

Molecules regulating the immunosurveillance of tissues

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Abstract

Very many of the body's T cells are not conventionally MHC-peptide restricted, but often compose oligoclonal repertoires constitutively associated with tissues. It was proposed 20 years ago that these cells may respond rapidly to generic molecular markers of tissue dysregulation, and consistent with this, we have now shown that epidermal gamma delta T cells quickly respond to the upregulated expression in keratinocytes of a single stress-associated MHC-related molecule, *Rae-1*, and that this leads to a several downstream events including an unanticipated tissue infiltration by NKT cells. The functional orthologues of *Rae-1* in humans include the *MICA* gene that is strongly implicated in the regulation of human responses to viral infection, inflammation, and to malignant transformation. Indeed, *MICA* is a highly polymorphic gene, with >50 alleles described. The finding that skin-associated T cells respond to *Rae-1* upregulation suggests they may play a pivotal role in immunosurveillance, upstream of DC or other cells. Current studies aim to define the consequences of this T cell driven immunosurveillance under different circumstances.

The early activation of *Rae-1* is a common characteristic of skin carcinogenesis that we have shown to be limited by the action of skin-associated gamma delta T cells, but only of the "wild type" / "canonical" repertoire. How specific repertoires of tissue-associated T cells form has long been a matter of speculation, but we recently helped identify a novel gene, *Skint-1*, that is the prototypic member of a novel family of immunoglobulin (Ig)-like genes that are specifically expressed in skin and thymus epithelium. The mechanism-of-action and the regulation of the *Skint* genes is under investigation, with its potential to cast light on epithelial-T cell interactions. We are also studying the immunological roles of the closest sequence-homologs to *Skint-1*, namely the *Btnl* genes that also encode Ig superfamily molecules expressed by epithelial cells, but specifically in the gut rather than the skin. The gut is a key area of immunosurveillance, where we remain largely ignorant of immune interactions of epithelial cells. In sum, we wish to use animal models and biochemical and molecular techniques to better define the molecular basis and implications of epithelial-T cell cross-talk mediated by *Skint*, *Btnl*, and other related molecules. We have also commenced clinical translation of lessons learned to immunotherapy of carcinomas.

References

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