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Transcriptional and signalling regulation of skin epithelial stem cells in homeostasis, wounds and cancer

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Abstract

The epidermis and skin appendages are maintained by their resident epithelial stem cells, which undergo long-term self-renewal and multilineage differentiation. Upon injury, stem cells are activated to mediate re-epithelialization and restore tissue function. During this process, they often mount lineage plasticity and expand their fates in response to damage signals. Stem cell function is tightly controlled by transcription machineries and signalling transductions, many of which derail in degenerative, inflammatory and malignant dermatologic diseases. Here, by describing both well-characterized and newly emerged pathways, we discuss the transcriptional and signalling mechanisms governing skin epithelial homeostasis, wound repair and squamous cancer. Throughout, we highlight common themes underscoring epithelial stem cell plasticity and tissue-level crosstalk in the context of skin physiology and pathology.

Keywords

cutaneous squamous cell carcinomas; epigenetic regulators; lineage plasticity; signalling transduction; skin epithelial stem cells; transcription factors

1 | INTRODUCTION

As the largest organ of the human body, our skin serves as a physical barrier between the individual and the environment. The skin preserves body fluid, guards against irradiation and pathogens and conducts sensations. The epidermis is composed of several epithelial layers. The basal cells attach to the basement membrane above the dermis, joined by hemidesmosomes and adherens junctions, and are home to the epidermal stem cells (EpdSCs), which undergo long-term self-renewal and continuously fuel the upward flux of differentiating cells, forming the skin barrier.[1] EpdSC progenies transition through the

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CONFLICT OF INTEREST

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multiple differentiated layers, starting with the suprabasal spinous layer, rich in desmosomes[2]; then the granular layer, containing keratohyalin and lamellar granules; and finally the stratum corneum, composed of flattened denucleated corneocytes with heavily cross-linked keratin cables and a cornified envelope, eventually sloughed off the skin surface.[3] Connecting to the epidermis are many epidermal appendages, among which the most abundant are the sweat glands and the pilosebaceous units. Sweat glands are responsible for thermoregulation,[4,5] while the pilosebaceous unit is composed of the sebaceous gland and hair follicle. The sebaceous glands secrete lipids (known as sebum) onto the skin surface for repulsion of water and protection against microbes,[6,7] while the hair follicles produce hair to cover the body surface for thermoregulation and appearance.[8,9] The stem cells of the hair follicles, particularly those in the bulge, undergo long-term self-renewal and cyclic bouts of multilineage differentiation to produce the hair, and, upon wounding, regenerate the entire pilosebaceous unit and the epidermis.[10-17]

Multiple cell types live with keratinocytes in the skin, establishing a closely intertwined community. Dermal fibroblasts comprise heterogeneous populations and secrete matrix proteins that provide skin with mechanical strength and coordinate wound healing, and some specialized fibroblasts associate with hair follicles to regulate the hair cycle.[18] Adipocytes reside in the dermis and hypodermis, where they provide insulation and regulate wound repair.[19] The blood and lymphatic vessels densely infiltrate the skin, exchanging nutrients and metabolites, and closely associate with the epidermis and its appendages.[20,21] Immunocytes such as Langerhans cells, macrophages, neutrophils, mast cells, innate lymphoid cells, γδT cells and regulatory T cells together fulfil the responsibility of cutaneous surveillance and immunity.[22-24] Skin is also heavily innervated.[9] Epithelial-derived mechanosensory Merkel cells interact with sensory neurons and encode mechanical inputs.[25,26] Melanocytes deliver skin pigmentations whose activities are critically dependent on their epithelial and neuronal niches.[27,28] Sensory nerves,[29] sympathetic nerves,[30] and arrector pili muscles[31] directly interact with HFSCs to coordinate tissue production. Therefore, the skin is essentially an organ hosting a “zoo” of cell types and tissue-level communications. Upon acute injury or infection, all units come together to dissipate danger, repair damage and restore tissue function, a captive choreography that goes awry in chronic or malignant diseases.

The murine skin, although notably different from that of humans, harbours almost every cell type of its human counterpart and employs highly conserved genes and pathways to execute similar biological functions.[32] Additionally, the study of murine skin offers an arsenal of genetic tools and valuable experimental assays for examining molecular mechanisms of skin development and diseases.[33] For example, we now appreciate the considerable plasticity in both the epithelial and mesenchymal compartments, especially under pathologic conditions, including cutaneous inflammation (eg dermatitis, psoriasis, acne, eczema), degeneration (eg blistering, alopecia) and malignancy (eg basal cell carcinoma, cutaneous squamous cell carcinoma [cSCC], melanoma).

Our current essay summarizes the literature on the transcriptional and signalling aspects of epithelial plasticity in the skin. We first take a deep dive into several key squamous lineage transcription factors (TFs) that have been extensively characterized using genetically

engineered mouse models and discuss their roles in skin development, wound repair and cSCC. We then survey a group of signalling transduction pathways whose effector TFs have been shown to genetically and functionally interact with squamous lineage TFs and impact dermatologic diseases. Finally, we review regulatory mechanisms impacting these TF levels and activities, including epigenetic regulators that shape skin epithelial stem cell function and direct fates upon niche stimulations. During our discussion, we touch upon a few skin diseases wherever applicable. We direct a main focus on cSCC, the second most common skin cancer,[34] presenting a prototype for tumors as wounds that do not heal.[35-37]

2 | SQUAMOUS LINEAGE TFS CONTROL SKIN EPITHELIA FORM, FUNCTION AND DISEASES

Several TFs known to govern skin epithelial lineage specification, stratification and barrier formation may be considered squamous lineage TFs. The deregulation of these TFs often leads to congenital, degenerative and malignant diseases in the skin. We discuss several TFs in this category, starting with a special focus on p63 (encoded by *TP63*), a highly studied, "poster child" squamous lineage TF in the context of skin development and squamous cancer. While p63 has multiple alternatively spliced forms[38,39] with distinct functions, here we focus on ΔNp63 (referred to as p63 hereafter). Readers are referred to excellent reviews[40-43] for related TFs.

p63 specifically labels the basal layers of stratified epithelia (skin, oral, oesophageal), transitional epithelia (cervix, anogenital, urothelial) and glandular epithelia (breast, prostate).[44] Germline mutation of p63 in humans leads to a spectrum of congenital syndromes manifesting various defects of ectodermal derivatives.[45,46] Recapitulating human diseases, p63−/− mice fail to stratify the squamous epithelia and lack epithelial appendages including hair follicles, teeth and mammary glands.[47,48] Their limbs are truncated and often absent owing to failed differentiation of the apical ectodermal ridge.[47] These mice die shortly after birth owing to dehydration and lack of a skin barrier.[47,48] Fulfilling p63's role as the defining member of the squamous lineage TF family, the targets of p63 encompass almost all the known pathways regulating development and maintenance of the skin epithelia, as we elaborate below (Figure 1).

2.1 | p63 coordinates epidermal proliferation, stratification and adhesion

A distinguishing feature of skin epithelial stem cells is their longevity and ability to maintain self-renewal over an individual's lifetime. A well-characterized function of p63 is its maintenance of epithelial stem cell proliferation[49-51] (Figure 1B). As a p53 family TF, p63 is able to bind and activate the p53 response element in heterologous reporter assays.[52,53] p63 antagonizes apoptosis induced by p53[54,55] and another close family member, p73.[56] Knockdown of p53 rescues the proliferative defect of p63-depleted cells in human organotypic epidermal culture,[57] suggesting that a main consequence of p63 loss in this context is the aberrant activation of p53. p63 directly suppresses the cell cycle inhibitor p21(WAF1) in proliferating keratinocytes.[58] Remarkably, the arrested epidermal development of p63-null mice can be rescued by inactivating either of the cell cycle inhibitors p16(INK4A) and p14(ARF),[59] suggesting that cell cycle regulation is a major

function of p63. Consistently, p63+/− mice exhibit premature ageing, correlated with increased p53 activity, elevated p16(INK4A) levels and senescence.[60] p63 additionally induces the squamous miRNA miR-205, which suppresses epidermal differentiation genes and maintains proliferation of basal cells.[61,62]

Meanwhile, p63 suppresses epidermal differentiation through multiple mechanisms (Figure 1B). For example, p63 directly suppresses 14-3-3σ (also known as stratifin or Sfn), a member of the 14-3-3 family harbouring phosphoserine protein that binds the pleckstrin homology domain.[58] Unlike other relatively ubiquitous 14-3-3 family members, Sfn is preferentially expressed in the epithelial lineage and promotes stem cell differentiation.[50,63] Sfn is down-regulated in epithelial cancer, and its mutation leads to hyper-plasic epithelia.[64] Besides regulating Sfn, p63 maintains EpdSCs by preventing the activation of Notch signalling,[65-68] a master differentiation programme (discussed below).

p63 governs another key property of squamous epithelia, their cellular junctions and adhesions, to maintain epithelial integrity (Figure 1C). Initially identified as a p53 target gene regulating apoptosis, the tetraspan membrane protein Perp is a p63 target that influences cellular adhesion by localizing to and regulating desmosomes.[69] In turn, Perp deletion leads to skin blistering disease[69] and accelerates tumorigenesis.[70] p63 targets also include components of tight junctions, adherens junctions, intermediate filaments and extracellular matrix, by which p63 helps maintain junction integrity and skin barrier function[71-75] (Figure 1A). Remarkably, in a system orthogonal to the skin epidermis, p63−/− mammary epithelial cells undergoing anoikis can be rescued by Itgb4 expression,[73] suggesting that certain p63-targeted adhesion components may play dominant roles in maintaining epithelial integrity.

2.2 | Squamous TFs join efforts to drive epidermal stratification and hair follicle differentiation

As EpdSCs exit self-renewal and undergo lineage commitment, a stratification programme is activated in their progenies. In the coordination of this epidermal stratification and differentiation, p63 is joined by many squamous TFs (Figure 1D). For instance, 63 induces interferon regulatory factor 6 (IRF6),[76] whose mutations underlie a group of human ectodermal dysplasia syndromes including cleft palate.[77] While the IRF family is well known for their regulation of interferon responses upon viral infection, IRF6 appears to be an outlier specifically involved in epidermal stratification, and its deletion in mice leads to hyperproliferative epidermis.[78-80] Interestingly, disruption of an IRF6 enhancer is also associated with cleft lip, and this enhancer is bound by the activating enhancer binding protein 2 (AP2).[81] Notably, both AP2α and AP2γ are known to regulate squamous development.[82-84] p63 and AP2 likely share many targets and coordinate their function during epidermal specification.[62]

p63 also targets the grainyhead–like transcription factor 3 (GRHL3),[62] whose mutation again leads to human cleft lip and palate.[85] GRHL3 is the mammalian homolog of *Drosophila* grainyhead (GRH), whose mutation leads to “grainy” and discontinuous head skeletons, hence its name.[86] GRHL3 deficiency in mice leads to the curly tail phenotype and neural tube defects[87]; severe skin barrier defects due to the loss of a skin stratum corneum

cross-linking enzyme, transglutaminase 1[88]; exacerbated inflammatory response upon challenge[89]; and defects in epithelial wound repair.[90,91] Grainyhead–like family member GRHL1 is similarly expressed in the suprabasal layer of the adult epidermis and regulates desmosomes.[92]

Another squamous lineage TFs integrated into the stratification programme is zinc finger protein 750 (ZNF750),[93] which is down-regulated in human patients with cleft palate syndrome harbouring mutant p63.[94] ZNF750 promotes epidermal differentiation by closely associating with Krüppel-like factor 4 (KLF4),[93,95,96] which is critical for skin barrier formation.[97,98] Of note, mutations of ZNF750[99] and KLF4[100] have been linked to psoriasis, an inflammatory skin disease strongly associated with defects in innate immunity and skin barrier function. These studies share a common theme in which germline mutations of squamous lineage TFs are frequently found in an overlapping spectrum of human ectodermal diseases, suggesting that these TFs are instrumental for early ectoderm specification and subsequently are repurposed to regulate squamous differentiation. Moreover, the squamous stratification programme, while essential for skin epidermal development and barrier formation, may, when compromised, predispose an individual to skin immunologic deregulations or malignant transformations (as we will discuss later).

2.3 | Squamous TF deregulation in cSCC

In parallel to their instrumental roles in skin epithelial development, squamous lineage TFs are critically involved in cSCC (Figure 1A). p63 is frequently amplified in SCCs of the head and neck, lung, oesophagus and cervix.[101] Overexpression of p63 in the lung epithelia induces K5/K14 expression and squamous metaplasia in an otherwise simple epithelium.[102,103] p63's oncogenic activity in squamous malignancies has been associated with various mechanisms, such as interaction with NF-κB[104,105] and SOX2.[106-108] Other squamous lineage TFs, such as GRHL2, ZNF750 and KLF4,[109] have been associated with cSCC,[101] further strengthening the notion that deregulation of squamous lineage TFs constitutes a signature for this type of skin malignancy.

In an unexpected twist to p63's tumor-promoting role, aged p63+/− mice undergo frequent loss of heterozygosity and exhibit increased tumorigenesis ranging from adenocarcinomas and sarcomas to, most intriguingly, SCCs,[110] suggesting p63's tumor-suppressive function. Consistently, it has been observed that squamous cancer cells became more invasive when p63 was suppressed.[111,112] It is intriguing to speculate that p63 loss may promote stem cell lineage infidelity (discussed below), where genes outside the squamous lineage become permissively induced,[111] reversing the development trajectory.[62,113,114] The tissue microenvironment is likely another major culprit, highlighted in human SCC patient samples where a similar loss of epithelial identity along with aberrant tumor stroma reaction and immune infiltration has been frequently documented.[115-117]

3 | GROWTH AND STRESS SIGNALLING PATHWAYS DICTATE RESPONSIVENESS TO NICHE STIMULI DURING WOUNDING AND ARE HIJACKED IN SKIN MALIGNANCY

As important as lineage development and homeostatic turnover are, another key function of adult stem cells is coordinated wounding response and tissue repair.[37] During tissue remodelling, many signalling pathways regulating growth are repurposed for damage control to restore organ function. In the context of wound repair, rather than homeostatic function, we generally refer to these regulators as stress signalling pathways and TFs. We discuss the roles in wound repair and cSCC of several extensively studied pathways in this category, including two pro-mitogenic and two pro-differentiation pathways in the skin (Figure 2).

3.1 | ETS transduces RAS MAPK signalling in the skin epithelia

The TF superfamily E-twenty-six (ETS) is activated by rat sarcoma (RAS) mitogen-activated protein kinase (MAPK) signalling[118,119] (Figure 2A) and collectively recognizes the ETS motif.[120] ETS proteins comprise several subfamilies based on structural similarities and divergences, and many of these proteins are rapidly phosphorylated and activated by MAPK signalling,[121] constituting one of the earliest detectable events upon mitogen stimulation.[122,123] Paralleling the function of their counterparts in mammals, ETS homologs in *Drosophila*[124] and *Caenorhabditis elegans*[125] are also key downstream effectors of RAS MAPK. ETS protein activation is further enabled through interaction with partner TFs, such as runt-related transcription factor 1 (RUNX1) in the context of haematopoiesis,[126,127] and subsequent recruitment of cofactors such as the histone acetyltransferase EP300[128,129] (Figure 2A).

Mammalian ETS family members are widely expressed in developing and adult tissues, including many epithelial lineages.[130] Germline loss of ETS family members yields dramatic phenotypes in the developing immune and endothelial tissues.[131] In the skin specifically, mice lacking ETS2 have wavy hair, curly whiskers and abnormal hair follicle shape and arrangement.[132] These phenotypic changes highly resemble those of mutants lacking EGF signalling,[133-135] consistent with the notion that ETS2 is the conserved “bona fide” downstream effector of MAPK signalling in the skin epithelia. ETS TFs also directly target epidermal stratification genes[96,136-139] and hence are likely closely integrated into the squamous TF network.

In addition to stratification, ETS targets have been reported in pathways controlling the cell cycle, DNA damage, matrix remodelling, immune regulations and others (Figure 2A),[140-143] closely linking its function to tumorigenesis. Notably, the ETS family is frequently bound by mutant p53, and they together promote malignant progression.[144-147] While oncogenic fusion proteins involving ETS proteins are well documented in leukaemias,[148,149] sarcomas[150] and prostate cancers,[151] ETS function is only starting to be revealed in cSCC. ETS1 is increased in malignant cSCC,[152] and in transgenic mice, ETS1 overexpression in suprabasal layers induced dysplastic changes in the epidermis, accompanying elevated angiogenesis.[153] ETS2, on the other hand, is functionally required for cSCC development in vivo.[143,154] Interestingly, ETS2 is also essential for wound repair, and ectopic expression of

constitutively active ETS2 in the otherwise homeostatic skin epithelia is sufficient to induce stem cell lineage infidelity (coexpression of and functional dependence on mixed lineage markers) in vivo, causing these epithelial cells to resemble activated stem cells during wound repair and tumorigenesis.[37,154] This in vivo evidence is consistent with the view that RAS MAPK–mediated ETS2 phosphorylation and activation serve as an initiating event upon mitogen stimulation, kicking off a downstream signalling cascade in wounds and cancer.

3.2 | AP-1 mediates TPA and mitogen signals in cancer and inflammation

In its role as a physical barrier, skin directly responds to insults, such as carcinogens. The phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA) is a well-known tumor promoter, [155] acting by intercalating into the cell membrane, presumably altering phosphatidylinositol and diacylglycerol levels, leading to protein kinase C signalling activation[156] (Figure 2B). Protein kinase C is typically activated downstream of the calcium-sensing G protein–coupled receptor and phospholipase C, or by intracellular calcium. Interestingly, both TPA and calcium treatment of cultured keratinocytes increased the expression of epidermal differentiation genes,[157,158] even though their phenotypic outcomes differ significantly, with TPA promoting tumorigenesis[155] and calcium inducing stratification,[159] indicating diverging effectors downstream of TPA and calcium in the skin.

The transcriptional effector of TPA signalling is a group of TFs collectively known as the activator protein-1 (AP-1).[160,161] Composed of core families Jun and Fos, plus the extended families Atf and Maf, AP-1 proteins form mono- or heterodimers to regulate gene expression via enhancers that contain an AP-1 motif.[162-165] Many keratinocyte differentiation genes harbour AP-1–binding sites at their promoters,[166] underlying their responsiveness to TPA. In addition to its activation by TPA, AP-1 is rapidly activated by serum and growth factors,[167-172] placing AP-1 downstream of receptor tyrosine kinase MAPK signalling. TPA and growth factors, via AP-1, induce the expression of a plethora of targets,[173-177] many of which are directly associated with tumorigenesis activity (Figure 2B).

cJun and JunB are among the most-studied family members of AP-1. Mice with either cJun or JunB single conditional knockout in the skin are born with a normal skin appearance. However, those with single cJun knockout have defective epithelial migration during development and open eye phenotype, likely due to reduced epidermal growth factor receptor (EGFR) signalling,[178,179] and those with single JunB knockout become hyperproliferative and have elevated immune response upon further challenge.[180-182] These observations suggest redundant yet often contrasting functions of AP-1 family members in the homeostatic skin. Strikingly, cJun and JunB double deletion in the embryonic skin epithelia leads to perinatal lethality owing to severe cachexia, caused by loss of the AP-1 target tissue inhibitor of metalloproteinase 3 (TIMP3), and consequently leads to uncontrolled activity of a disintegrin and metalloprotease domain 17 (ADAM17) and tumor necrosis factor-alpha (TNF-α) shedding. Double deletion of cJun and JunB in the adult skin epithelia results in a pleiotropic phenotype similar to psoriasis, including hyperkeratosis, massive immune infiltration and arthritic lesions.[183] Downstream mediators of these

psoriatic phenotypes include S100 calcium-binding proteins, which are direct AP-1 targets,[183,184] as well as an indirect signalling axis involving miR-21,[185] a potent oncogenic miRNA in cSCC.[186]

During skin tumorigenesis, both cJun[179,187-189] and cFos[190,191] have been shown to promote cSCC in vivo. Interestingly, cFos overexpression induces infiltration of CD4+ T cells,[191] whereas loss of AP-1 induces infiltration of neutrophils and macrophages,[183] highlighting the diverse mechanisms of epithelial-immune crosstalk mediated by epithelial AP-1 functions. Similarly, activated immune infiltration and barrier defects have been observed in epidermal-specific loss of fibroblast growth factor receptors,[192] further associating MAPK signalling with AP-1 at the genetic level. Like EGF signalling,[193,194] FGF signalling is heavily involved in epithelial growth, wound repair, inflammation and tumorigenesis,[195,196] and both pathways are frequently altered in human SCCs.[101]

3.3 | Notch signalling governs epithelial differentiation and mediates microenvironment crosstalk

Notch signalling regulates gene transcription through converting the recombination signal binding protein for immunoglobulin kappa J region (RBPJ) from a transcriptional repressor to an activator,[197] leading to hairy and enhancer of split-1 (HES1)–mediated transcriptional activation (HES1 itself is an RBPJ target)[198] (Figure 2C). The direct transcriptional output of Notch activation is to induce epidermal differentiation and suppress EpdSC self-renewal.[65,197-199] At the cellular level, Notch signalling acts in either an autocrine or a juxtacrine fashion. In autocrine Notch signalling, the ligand and receptor are provided by a pair of juxtaposed cells. For instance, high expression of Delta-like 1 (DLL1, a Notch ligand) is restricted to the basal stem cells of human epidermis and directs the neighbouring cells expressing NOTCH1 to differentiate.[200] Basal p63 activates Jagged-1 (JAG1, a Notch ligand) to induce neighbouring cells' Notch signalling activation and subsequent stratification[201] (Figure 1B). JAG1/2 and NOTCH1/2 may also be coexpressed in differentiating keratinocytes at the suprabasal layer to reinforce terminal differentiation.[197,202,203] Of note, EpdSCs expressing high levels of the ligand DLL1 are non-receptive to Notch signalling, as they lack receptors, although it is an interesting conundrum that the ligands, themselves being Notch signalling targets, manage to accumulate at high levels without detectable Notch activity in these EpdSCs. Several classic models are plausible to explain such cell fate segregations,[204] all of which have supportive evidence in epidermal development, including cell sorting,[200] lateral inhibition,[205] intrinsic bias due to polarized localization of Notch signalling components[206,207] and extrinsic bias owing to the distance to the cellular source emanating the stemness signal.[208]

Notch is among the top frequently altered pathways in cSCC.[101,209] Although the oncogenic role of the Notch pathway is well established in many cancer types, its mutations are likely loss of function in SCCs.[210,211] In the context of cSCC, the Notch pathway has been consistently revealed to be tumor suppressive in mouse models.[212-216] Strikingly, treatment with an inhibitor of γ-secretase (Notch processing enzyme required for pathway activation) increased the frequency of SCCs in human patients,[217] consistent with the well-established function of the Notch pathway in governing squamous stratification. Of interest, calcineurin

inhibitors, a mainstream immunosuppressant used in organ transplant patients, increased cSCC in humans[218] and in mice,[219] phenocopying Notch suppression. Notch and calcineurin signalling may be closely associated given the role of Notch in epidermal stratification and the role of calcineurin in calcium responsiveness and the fact that a high calcium concentration induces epidermal differentiation in cultured keratinocytes.[159] Indeed, Notch has been found to indirectly activate the calcineurin pathway, and loss of calcineurin in the skin epithelia leads to deregulation of Notch responsive genes and cyclic alopecia.[220] Therefore, cSCC in these patients may originate indirectly, from suppression of immunocytes, as these immunosuppressant agents initially intended to do, or directly, from modification of tumor parenchyma by interfering with epidermal differentiation pathways.

Adding to the complexity of tissue-level crosstalk, epidermal-specific inactivation of Notch leads to transcriptional derepression of thymic stromal lymphopoietin (TSLP) and granulocyte colony-stimulating factor (G-CSF), followed by aberrant immune infiltrates.[221-225] Additionally, Notch signalling in the dermal fibroblast compartment impacts epidermal development.[226] Altogether, these findings highlight the tissue microenvironment as a likely major contributor in Notch-driven cSCC.

3.4 | NF-κB integrates damage signals and immunity in squamous tissues

The nuclear factor of kappa light polypeptide gene enhancer in B-cell (NF-κB) pathway is essential for immune organ development and survival and is also a central player in mediating epithelial and immune crosstalk.[227,228] In its epithelial role, NF-κB is essential for mounting innate immune responses upon infection[229] or eliciting inflammation upon tissue damage[230] while protecting tissues against apoptosis.[230] In the meantime, within the haematopoietic lineage, NF-κB is required for immunocyte survival[231] in addition to relaying inflammatory signals for further tissue remodelling.[232-234]

NF-κB functions in the skin not only follow similar paradigms, but also deviate with several interesting twists (Figure 2D). First, analogous to the conventional TNF-α/TNFR/NF-κB pathway, the strikingly parallel pathway ectodysplasin A (EDA)/EDAR/NF-κB is employed in ectoderm appendage development to initiate the specification of a group of hair follicles within a narrow window during embryogenesis.[235-239] Second, ultraviolet irradiation, a well-known skin carcinogen, activates NF-κB via TNFR1 and its downstream partner TNF receptor-associated factor (TRAF2) independent of TNF-α,[240] or by p38 MAPK and casein kinase II–mediated phosphorylation of inhibitor of NF-κB (IκB), independent of the IκB kinase (IKK).[241] On the other hand, IKKα, a direct p63 target[75,242,243] (Figure 1B), is critically required for epidermal differentiation but is uncoupled from many known components within the NF-κB pathway—it promotes squamous stratification independent of its kinase activity but is dependent on its nuclear localization.[244-248] In sharp contrast, in other systems such as B-cell maturation[249] and mammary gland development,[250,251] downstream NF-κB effector TFs are essential to IKKα function. Consistent with its pro-differentiation function in the skin epidermis, IKKα is decreased in human SCCs,[252-254] and its forced expression suppressed tumorigenesis in vivo.[252] Mechanistically, IKKα has been suggested to cooperate with transforming growth factor β (TGF-β) signalling to induce the expression of MYC antagonists and suppress SCCs.[254,255] Lastly, opposite to its oncogenic

transformation activity in haematopoietic systems,[256,257] NF-κB restrains hyperproliferation in the skin.[258-260] In contrast to the loss of TNF-α, which renders skin resistant to tumorigenesis,[261] loss of NF-κB promotes skin tumorigenesis,[262-264] consistent with NF-κB function in suppressing p63 and promoting epidermal stratification.[65]

Of significance, the growth and mitogenic pathways discussed above interact extensively to regulate oncogenic responses and skin tumorigenesis (Figure 2). For example, ultraviolet B–induced genes highly overlap with those induced by TPA in the skin.[265] The AP-1 inducer TPA has been reported to induce NF-κB[266] and ETS,[127] and conversely, ultraviolet radiation has been shown to induce ETS proteins.[267,268] NF-κB can be induced by calcium or the Notch pathway.[203] As aforementioned, calcineurin inhibition leads to enhanced SCCs in vivo, and this effect could be mediated by the activity of the extended AP-1 family member ATF3.[219] Downstream of mitogens, both ETS and AP-1 are essential effectors and are known to cooperate on the chromatin level to regulate target transcription.[154,269-273] Further illustrating the downstream convergence of these TFs is the regulation of angiogenesis and inflammation—for example, the induction of interleukin-8 by ETS2[143] and NF-κB[274] and the induction of matrix metalloproteinases by AP-1, ETS and NF-κB.[177,191,275-277] These findings altogether depict the intertangled relationships between these TFs (Figure 2), positioning epithelial cells at the centre stage for secreting signalling molecules and directing the epithelial-immune interactions.[278]

4 | COOPERATION OF SQUAMOUS, STRESS AND EPIGENETIC REGULATORS IN DRIVING SKIN EPITHELIAL STEM CELL PLASTICITY

Both the levels and the activity of TFs are tightly regulated to achieve precise cell signalling and stem cell fate decisions in skin development and diseases (Figure 3A). For example, p63 protein levels are subjected to degradation closely coupled to DNA damage,[76,279-281] and its transcripts are modulated by miRNAs[282-284] and by alternative splicing,[38,39] all of which impact p63's activity in shaping the cellular transcriptional landscape. Upon serum and growth factor stimulation, the immediate early response is independent of transcription and is instead transduced at the level of post-translational modifications of signalling proteins followed by the activation of TFs, for instance, the phosphorylation of ETS[285,286] and AP-1.[168] Subsequently, signals are amplified and stabilized by feedback mechanisms. For example, both p63[287] and AP-1[288-290] are able to bind to their own promoters and further induce their own transcriptional activation, forming a positive feedback loop.

The spatial and temporal distributions of TFs are dynamically regulated during development and wounding to direct changes in stem cell fate. For example, GRHL3 and the LIM domain TF LMO4 localize to basal and suprabasal epithelia, respectively, in adults,[291] but become colocalized and physically interact with each other to regulate epithelial migration during eyelid closure.[291-293] Analogously, SOX9 and KLF5 demarcate HFSCs and EpdSCs, respectively, under adult homeostasis but become coexpressed in wound-activated HFSCs and EpdSCs (Figure 3B). This phenomenon of stem cell plasticity has been referred to as lineage infidelity, where wounded stem cells expand their fates beyond homeostatic patterns, coexpressing otherwise lineage-restricted genes.[154] In this case, HFSCs expand fates to

regenerate not only hair follicles but also the epidermis during re-epithelialization. Stem cell lineage infidelity is transient in wound repair but sustained in cancer and is functionally required for epithelial regeneration in wounds and malignant progression in SCCs.[154] Mechanistically, stem cell fate changes correlate with genome-wide remodelling of the transcriptional and epigenetic landscape. Transcriptional responsiveness to upstream signalling can be differentially dictated based on configurations of in *cis* elements and in *trans* regulators.[294,295] As HFSCs exit homeostasis and become activated upon injury, core HFSC TFs are decommissioned, and stress TFs are assembled to drive wound-specific epicentres. In both cases, SOX9 is expressed, yet is dependent on different niche signals. Such distinct context dependency at the chromatin level could be reflected by an enhancer switch[143,154,296] (Figure 3B). Several speculations may be drawn from the observations of stem cell lineage infidelity. Upstream signalling transductions are specifically induced upon injury. For example, activation of ETS2 and AP-1 results in the ectopic induction of mixed lineage gene expressions, among which the lineage TFs KLF5 and SOX9 may cooperate with ETS2 and AP-1 and form a feedforward circuit to further promote stem cell fate change. Downstream targets may be remodelled to drive fate transition. For instance, KLF5 and SOX9 may be redirected from maintaining homeostatic functions to regulating damage-related cellular pathways that are essential for wound repair and tumorigenesis. Both directions will be worthwhile to further explore and improve our understanding of context-dependent transcriptional and signalling regulations.

One strategy in which squamous TFs regulate gene activation (or repression) and coordinate genome-wide transcriptional regulations is by interacting with epigenetic regulators,[297-299] including chromatin binding, modification and remodelling factors (Figure 3C). Loss of histone deacetylases HDAC1 and HDAC2 induced p53 activity along with derepressed p21, p16, Sfn and epidermal hypoplasia,[300,301] phenocopying the effects of p63 deficiency.[59] Interestingly, suppression of unscheduled cell cycle exits or differentiation, and hence maintaining the stem cell pool, appears to be a common mechanism for many epigenetic regulators in the skin. The skin epidermis lacking EZH2, a component of polycomb repressive complex 2 (PRC2) that catalyses H3K27 methylation, aberrantly induces p16 and undergoes cell cycle arrest.[302] Similarly, deletion of chromobox homolog 4 (CBX4, the E3 ligase component of PRC1) induces epidermal senescence.[303] Depletion of the maintenance DNA methyltransferase DNMT1, or of ubiquitin-like with PHD and ring finger domains 1 (UHRF1, an E3 ligase that targets DNMT1 to hemi-methylated DNA), leads to aberrant differentiation.[304-306] In contrast, the de novo DNA methyltransferases DNMT3a/b are required for epidermal differentiation, and their loss promotes cSCC.[307,308] Similarly, HDAC3 governs skin barrier formation by interacting with KLF4, although, interestingly, HDAC3's histone deacetylase activity is dispensable in this particular context.[98]

Indeed, a reiterative theme arises upon study of squamous lineage TF function. The interactions of these TFs with epigenetic regulators significantly impact epidermal differentiation and cSCC tumorigenesis. The ATP-dependent chromatin remodelling complex BAF (BRG1- or BRM-associated factor) has been shown to regulate chromatin accessibility at key lineage genes in cooperation with p63[309] and AP-1.[310] For example, p63 induces brahma-related gene 1 (BRG1), a catalytic subunit of the BAF complex, to direct the localization of the epidermal differentiation complex (EDC) locus from the nuclear

periphery to the interior for its transcriptional activation.[311] An analogous regulation of EDC by p63 has been observed through the special AT-rich sequence binding protein 1 (SATB1),[312] another chromatin remodelling factor mediating long-range looping. Meanwhile, p63 is coamplified with the regulatory subunit actin-like protein 6a (ACTL6A) of the BAF complex,[313] which prohibits BAF from binding to and activating KLF4, consequently promoting cSCC.[314]

Furthermore, GRHL3 recruits the trithorax group protein mixed lineage leukaemia (MLL) complex (H3K4 methyltransferases) to facilitate the activation of differentiation genes,[315] and notably, both MLL2 and MLL3 are frequently mutated in SCCs.[101] The H3K27me3 demethylase Jumonji domain-containing protein 3 (JMJD3) promotes epidermal differentiation by erasing this marker of H3K27me3 upon calcium switch.[316] In addition, the H3K9me3 demethylase JMJD2A facilitates the binding of the AP-1 proteins to the promoters of Jun and Fosl1 genes themselves, enhancing AP-1 activity and SCC metastasis.[317] Finally, the c-Jun N-terminal kinase (JNK) phosphorylation of JUN (encoded by Jun) released it from HDAC3 suppression,[318] and the extracellular signal-regulated kinase (ERK) phosphorylation of Fos-related antigen 1 (Fra-1, encoded by Fosl1) released it from EZH2 suppression to activate EDC genes.[319] These observations together illustrate the convergent functions of squamous TFs and epigenetic regulators in governing skin epithelial stem cell maintenance while coordinating stratifications (Figure 3C).

5 | CONCLUSION

Our conceptual advancement of the genetic and developmental principles in skin biology has been instrumental to our understanding of skin diseases. These observations in aggregate illustrate the importance of contextual information including temporal and spatial expression, interacting partners and signalling activities as key aspects of transcriptional regulation in development and diseases. It has become increasingly clear that cancer driver genes rewire existing signalling and transcriptional networks to fuel malignancy, and they do so by hijacking development and regeneration pathways. Investigating these pathways and gene networks will greatly expedite the mechanistic understanding of the context dependency of TFs, thereby revealing cancer-specific vulnerability. Facilitated by rapidly evolving single-cell technology and microscopy, our depicting of stem cell biology in the skin has achieved hitherto unprecedented complexity and depth. We begin to capture signalling events and molecular interactions at high resolution and appreciate intercellular communications at a single-cell level across the tissue and organism. These technical advances are likely the main driver for our understanding of complex skin inflammatory and malignant diseases with regard to cellular crosstalks.

The fascination with transcriptional regulation is further bolstered by the finding that under certain contexts, TFs may sit at the top of a chromatin hierarchy to elicit stem cell plasticity. For example, LEF1 overexpression or bCat activation drives ectopic hair follicle specification and de novo hair follicle tumor formation.[320-325] During skin wounding, fibroblasts can be reprogrammed to regenerate the epidermis by a combination of p63, GRHL2, AP2α and MYC.[326] In the context of SCCs, in addition to the tissue types frequently giving rise to this cancer type, a few more organs develop squamous-like

carcinomas, such as the pancreas and bladder,[327-331] suggesting a squamous network in these cancers, whose functional significance and clinical implications await further investigations. The next chapter in skin research is likely to include further advanced applications in regenerative and cancer medicine. The dissection of TF interactions with epigenetic regulators and their signalling crosstalk will facilitate the discovery of druggable targets and appealing therapeutics.

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Abbreviations:

ACTL6A	actin-related proteins 6a
BAF	BRG1-or BRM-associated factor
BRG1	brahma-related gene-1
cSCC	cutaneous squamous cell carcinoma
DLL1	delta-1
DNMT	DNA methyltransferase
EDA	ectodysplasin A
EDC	epidermal differentiation complex
EGFR	epidermal growth factor receptor
EpdSC	epidermal stem cell
ETS	e-twenty-six
FGFR	fibroblast growth factor receptor
GRH	grainyhead
GRHL3	grainyhead–like transcription factor 3
HES1	hairy and enhancer of split-1
HFSC	hair follicle stem cell
IkB	inhibitor of NF-κB
IKKα	IkB kinase alpha
IRF6	interferon regulatory factor 6
JAG1	jagged-1

JMJD	Jumonji domain-containing protein
JNK	c-Jun N-terminal kinase
KLF4	Krüppel-like factor 4
MAPK	mitogen-activated protein kinase
MLL	mixed lineage leukaemia
NF-κB	nuclear factor of kappa light polypeptide gene enhancer in B cells
PRC2	polycomb repressive complex 2
RAS	rat sarcoma
RBPJ	recombination signal binding protein for immunoglobulin kappa j region
RUNX1	runt-related transcription factor 1
TF	transcription factor
TGF-β	transforming growth factor-β
TIMP3	tissue inhibitor of metalloproteinase inhibitor 3
TNF-α	tumor necrosis factor-alpha
TPA	12-O-tetradecanoylphorbol-13-acetate
UHRF1	ubiquitin-like with PHD and ring finger domains 1
ZNF750	zinc finger protein 750

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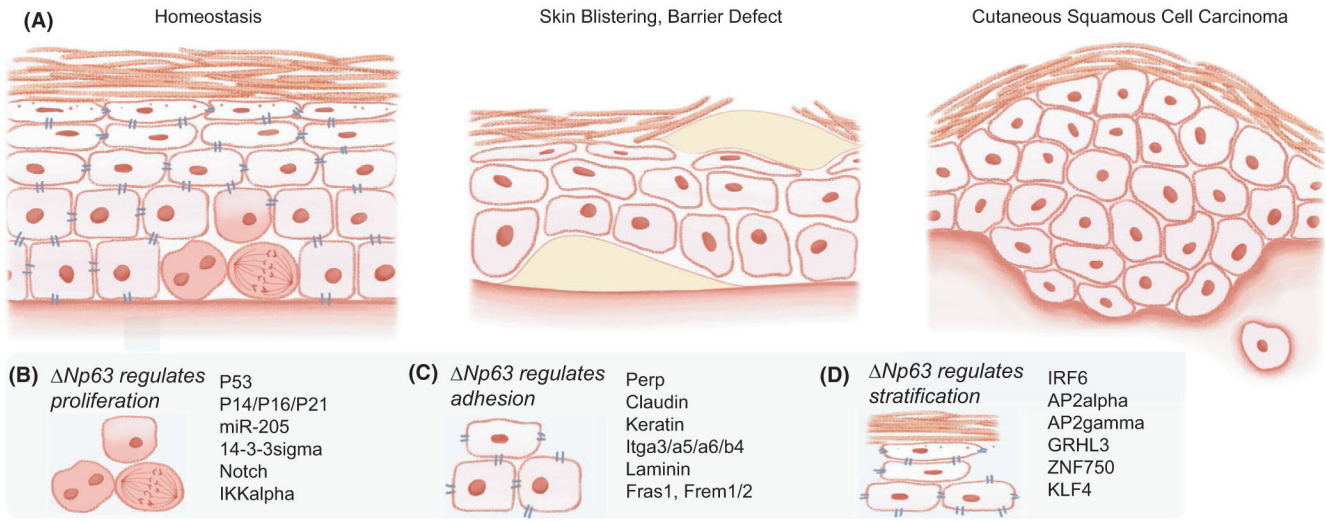

FIGURE 1.

Squamous lineage transcription factors (TFs) control skin epithelia form, function and diseases. (A) The stratified skin epidermis is composed of several epithelial layers, including the basal layer, harbouring epidermal stem cells (EpdSCs), suprabasal spinous and granular layers, and the stratum corneum (left). Skin blistering diseases occur when the epidermal adhesions and junctions are compromised, and barrier defects originate from disruptions of the stratification programme, including genes of cross-linking enzymes, cornified envelop and lipid metabolism. A common non-melanoma skin cancer, cutaneous squamous cell carcinoma (cSCC), arises from the skin epithelium and mimics wounds that never heal. (B) p63 maintains EpdSC proliferation and prevents precocious stratification by antagonizing p53, cell cycle inhibitors, 14-3-3σ, Notch, IKKα and activating miR-205. (C) p63 also regulates the expression of many cell adhesion and junction components, including Perp (desmosome), claudin (tight junction), keratins (intermediate filaments), integrins (adherens junctions), laminins (basement membrane), and Fras1 and Frem1/2 (extracellular matrix). (D) Squamous lineage TFs are p63 targets and join p63 to regulate epidermal stratification; many of these TFs are deregulated in congenital ectodermal conditions and skin inflammatory and malignant diseases

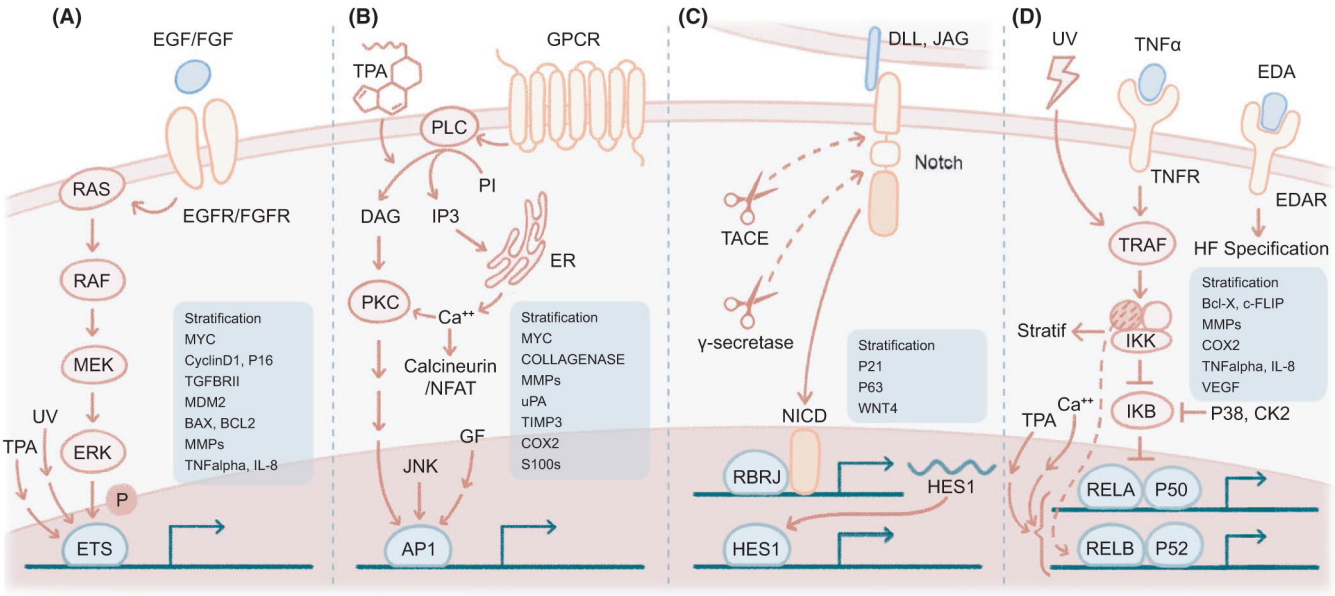

FIGURE 2.

Growth and stress signalling pathways dictate responsiveness to stimuli and are hijacked in skin malignancy. (A) ETS family TFs are phosphorylated by the RAS MAPK pathway, downstream of receptor tyrosine kinase (RTK) signalling, for example EGF/EGFR and FGF/FGFR. ETS is also stimulated by ultraviolet light and TPA exposure. Targets of ETS TFs include stratification genes (cross-linking enzymes, cornified envelop, lipid metabolism), cell cycle (MYC, Cyclin D1, P16, TGFBR2), apoptosis (MDM2, BAX, BCL2), matrix metalloproteases (MMPs) and cytokine/chemokine genes (IL-8, TNF-α). (B) AP-1 TFs are the principal effector TFs of TPA signalling. AP-1 is also activated by serum, growth factors and JNK signalling, and shares some common effectors with calcium signalling, such as protein kinase C (PKC). AP-1 induces stratification, matrix remodelling (collagenase, MMPs, uPA, TIMP3) and inflammation (COX2, S100), among others. uPA, urokinase-type plasminogen activator. (C) Notch receptor binds its ligands (DLL1, JAG1/2) in a juxtacrine or autocrine fashion and is activated by two consecutive protease activities (TACE, γ-secretase), resulting in activation of HES1, p21 and stratification genes and repression of p63 and WNT4. TACE, tumor necrosis factor-alpha–converting enzyme, also known as ADAM17 (ADAM metallopeptidase domain 17). NICD, notch intracellular domain. (D) NF-κB signalling has several skin-specific functions: EDA/EDAR regulates hair follicle (HF) specification, ultraviolet light activates TRAF2, IKKα regulates squamous stratification, and NF-κB functions as a tumor suppressor promoting epidermal differentiation. NF-κB is also activated by TPA and calcium, and its downstream targets include stratification, survival (Bcl-x, c-FLIP), inflammatory enzymes (COX2), matrix remodelling (MMPs), cytokines/chemokines (TNF-α, IL-1, IL-6, GM-CSF, IL-8, KC, MIP2) and angiogenesis (VEGF)

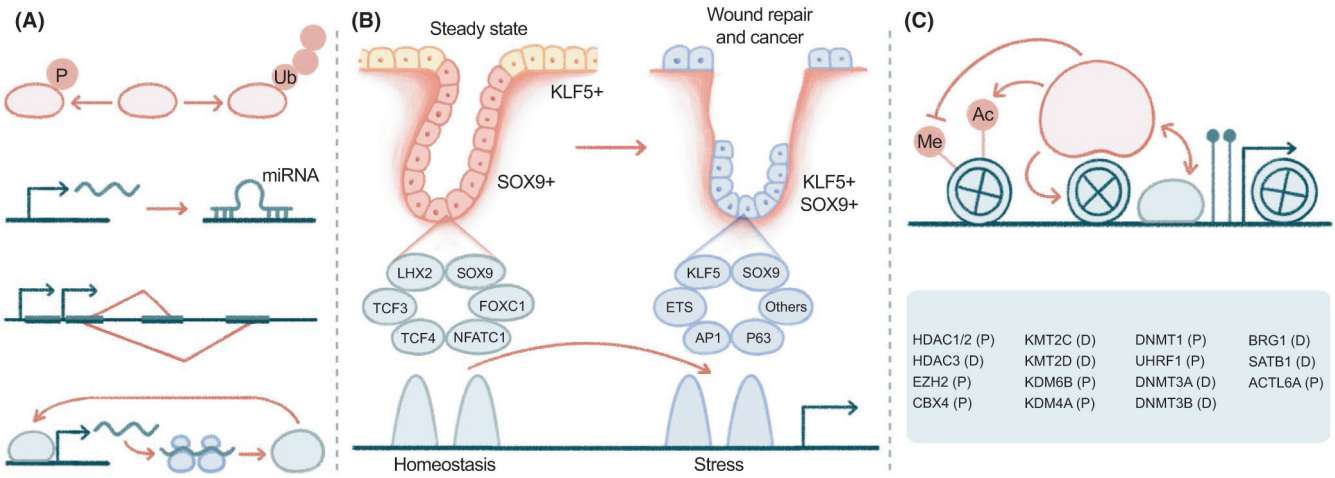

FIGURE 3.

Cooperation of squamous, stress and epigenetic regulators in driving skin epithelial stem cell plasticity. (A) TFs such as p63 are regulated at multiple levels, including post-translational modifications by phosphorylation and ubiquitination, post-transcriptional regulation by miRNAs, alternative splicing and positive feedback regulations. (B) A group of TFs govern hair follicle stem cell (HFSC) quiescence, including SOX9, LHX2, TCF3, TCF4, NFATC1 and FOXC1, while KLF5 is specifically enriched in EpdSCs. Upon wounding, HFSCs induce the expression of KLF5, which is coexpressed with SOX9, ETS2, AP-1 and p63, among others, resulting in stem cell lineage infidelity, an epigenetically rewired state that is functionally required for wound repair. (C) Several groups of epigenetic factors are integrated in the regulation of EpdSC proliferation (P) and differentiation (D), including histone deacetylases (HDAC1/2, HDAC3), histone methyltransferases, demethylases, and their regulators (EZH2, CBX4, KMT2C/D, KMT4A, KMT6B), chromatin remodelers (BRG1, SATB1, ACTL6A), and DNA methyltransferases and regulators (DNMT1, DNMT3A/B, UHRF1). KMT2C is also known as MLL3, KMT2D as MLL2, KDM4A as JMJD2, and KDM6B as JMJD3. The hypothetical epigenetic factor is depicted arbitrarily with multiple activities