Abstract

The inhibitor of κB kinase 2 (IKK2) is the main catalytic subunit of the IκB kinase (IKK) complex that is required for nuclear factor κB (NF-κB) activation in response to various stress-associated stimuli such as pathogen associated molecular patterns (PAMPs), inflammatory cytokines and UV-light.

The importance of NF-κB in maintaining skin homeostasis is witnessed by the paradox that NF-κB overactivity as well as the ablation of NF-κB regulators like IKK2 and NEMO can cause skin inflammation. However, epidermis-restricted ablation of the NF-κB family member p65 is not sufficient to cause skin inflammation, raising the possiblity that loss of p65 is compensated by other NF-κB subunits. In addition, the long-time supposed growth inhibitory role for IKK/NF-κB in keratinocytes is still debated. In this study we investigated mice expressing constitutively active IKK2 (NF-κB), the main kinase inducing canonical NF-κB activation, specifically in epidermal keratinocytes. We also generated mice with combined epidermis-specific deletion of the different NF-κB family members in order to dissect the potential redundancy between the different NF-κB family subunits.

The results presented in this project show firstly that balanced activation of IKK2/NF-κB in epidermal keratinocytes is essential for both embryonic skin development and maintaining hair follicle homeostasis after completion of the first hair cycle. In addition, my results uncover both redundant and non-redundant functions of the different NF-κB members in regard to different aspects of skin homeostasis. Mice with epidermis-specific ablation of the different NF-κB transcriptionfactors were crossed to mice expressing constitutively active IKK2 (IKK2ca) to dissect the downstream effectors of IKK2ca. Remarkably, only p65 haploinsuffiency is able to prevent the perinatal death of IKK2ca expressing mice, indicating that NF-κB dimers containing p65/RelA mediate of IKK2ca effects on skin embryonic development. Moreover, further crossing experiments revealed that NF-κB dimers containing c-Rel are responsible for hair follicle degeneration following constitutive IKK2 activation. In contrast, regarding the role of IKK2/ NF-κB signaling in the regulation of immune homeostasis, we provide genetic evidence of the redundant functions of the p65 and c-Rel NF-κB family members. Mice lacking both NF-κB subunits p65 and c-Rel in the epidermis phenocopy the severe skin inflammation leading to death seen in mice with epidermis-specific deletion of IKK2. In conclusion, the results presented in this thesis identify distinct roles of specific NF-kB subunits p65/RelA and c-Rel in keratinocytes to assure intrafollicullar epidermis and skin appendages morphogenesis, contrasting with their functional redundancy downstream of the IKK complex to prevent the development of skin inflammation.