CDB SEMINAR

Cheng-Ming Chuong

Department of Pathology, Univ. Southern California

Monday, May 12, 2008

16:00~17:00 C1F CDB Auditorium

Macro- and Micro- environmental regulation of ectodermal organ stem cells

Here we further develop the concept of environmental regulation of stem cell activities. We propose that throughout the duration of an organism's life, skin appendage stem cells are modulated by a combination of micro-environmental 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**. 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 consolidating the 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. Starting from mice with different "hair styles" (cyclic alopecia), we did year long follow up to show that the hair cycle domains are a manifestation of regenerative hair waves. These domains form because hair regeneration propagates in waves; boundaries form because there are refractory regions where the wave can not pass through. By analyzing the dynamics of hair growth, time required for regeneration after plucking, *in situ* hybridization and reporter activity, we showed 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 those using the mouse skin as a model for carcinogenesis study, drug delivery or stem cell research.

References

Yu, M., Wu, P., Widlitz, R.B., and Chuong, C.-M. 2002. The Morphogenesis of feathers. *Nature* 420:308-312.
Yue, Z., Jiang, T.-X., Widelitz. R. B., and Chuong, CM. 2005. Mapping stem cell activities in the feather follicle. *Nature*, 438:1026-1029.
Plikus MV, Mayer JA, de la Cruz D, Baker RE, Maini PK, Maxson R and Chuong CM. 2008. Cyclic dermal BMP signaling regulates stem cell activation during hair regeneration. *Nature*. 451:340-344.
Maini, PK, Baker, RE, Chuong, CM., 2006. The Turing model comes of molecular age. *Science.* 314: 1397-1398.

Host:
Masatoshi Takeichi
Cell Adhesion and Tissue Patterning, CDB
takeichi@cdb.riken.jp
Tel:078-306-3116 (ext:1321)