c-Rel in Epidermal Homeostasis: A Spotlight on c-Rel in Cell Cycle Regulation

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To maintain proper skin barrier function, epidermal homeostasis requires a subtly governed balance of proliferating and differentiating keratinocytes. While differentiation takes place in the suprabasal layers, proliferation, including mitosis, is usually restricted to the basal layer. Only recently identified as an important regulator of epidermal homeostasis, c-Rel, an NF-κB transcription factor subunit, affects the viability and proliferation of epidermal keratinocytes. In human keratinocytes, decreased expression of c-Rel causes a plethora of dysregulated cellular functions including impaired cell viability, increased apoptosis, and abnormalities during mitosis and cell cycle regulation. On the other hand, c-Rel shows aberrant expression in many epidermal tumors. Here, in the context of its role in different cell types and compared with other NF-κB subunits, we discuss the putative function of c-Rel as a regulator of epidermal homeostasis and mitotic progression. In addition, implications for disease pathophysiology with perturbed c-Rel function and abnormal homeostasis, such as epidermal carcinogenesis, will be discussed.

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INTRODUCTION

The turnover of the mammalian epidermis involves many precisely tuned cellular processes, which collectively provide the mechanistic basis for the protective barrier function against various environmental threats such as microbes or UV light. Within the healthy, multilayered epidermis, keratinocyte proliferation is restricted to the innermost basal layer; next, there are various stages of differentiation in the suprabasal layers, finally producing the outermost water-impermeable stratum corneum. Maintenance of this steady-state status, commonly termed *epidermal homeostasis,* requires a delicate balance of proliferating and differentiating keratinocytes (Blanpain and Fuchs, 2009).

Multiple transcription factors are involved in the regulation of epidermal homeostasis and differentiation, including the p53 protein family member p63, the NF-κB signaling pathway, the activator protein 1 and activator protein 2 transcription factor family, Notch, Krüppel-like factor 4, grainyhead-like 3, and the more recently identified basic leucine zipper transcription factors MAF and MAFB (Angel et al., 2001; Blanpain and Fuchs, 2009; Chalmers et al., 2006; Koster et al., 2004; Lopez-Pajares et al., 2015; Okuyama et al., 2004; Segre et al., 1999; Seitz et al., 1998; Wang et al., 2008). Proper interaction and crosstalk among each other, but also activation or inhibition of downstream targets, is crucial for the coordination of homeostasis.

The five NF-κB transcription factor family members, p50, p52, p65 (RelA), RelB, and c-Rel, form different homo- or heterodimer complexes. Inactive NF-κB dimers are largely restricted to the cytoplasm through binding to inhibitor of κB proteins. Upon activation by inhibitor of κB kinase (IKK) proteins, they translocate into the nucleus, where they specifically activate their target genes. In principle, two types of signaling can induce NF-κB activity: the canonical pathway, on one hand, is initiated through stimuli such as tumor necrosis factor (TNF) α or lipopolysaccharide, which activate a trimeric IKK complex (IKKα, IKKβ, and IKKγ) and, consequently, initiate inhibitor of κB α degradation. This process results in the release of the p65/p50 and c-Rel/p50 dimers (Xia et al., 2014).

The noncanonical pathway, on the other hand, can be induced by different stimuli (e.g., CD40, lymphotoxin-β), involves IKKα, and leads to activation of p52/RelB dimers (Razani et al., 2011). In addition to these classic NF-κB signaling pathways, c-Rel activation can also occur through yet another mechanism, which leads to its direct phosphorylation by IKKε and TANK-binding kinase 1 (Harris et al., 2006).

Although the concept of NF-κB being involved in epidermal homeostasis is not new, only the two most prominent of the five NF-κB subunits, p50 and p65, have been initially implicated in epidermal growth regulation (Seitz et al., 1998; Sur et al., 2008; van Hogerlinden et al., 1999). In particular, overexpression of these subunits in keratinocytes resulted in growth inhibition, whereas inactivation led to growth promotion (Table 1) (Seitz et al., 1998; van Hogerlinden et al., 1999; Zhang et al., 2004). In contrast, only limited data exist for the p52 and RelB subunits. Whereas RelB appears to be expressed in the epidermis (Hinata et al., 2003; Takao et al., 2003), there is conflicting data on p52 expression. Although some researchers could not detect p52 in human skin by immunohistochemistry or p52 messenger RNA in keratinocytes (Takao et al., 2003), others showed p52 protein expression in primary human keratinocytes (Hinata et al., 2003). Although the skin has not been the primary focus when *p52*$^{-/-}$ mice were studied, these animals showed no overt epidermal defects (Franzoso et al., 1998). In contrast, murine *RelB*$^{-/-}$ mutants showed a strong

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Abbreviations: CDK, cyclin-dependent kinase; IKK, inhibitor of κB kinase; MCC, mitotic checkpoint complex; SAC, spindle assembly checkpoint; TNF, tumor necrosis factor

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Table 1. NF-κB mouse mutants and their epidermal phenotypes

NF-κB protein	Mutant Mouse Type	Epidermal Phenotype
p50	*K14-p50/K5-p50* mice overexpression	Growth inhibition (Seitz et al., 1998, van Hogerlinden et al., 1999)
p65/RelA	$p65^{-/-}$ embryonic skin transplanted on *scid/scid* mice	Growth promotion, TNFR1 and JNK-dependent (Zhang et al., 2004)
	K14-$p65^{-/-}$ mice	Increased contact hypersensitivity response (Grinberg-Bleyer et al., 2015)
c-Rel	*c-*$Rel^{-/-}$ mice	Growth inhibition, reduced bleomycin-induced skin fibrosis (Fullard et al., 2013)
	K14—c-$Rel^{-/-}$ mice	Increased contact hypersensitivity response (Grinberg-Bleyer et al., 2015)
p65/RelA and c-Rel	$p65^{-/-}$ *c-*$Rel^{-/-}$ $TNF\alpha^{-/-}$ mice	Hypoproliferative epidermis, cell cycle-phase and colony-forming defects (Gugasyan et al., 2004)
	K14-$p65^{-/-}$ *c-*$Rel^{-/-}$ mice	Temporary dermatitis with psoriasiform lesions (Grinberg-Bleyer et al., 2015)
RelB	*RelB*$^{-/-}$ mice	Profound dermatitis, T-cell mediated (Barton et al., 2000)
p52	*p52*$^{-/-}$ mice	No epidermal phenotype (Franzoso et al., 1998)
IκBα	*K14-IκBα*M mice overexpression (p50 and p65/RelA inhibition)	Increased keratinocyte proliferation (Seitz et al., 1998)
	*K5-IκBα*M mice overexpression (p50 and p65/RelA inhibition)	Increased keratinocyte proliferation due to inflammation; SCC development (van Hogerlinden et al., 1999)
	IκBα$^{-/-}$ mice	Profound dermatitis, early postnatal death (Klement et al., 1996)

Abbreviations: JNK, c-Jun N-terminal kinase; SCC, squamous cell carcinoma; TNFR1, tumor necrosis factor receptor 1.

inflammatory response characterized as T-cell—dependent dermatitis (Barton et al., 2000), similar to upstream regulator IκBα-deficient mice that die a few days after birth (Table 1) (Klement et al., 1996). In this context, the emerging role of the fifth NF-κB subunit, c-Rel, now appears to provide an interesting twist and extension to the regulation of epidermal homeostasis by NF-κB (Fullard et al., 2013; Gugasyan et al., 2004; Lorenz et al., 2014).

We discuss this insight herein; other aspects of NF-κB and its upstream mediators in epidermal biology have been reviewed elsewhere (Pasparakis, 2012; Sur et al., 2008).

GENERAL FUNCTIONS OF THE c-Rel SUBUNIT OF NF-κB

The expression of c-Rel during mouse ontogenesis coincides with the development of hematopoietic organs (Carrasco et al., 1994). Accordingly, *c-*$rel^{-/-}$ mice showed B- and T-lymphocyte dysfunctions (Köntgen et al., 1995). It is thought that c-Rel is involved in the proliferation and apoptosis of B cells (Grumont et al., 1998; Tumang et al., 1998) and in the activation and proliferation of T cells (Liou et al., 1999). Specifically, the number of FoxP3-expressing regulatory T cells is reduced in *c-*$rel^{-/-}$ mice, suggesting a role of c-Rel in regulatory T-cell differentiation (Figure 1a) (Isomura et al., 2009; Ruan et al., 2009).

In addition, more recent investigations have found additional functions of c-Rel in other tissues, cell types, and physiological functions (Fullard et al., 2012), including cardiac hypertrophy and remodeling (Gaspar-Pereira et al., 2012), neuroprotection (Pizzi et al., 2005; Sarnico et al., 2008), long-term memory (Ahn et al., 2008; Levenson et al., 2004), and hepatocyte proliferation and healing responses (Figure 1a) (Gieling et al., 2010).

In murine epidermis, c-Rel messenger RNA is expressed shortly before birth at embryonic day E18.5 in the basal, spinous, and granular cell layers of the epidermis and in hair follicles (Gugasyan et al., 2004). Mice lacking both c-Rel and p65 in a TNFα-deficient background (*rela*$^{-/-}$ *c-*$rel^{-/-}$ *tnfα*$^{-/-}$) showed a hypoproliferative skin phenotype (Gugasyan et al., 2004). Furthermore, keratinocytes derived from these mice displayed defects in colony formation and a delay in G1/S phase progression without affecting expression of certain cell cycle regulators such as cyclins D1 and D2 or cyclin-dependent kinase (CDK) inhibitors p21 and p27 (Gugasyan et al., 2004). Another study directly examining epidermal structures in *c-*$rel^{-/-}$ mice showed reduced epidermal thickness and keratinocyte proliferation without overt alterations of differentiation (Fullard et al., 2013).

More recently, a role for c-Rel in the pathogenesis of inflammatory skin diseases has emerged. For instance, genome-wide studies identified the c-Rel gene within an important human psoriasis susceptibility locus (Chandran, 2013). In line with this notion, the c-Rel staining pattern in psoriatic skin is altered compared with that of normal skin (Table 1) (Fullard et al., 2013). Furthermore, keratin 14-promoter—driven *c-*$rel^{-/-}$ knockout mice showed increased ear swelling in a contact hypersensitivity model (Grinberg-Bleyer et al., 2015) and reduced bleomycin-induced skin fibrosis (Table 1) (Fullard et al., 2013). However, further studies are needed to elucidate the details of c-Rel regulation in inflammatory skin diseases.

NF-κB AND c-Rel IN CELL CYCLE REGULATION

The association of NF-κB with cell cycle regulation in murine fibroblasts was first reported more than two decades ago (Baldwin et al., 1991). Since then, many NF-κB target genes relevant for cell cycle regulation have been identified in various tissue types. Some of them, such as cyclin D1, are regulated by several or all NF-κB subunits (Guttridge et al., 1999; Ledoux and Perkins, 2014), whereas others, such as CDK2, which is activated by p65 in laryngeal squamous cell cancer, seem to be governed by particular subunits (Liu et al., 2011).

In addition, c-Rel was shown to affect cell cycle regulation and target gene expression in a tissue- and cell-type—specific manner: for example, c-Rel affects G1/S cell cycle transition of HeLa cells (Bash et al., 1997), and it regulates the DNA damage checkpoint protein claspin in osteosarcoma cells (Kenneth et al., 2010). Moreover, *c-*$rel^{-/-}$ hepatocytes show decreased mitotic transcriptional regulator FoxM1 activity after partial hepatectomy, thus further affecting the mitotic regulators cyclin B1 and Cdc25C (Gieling et al., 2010). These findings imply a role for c-Rel during G2/M phase in certain cell types. A direct function of any NF-κB protein in mitosis has not been shown yet. However, after treatment with

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