INFLAMMATION

Linear relationships

The protein p120 is a conserved member of the Armadillo-repeat family of catenins. Although its roles in regulating adherens-junction stability and the activities of small Rho-family GTPases have been studied *in vitro*, the physiological importance of this protein *in vivo* has remained unclear. Perez-Moreno *et al.* now provide important insights into the function of p120 by showing that it mediates inflammatory responses in the skin.

In an attempt to investigate the role of p120 *in vivo*, the authors generated *p120* conditional-skin knockout mice (cKO). To their surprise, they found that even though the cKO epidermis showed reduced levels of intercellular adherens-junction components this was not accompanied by a disruption of epidermal integrity and barrier function. With ageing, cKO mice had classic features of chronic subcutaneous inflammation, including hair disintegration, muscle wasting, hyperplasia and enhanced vasculature — phenotypic abnormalities that distinguished them from their wild-type counterparts.

To explore whether the observed hyperplasia and hair-loss phenotypes were a cause or a consequence of the associated inflammatory skin disease, the authors carried out skin-graft experiments on immunocompromised nude mice. They treated animals with dexamethasone — a potent immunosuppressant — and were able to, in fact, identify a causal role for inflammation in hair loss and hyperproliferation, in a way that seemed to be independent of intercellular adhesion. As dexamethasone treatment exerts its effects partly by inactivating nuclear factor-κB (NF-κB) signalling, the authors evaluated the status of NF-κB activity in both cKO skin and keratinocytes. The overall NF-κB protein levels were similar in wild-type and *p120*-null epidermis, but in *p120*-null epidermis there was a sustained activation of NF-κB activity, which was accompanied by increased levels of downstream targets of this pathway including several inflammatory cytokines.

But how does the loss of p120 lead to NF-κB activation? Given p120's previously postulated role in the regulation of small GTPases, the authors investigated whether the activity of Rho might be altered in the absence of p120. Indeed, in the absence of p120, RhoA activity was enhanced and was associated not only with altered cytoskeletal–membrane dynamics, but also with NF-κB activation. The authors proposed a model in which p120 functions upstream of RhoA activation, which is upstream of NF-κB activation, which, in turn, regulates the expression of several cytokines resulting in an inflammatory skin disease.

These findings provide new insights into why reductions in p120 have been associated with epithelial hyperproliferation and tumorigenesis, and they open new avenues for exploring the relationship between intercellular adhesion molecules, small GTPases and inflammatory events that are a hallmark of several human skin disorders.

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ORIGINAL RESEARCH PAPER Perez-Moreno, M. *et al.* p120-catenin mediates inflammatory responses in the skin. *Cell* **124**, 631–644 (2006)
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