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Ectoderm-Targeted Overexpression of the Glucocorticoid Receptor Induces Hypohidrotic Ectodermal Dysplasia

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Hypohidrotic ectodermal dysplasia is a human syndrome defined by maldevelopment of one or more ectodermal-derived tissues, including the epidermis and cutaneous appendices, teeth, and exocrine glands. The molecular bases of this pathology converge in a dysfunction of the transcription factor nuclear factor of the κ-enhancer in B cells (NF-κB), which is essential to epithelial homeostasis and development. A number of mouse models bearing disruptions in NF-κB signaling have been reported to manifest defects in ectodermal derivatives. In ectoderm-targeted transgenic mice overexpressing the glucocorticoid receptor (GR) [keratin 5 (K5)-GR mice], the NF-κB activity is greatly decreased due to functional antagonism between GR and NF-κB. Here, we report that K5-GR mice exhibit multiple epithelial defects in hair follicle, tooth, and palate development. Additionally, these mice lack Meibomian glands and display underdeveloped sweat and preputial glands. These phenotypic features appear to be mediated specifically by ligand-activated GR because the synthetic analog dexamethasone induced similar defects in epithelial morphogenesis, including odontogenesis, in wild-type mice. We have focused on tooth development in K5-GR mice and found that an inhibitor of steroid synthesis partially reversed the abnormal phenotype. Immunostaining revealed reduced expression of the inhibitor of κB kinase subunits, IKKα and IKKγ, and diminished p65 protein levels in K5-GR embryonic tooth, resulting in a significantly reduced κB-binding activity. Remarkably, altered NF-κB activity elicited by GR overexpression correlated with a dramatic decrease in the protein levels of ΔNp63 in tooth epithelia without affecting Akt, BMP4, or Foxo3a. Given that many of the 170 clinically distinct ectodermal dysplasia syndromes still remain without cognate genes, deciphering the molecular mechanisms of this mouse model with epithelial NF-κB and p63 dysfunction may provide important clues to understanding the basis of other ectodermal dysplasia syndromes. (*Endocrinology* 146: 2629–2638, 2005)

GLUCOCORTICOIDS (GCs) ARE a vital class of steroid hormones that mediate profound and diverse physiological effects in vertebrate development, metabolism, neurobiology, and programmed cell death (1). Natural GCs and their synthetic analogs function through the GC receptor (GR), a member of the nuclear hormone receptor superfamily of ligand-activated transcription factors. Many morphogenetic processes depend on the precise spatiotemporal expression pattern of GR and its ligand; birth defects are reported after maternal exposure to GCs. However, the precise mechanisms underlying GC teratogenic effects are not fully understood.

Hypohidrotic ectodermal dysplasias (HEDs) are malformation syndromes in humans and mice characterized by severe defects in hair formation (hypotrichosis, partial or total alopecia), abnormal or absent teeth, and hypoplastic or aplastic sweat glands (2, 3). These organs derive from the embryonic ectoderm and thus share similar early morphogenesis (4). It has been shown that, among other common molecular mechanisms, the nuclear factor-κB (NF-κB) family of transcription factors is required for the normal development of ectodermal-derived tissues (5, 6). NF-κB comprises five different proteins in mammals (p50-NF-κB1, p52-NF-κB2, p65/RelA, c-Rel, and RelB) that can form hetero- or homodimers that are sequestered by cytoplasmic inhibitor of κB (IκB) proteins. Various cellular stimuli including proinflammatory cytokines, bacterial and viral products, and mitogens activate an IκB kinase (IKK) complex to phosphorylate the IκBs, thereby triggering their proteasomal degradation and the subsequent release of NF-κB (7).

IKK is formed by the catalytic subunits IKKα and IKKβ, the essential regulatory subunit IKKγ (or NF-κB essential modulator), and the recently cloned regulatory protein ELKS [derived from the relative abundance of its constitutive amino acid glutamic acid (E), leucine (L), lysine (K), and serine (S)] (7–9). IKK is the bottleneck common to many activation pathways that lead to the nuclear translocation of NF-κB. Interestingly, the lack of NF-κB essential modulator function causes the disease incontinentia pigmenti (IP) in humans and mice (5, 10, 11). IP is a rare X-linked dominant genodermatosis causing lethality in males and a complex dermatological disease in females that is characterized by

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Abbreviations: BMP-4, Bone morphogenetic protein-4; DEX, dexamethasone; dpc, d post conception; Eda, ectodysplasin-A; ED, ectodermal dysplasia; Foxo3a, forkhead box class O-3a; GC, glucocorticoid; GR, GC receptor; HED, hypohidrotic ectodermal dysplasia; IKK, inhibitor of κB kinase; IP, incontinentia pigmenti; K5, keratin 5; NF-κB, nuclear factor-κB; P0, postnatal d 0; wt, wild type.

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