The Role of Epidermal Stem Cells in the Origin of Basal Cell Carcinoma

FR - El papel de las células madre epidérmicas en el desarrollo del carcinoma basocelular

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The epidermis and its appendages are host to different types of stem cells (SCs). The interfollicular dermis contains progenitor cells that proliferate and give rise to layers of stratified epithelium and form the skin barrier. The epithelium of the sebaceous glands is also continuously renewed during the hemostasis process in adults. The hair cycle, however, is characterized by alternating phases of growth and degeneration. In hair follicles, SCs are therefore only required at certain times, whereas the sweat glands are in a quiescent state in normal conditions. The SCs of different compartments express specific markers, and so techniques such as lineage tracing can be used to specifically label the cells of interest and assess their growth over time. Basal cell carcinoma (BCC) is a tumor with locally invasive growth that is associated with activation of the Hedgehog (Hh) pathway. The Hh-activated (PTCH) and Smoothened (SMO) receptors participate in the pathway and activation of these receptors promoting expression of genes implicated in carcinogenesis. For a long time, it was postulated that bulge cells originated in the hair follicle.

Investigators of Cédric Blanpain’s group, at the Brussels Free University, have used a murine model of BCC based on SMO activation to investigate the capacity of SCs of different compartments to give rise to this tumor. In their experiments, they used genetically modified mice (conditional knockin using the CREER-LoxP system), with the SmoM2 gene. CREER refers to the Cre-recombinase estrogen receptor. Administration of tamoxifen induces Cre recombination, with the subsequent activation of the SmoM2 oncogene, which turn activates the Hh pathway. Association of CREER/SmoM2 with a SC-specific marker in each compartment enables selective overexpression of the SmoM2 oncogene in the different types of epidermal SCs, thereby permitting study of which cells are responsible for onset of BCC. The investigators used K14-CREER/SmoM2 mice (administration of tamoxifen induces activation of the Hh pathway in most cells of the basal layer of the...
epidermis), Shh-CREER/SmoM2 (activation of the Hh pathway transit-amplifying cells of the hair follicle), K15 and K19-CREER/SmoM2 (activation of the Hh pathway in bulge cells), thereby demonstrating that activation of SmoM2 in the bulge or transit-amplifying cells of the hair follicle does not induce formation of BCC. Clonal analysis (which allows labelling of a certain number of cells of interest and real-time measurement) has shown that 90% of surface BCCs originate from SCs residing in the interfollicular epidermis, whereas the remaining BCCs originate in the infundibulum. Moreover, the transcription profile for adult interfollicular epidermal cells that overexpress SmoM2 has demonstrated that, before giving rise to invasive BCC, the tumor initiating cells are reprogrammed and resemble the profile of the progenitor cells of the hair follicle. Thus, the gradual expression of hair follicle markers by cells of the interfollicular epidermis that overexpress the oncogene and that progress to BCC shows that expression of markers can give rise to a false interpretation of the origin of BCC. These results contradict those published by investigators of Ervin Epstein’s group in the United States, who used heterozygotic mice for the PTCH receptor and found that BCC originated mainly in the SCs residing in the bulge region of the hair follicle.

References