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Crosstalk Between Intraepithelial γδ T Cells and Their Neighbors

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Intraepithelial γδ T cells play unique roles in homeostasis, tissue repair, inflammation and protection from malignancy. Antigens that activate these T cells are not well defined and they do not express classic costimulatory or coreceptor molecules. We have used molecular, biochemical and functional approaches to define molecules that activate the functions of intraepithelial γδ T cells. In murine skin γδ T cells express an invariant γδ T cell receptor that recognizes an unknown antigen expressed by damaged or malignant keratinocytes. We have produced soluble γδ T cell receptor molecules to use as a tool to detect expression and facilitate isolation and characterization of this unidentified antigen. Using this reagent we have identified antigen-bearing keratinocytes in wound sites. We have also identified several molecules expressed by skin and intestinal γδ T cells or epithelial cells that provide important signals for activation of γδ T cells. One molecule, JAML, is uniquely costimulatory for epithelial γδ T cells. Structural studies suggest a novel signaling model for intraepithelial γδ T cell activation. We have also found that the semaphorin Sema4D (CD100) is expressed by skin and intestinal γδ T cells upon activation. CD100 binds to the semaphorin receptor Plexin-B2 expressed on epithelial cells. Interactions between CD100 and Plexin-B2 deliver key signals to both the T cells and epithelial cells in the skin and intestine that regulate cell morphology and function. In the absence of CD100-mediated signals there is increased damage and delayed repair in skin wound healing and in a model of colitis. Together we have identified several molecules that are key regulators of intraepithelial γδ T cell recognition of damaged epithelial cells leading to activation and participation in local immune responses including tissue homeostasis and repair.

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