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Epigenetic Regulation of Epidermal Development and Keratinocyte Differentiation

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In the era of tissue engineering and development of novel approaches for stem cell-driven organ regeneration, it is important to understand how multipotent stem cells establish distinct programs of gene expression during their differentiation into specialized cell lineages, and why these programs are altered during pathogenic tissue regeneration or expansion (cancer).

It is widely accepted now that lineage-specific gene expression programs are governed by signaling/transcription factor-dependent and epigenetic mechanisms. Understanding how these two key regulatory machineries operate in concert to coordinate expression of lineage-specific genes is highly important for effective modulation of stem cell activity/fate and successful translation of these data into the clinical practice.

Epigenetic mechanisms have an important role in the control of cellular functions in living organisms and are considered to be a driving force of the phenotypic plasticity and evolutionary adaptation (Feinberg, 2007). The variability in epigenetic status helps to explain the relationships between an individual genetic background and effects of the environment on age-related susceptibility to different diseases (Feinberg, 2013).

Epigenetic regulatory machinery operates at several levels including modulation of covalent DNA/histone modifications, as well as through higher-order chromatin remodeling to establish long-range topological interactions between the genes and their enhancer elements in three-dimensional (3D) nuclear space (Ho and Crabtree, 2010; Bickmore and van Steensel, 2013).

The keratinocyte nucleus is a complex and highly compartmentalized organelle, the 3D organization of which undergoes major changes during terminal differentiation in the epidermis (Gdula *et al*., 2013). The program of epidermal differentiation in mice begins at about embryonic day 9.5 (E9.5) and results in the formation of an epidermal barrier at E18.5 (Koster and Roop, 2007; Blanpain and Fuchs, 2009). The process of terminal differentiation in epidermal cells is accompanied by sequential changes of gene expression in the Keratin

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CONFLICT OF INTEREST

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type I/II loci, followed by the onset of expression of the epidermal differentiation complex (EDC) genes encoding the essential components of the epidermal barrier (Fuchs and Horsley, 2011).

The program of epidermal development and keratinocyte differentiation is governed by coordinated involvement of several transcription factors (p63, AP-1, Klf4, Arnt, and so on), signaling pathways (Wnt, Bmp, Hedgehog, EGF, Notch, FGF, and so on), and epigenetic regulators (DNA/histonemodifying enzymes, Polycomb genes, higher-order and ATP-dependent chromatin remodelers, and non-coding RNAs) that control expression of lineage-specific genes (reviewed in (Frye and Benitah, 2012; Botchkarev *et al.*, 2012; Perdigoto *et al.*, 2014)).

The p63 transcription factor serves as a master regulator of epidermal development and controls expression of a large number of genes encoding adhesion/signaling molecules, transcription factors, and cell cycle–associated and lineage-specific proteins (keratins and so on; reviewed in (Koster and Roop, 2007; Vanbokhoven *et al.*, 2011; Botchkarev and Flores, 2014)). *p63* knockout (KO) mice fail to form stratified epithelia and to express a number of epidermis-specific genes (Mills *et al.*, 1999; Yang *et al.*, 1999). p63 has several isoforms, including TAp63 and ΔNp63, that show distinct roles in the control of epidermal stratification, tumor development and aging (Keyes *et al.*, 2005; Su *et al.*, 2013).

Epigenetic regulators exhibit both activating and repressive effects on chromatin in keratinocytes (KCs): histone demethylase Jmjd3, ATP-dependent chromatin remodeler Brg1, and genome organizer Satb1 promote terminal KC differentiation, while DNA methyltransferase DNMT1, histone deacetylases HDAC1/2, and Polycomp components Bmi1 and Ezh1/2 stimulate proliferation of progenitor cells via repression of the genes encoding cell cycle inhibitors, as well as inhibit premature activation of terminal differentiation-associated genes (reviewed in (Eckert *et al.*, 2011; Frye and Benitah, 2012; Botchkarev *et al.*, 2012; Perdigoto *et al.*, 2014).

Our recent studies revealed that transcription factor-dependent and epigenetic regulatory mechanisms in KCs are highly connected, and p63 has a hitherto unrecognized role in the higher-order chromatin remodeling of the EDC locus via direct control of the genome organizer *Satb1* and ATP-dependent chromatin remodeler *Brg1* (Fessing *et al.*, 2011; Mardaryev *et al.*, 2014).

Among different epigenetic regulators, Satb1 has a unique role in the execution of lineage-specific gene expression programs by integrating high-order chromatin organization with regulation of gene expression (Cai *et al.*, 2006). Satb1 binds specialized DNA regions and folds chromatin into loops involving tissue-specific gene loci (T_{H2}-cytokine and major histocompatibility complex class I loci, globin locus, and so on). As well, it targets chromatin remodelers/transcription factors to gene loci (Kumar *et al.*, 2007). Satb1 also contributes to the progression of tumors and promotes reprogramming of the genome of breast cancer cells toward metastasis (Kohwi-Shigematsu *et al.*, 2013).

Satb1 is expressed in basal epidermal KCs and promotes cell differentiation via establishing a specific conformation of the EDC locus, while its ablation in mice results in the marked

elongation of the EDC central domain associated with alterations in expression of the EDC genes and in epidermal morphology (Fessing *et al.*, 2011).

ATP-dependent chromatin remodeler *Brg1*, on the other hand, promotes developmentally regulated relocation of the EDC locus from the nuclear periphery toward nuclear interior into the compartment enriched by nuclear speckles, which is associated with marked increase in expression of the EDC genes (Mardaryev *et al.*, 2014). Importantly, conditional ablation of Brg1 in the epidermis result in failure to form a functional barrier, thus partially resembling the phenotype of p63 KO mice (Indra *et al.*, 2005). These data suggest that chromatin remodeling genes represent a novel cohort of p63 targets that mediate its effects on execution of the lineage-specific gene expression program in KCs (Botchkarev *et al.*, 2012; Fessing, 2014).

However, additional efforts are required to fully understand the complexity of interactions between distinct signaling pathway, transcription factors, and epigenetic regulatory machinery in the control of epidermal development, regeneration, and stem cell activity. Recently, a number of molecules that are capable of modulating distinct components of the epigenetic machinery have been developed, and some of them are already approved for treatment of the distinct neoplastic conditions or under clinical trials (Heightman, 2011). Thus, understanding of epigenetic mechanisms controlling epidermal differentiation and skin stem cell activity and their alterations in different patho-logical skin conditions will help to develop a novel cohort of epigenetic drugs for the treatment of skin disorders.

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