E4F1 connects the Bmi1-ARF-p53 pathway to epidermal stem cell-dependent skin homeostasis.

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Skin homeostasis relies on epidermal stem cells (ESC) that are mobilized from their niche located in the basal layer of the interfollicular epithelium (IFE) and the bulge of hair follicles (HF) to fuel highly proliferative transit amplifying compartments (TAC). Differentiation programs then generate the spinous, granular, and cornified layers of the IFE or the different lineages of the mature HF.

E4F1 KO skin defects result from cell autonomous perturbations in resident stem cells. Hence, various ESC markers were strongly downregulated in E4F1 KO epidermis [α6high/CD34+, K15+, BrdU Long-term Retaining Cells (LRC)] and E4F1 KO keratinocytes exhibited a dramatically impaired clonogenic potential ex vivo. These defects correlated with deregulated expression of the Ink4a/Arf locus in ESC clones and accordingly, E4F1 KO skin phenotypes were delayed in mice with Ink4a/Arf and E4F1 compound gene deficiencies. Inactivation of the Ink4a/Arf locus or ectopic expression of the Ink4a/Arf locus transcriptional repressor Bmi1 or depletion of its downstream target, p53, partly rescued the ex vivo clonogenic potential of E4F1 KO ESC.

These results reveal a new regulatory network involved in ESC maintenance and proper skin homeostasis, implicating E4F1, Bmi1, the Ink4a/Arf locus and p53.

However, several questions remain unanswered. For instance, why are skin defects only developing after birth, althoughCre-mediated recombination of E4F1 occurs much earlier during embryonic development? Among many possible scenarios, Bmi1 and its downstream effectors might impact on ESC maintenance only at post-natal stages, as already suggested for hematopoietic stem cells (HSC). Interestingly, E4F1 has been previously shown to interfere with this HSC program. However, in this case, the shRNA-mediated depletion of E4F1 rescues Bmi1 KO HSC exhaustion, suggesting that the role of the E4F1-Bmi1 axis in stem cells maintenance differs from one tissue to another. Moreover, while the E4F1-Bmi1 genetic interaction identified in HSC was claimed to be independent of p53, we found that p53 is clearly involved in E4F1 KO ESC phenotypes. The later observation raises queries about the exact function of the E4F1-Bmi1-Ink4a/Arf-p53 network in stem cells homeostasis. In ESC, this pathway might play its usual "gate-keeper" function in response to genotoxic or developmental stresses, but it might also directly regulate normal programs of ESC self-renewal, as suggested in mammary gland progenitors where p53 impacts on asymmetric cell divisions.

Finally, given the multiple roles of E4F1, it will be necessary to evaluate the relative importance of E4F1-associated transcriptional and E3-ligase activities in ESC functions. Ongoing studies should clarify these points.

References


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Figure 1. E4F1, through its connection with the Bmi1-ARF-p53 axis, regulates epidermal stem cell (ESC) maintenance. Constant renewal of the Interfollicular Epithelium (IFE) and of Hair Follicles (HF) relies on the recruitment of epidermal stem cells (ESC) located in the basal layer of IFE and in the bulge region of HF, respectively. ESC fuel the highly proliferative transit amplifying compartments (TaC) in the basal layer of IFE and in the bulb of HF. TaC cells then embark on differentiation programs to generate the spinous, granular and cornified layers in IFE or the different lineages of mature HF. E4F1 inactivation in the entire skin or in the basal compartment of the epidermis induces skin homeostasis defects that result from cell autonomous alterations in ESC maintenance. These ESC defects are partially restored upon inactivation of the Bmi-Arf-Mdm2-p53 pathway, several components (p53, Bmi1 and Arf) of which have been described to physically and functionally interact with E4F1.\textsuperscript{1,4}