The making of animal coats 皮毛之道

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IN nature, animal integuments undergo a lot of wear and tear. As a result, there is need for constant renewal and regeneration. Different ectodermal organs evolve different modes of regeneration, either by continual renewal or episodic regeneration. We try to decipher the fundamental principles governing the development and regeneration of integument organs. We hope to apply what we learn from regenerative biology to tissue engineering and regenerative medicine.

We develop further the concept of 1) environmental regulation of stem cell activities and 2) topobiological arrangement of stem cells and organ shape. We propose that throughout the duration of an organism's life, skin appendage stem cells are modulated by a combination of micro-environmental factors and macro-environmental factors to regulate its regenerative cycles, and to shape its morphology. Micro-environmental factors are defined here as compartments in the follicle (ie. hair bulge niche, dermal papilla). Macro-environmental factors are defined here as environments outside of the follicle (ie. surrounding dermis, neighboring follicles, systemic hormones, external environment).

We use feather morphogenesis to illustrate micro-environmental regulation of stem cell topology. We show feather stem cells are configured in a ring shape at the bottom of the follicle. We demonstrate that topobiological arrangements of stem cells, TA cell and differentiated cells are key to the symmetry of feather branches. By modulating the activity ratio of morphogenesis related molecules (BMP, Wnt 3a, etc) in different time of growth phase, different feather morphology are shaped along the proximal distal axis of feather shaft (rachis). The environments are controlled by the dermal papilla. We also show how stem cells are patterned during feather induction. The beta catenin positive, homogeneous stem cells in the feather field (basal states) are organized into hexagonally-arranged placodes (state A) and inter-bud space (state B). We explore the role of a Turing reaction-diffusion mechanism in establishing chemical patterns, and the roles of mesenchymal condensation in consolidation of cellular pattern.

We use regenerative hair wave to illustrate macro-environmental regulation. It has been known that a single hair follicle go through regenerative hair cycling continuously during the adult life, but whether the thousands of hair follicles on one individual cycle randomly, simultaneously, or in coordination is not known. In mice with different "hair styles" (cyclic alopecia), patches form because hair regeneration propagates in waves and boundaries form because there are refractory regions where the wave can not pass through. We show there is oscillation of intra-follicular Wnt signaling which is synchronous with hair cycling, and there is oscillation of dermal Bmp signaling which is asynchronous with hair cycling. The interactions of these two rhythms lead to the recognition of refractory and competent phases in the telogen, and autonomous and propagating phases in the anagen. Boundaries form when propagating anagen waves reach follicles which are in refractory telogen. Further, we found hair waves are reset during pregnancy, implying a systemic level of regulation. The unexpected links with *Bmp2* expression in subcutaneous adipocytes give implications in system biology and Evo-Devo. The work also has practical significance for alopecia study and those using the mouse skin as a model for carcinogenesis study, drug delivery, and stem cell research.

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