direction of a keratinocyte promoter. 14 These mice, which exhibited up to 300% of normal thrombomodulin activity in the epidermis, exhibited normal re-epithelialization of the wound but presented evidence of altered collagen deposition during skin healing. 14 The objectives of the present study were to determine whether the expression of thrombomodulin is regulated during skin healing in humans and mice, and to determine whether wound healing is changed in mice deficient in thrombomodulin. Because mice with a total absence of thrombomodulin do not survive the embryonic period 17, we chose to compare wound healing in wild type mice and three groups of mice, generated by homologous recombination, which have a moderate deficit or severe in thrombomodulin. Our results demonstrate that the expression of thrombomodulin in keratinocytes during skin healing is similarly regulated in humans and mice, but that the deficiency of anticoagulant activity of thrombomodulin does not affect the reepithelialization of skin wounds .

To determine whether expression of thrombomodulin is regulated during cutaneous wound healing in mice, we examined full-thickness wounds in wild-type (TM+/+) mice. Compared to human epidermis, the epidermis of unwounded mouse skin was less stratified, and epider- mal staining for thrombomodulin was much less promi-nent. On day 3 of healing, strong staining for thrombomodulin was observed in keratinocytes within the stratifying neoepidermis. No staining for thrombomodulin was detected in keratinocytes in the marginal layer of the neoepidermis, which interacts directly with the provisional wound matrix. This pattern of thrombomodulin expression was similar to that observed in human partial-thickness wounds after 5 days of healing, except that expression of thrombomodulin by keratinocytes within the interior of the neoepidermis was even more exuberant in mouse wounds than in human wounds. On day 7 of healing of mouse wounds, a highly stratified, thrombomodulin-positive neoepidermis extended over most of the wound matrix. On day 30, mouse wounds were completely reepithelialized, with some residual hyperkeratinization and a more prominent thrombomodulin staining pattern than that seen in unwounded mouse skin. Thus, although thrombomodulin is expressed only weakly in unwounded mouse epidermis, its expression in keratinocytes is markedly up-regulated during cutaneous wound healing.

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