GENETICS AND GENODERMATOSES

DSRNA SENSING INDUCES LOSS OF CELL IDENTITY

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Introduction: How cell and tissue identity persist despite constant cell turnover is an important biologic question with cell therapy implications. Skin epithelium is constituted by heterogeneous keratinocytes in different body areas. The transcriptome of in vivo palmoplantar epidermis is globally unique including Keratin 9 (KRT9). While volar fibroblasts have the capacity to induce KRT9 in non-volar keratinocytes. If cells retain positional identity, can a single corrected clone be used for expanding and grafting back onto the skin and across the body? Will epidermal-dermal interactions dictate the cell's fate? The study of positional identity in tissues is important from many perspectives.

Objective: While many mechanisms exist, we investigated the controls for site-specific gene expression in skin given its diverse structures and functions.

Materials and Methods: We used volar (palmo-plantar) skin identity as a model system to understand how tissue identity is controlled.

Results: We demonstrate that volar keratinocytes continue to express KRT9 in vitro solo-cultures. Despite this, KRT9 expression is lost with volar keratinocyte passaging, in spite of stable hypo-methylation of its promoter. Coincident with KRT9 loss is a gain of the primitive Keratin 7 and a signature of dsRNA sensing, including the dsRNA receptor DDX58. Exogenous dsRNA inhibits KRT9 expression in early passage volar keratinocytes or in vivo footpads of wild-type mice. Loss of DDX58 in passaged volar keratinocytes rescues KRT9 and inhibits KRT7 expression. Additionally, DDX58 null mice are resistant to the ability of dsRNA to inhibit KRT9 expression.

Conclusions: we have shown that keratinocytes retain positional memory, but also receive important input from fibroblasts in controlling site-specific KRT9 expression. We also demonstrate for the first time that dsRNA sensing by the DDX58 receptor inhibits positional memory with passaging. This work has implications for both future human cellular trials and basic studies of nonimmune roles of dsRNA sensing.