Dissecting epigenetic effects of Polycomb-group proteins in epidermal self-renewal and differentiation

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Polycomb group proteins (PcG) are evolutionarily conserved epigenetic modifiers that are important for epidermal homeostasis, development, and cancer pathogenesis. These proteins play a central role in gene silencing by bringing gene loci to inactive chromatin states.

Although most Polycomb knockout phenotypes have been explained the role of these proteins in epidermal differentiation is still insufficiently understood. Importantly, epidermal knockout studies cannot isolate complex biological transformations between different strata of interfollicular epidermis i.e. the patches of skin located between hair follicles.

In this in vivo study conducted in collaboration with the Icahn School of Medicine at Mount Sinai (USA), we used a mouse model to examine the molecular mechanisms of stem cell differentiation governed by Polycomb proteins. Interfollicular epidermis contains several cell layers including the important basal stem cell layer and the immediate progenitor layer of suprabasal keratinocytes. We focused on PRC1 and PRC2 (Polycomb repressive complex 1 & 2), the most important members of the Polycomb group.

By comparing the global gene expression with histone modification marks left by Polycomb proteins in the basal and suprabasal layers, we identified differentially expressed targets of PRC1 and PRC2. We then merged these results with knockout gene expression data to find out which genes involved in epidermal differentiation were also controlled by Polycomb proteins.

Our analysis demonstrates that PRCs are essential for many important aspects of cell differentiation such as cell motility (Tns3, Fscn1), proliferation (Cspg4), cell attachment

(Lamb1), and epidermal barrier formation (Elovl4). It appears that PRC1 and PRC2 mostly work together, and that the relative contribution of Polycomb proteins is gene-specific.

Additionally, we have found that both Polycomb proteins participate in the silencing of a known tumor suppressor gene Sox7. This gene has been featured in many recent studies; it governs cell death, growth, and apoptosis. Therefore, the results of our study may find applications in the diagnostics and treatment of skin-related cancers.