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Mouse Models for Epsin Function

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The vertebrate skin is a barrier-forming organ in which keratinocytes form a highly organized, stratified epithelium protecting the organism from the outside environment. One of the major regulators of this structure is Notch signaling. Notch is a transmembrane receptor interacting with ligands expressed on the surface of neighboring keratinocytes. Keratinocyte-specific deletion of Notch signaling pathway impairs epidermal differentiation, resulting in skin-barrier defects and skin carcinogenesis. Our laboratory, by a genetic approach in mice, demonstrates that combined inactivation of Epsin1 and Epsin2 genes leads to embryonic lethality around E9.5-10. The phenotype of Epn1;Epn2 double knockout is characterized by a subversion of the three main developmental programs active at this developmental stage, i.e., cardiovascular development, somitogenesis, and neural tube differentiation. Collectively, these morphological alterations resemble the developmental defects observed in mutants of Notch genes or in genes essential for the activation of the Notch signaling pathway, suggesting a crucial role of Epsin in enabling Notch signaling during embryogenesis. Intriguingly, the apparently healthy Epn1+/-;Epn2-/- shows an high incidence of squamous papillomas on their skin. Furthermore, expression of another epsin family member originally localized exclusively to surface epithelia, Epsin3, dramatically increases in the hyperplastic lesions of the three-allele mutants and in human basal carcinomas. In order to get further insight on Epn3 function we performed morphological expression analyses during mouse development. In contrast with initial reports, both in embryos and adults, we could detect various levels of Epn3 expression in several tissues, i.e., surface epithelia, neural tissue and heart. Moreover, in vitro studies performed on human keratinocytes in culture show a prominent role of this Epsin in the regulation of Notch signaling in this cell compartment.

Keywords: endocytosis, mouse models, Notch signaling, skin