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Review Article

Tumor Protein P63 is a Key Regulator of Skin Functions in Ectodermal Dysplasia

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Abstract

Tumor protein (TP)-p63 has been discovered as TP53 homolog more than fifteen years ago and has become a master regulator of skin development, proliferation and stem cell maintenance. While *TP53* is known to be the most mutated gene in human cancer, TP63 mutations are mostly associated with the various types of ectodermal dysplasia. All TP53 family members, *TP53*, TP63 and TP73, function as transcription factors that regulate the cell cycle arrest, apoptosis, autophagy or metabolism through activation/repression of downstream target genes or protein-protein interactions with other protein regulators of transcription and splicing. Several downstream target genes or protein interactors of TP63 are involved in the molecular mechanisms underlying the ectodermal dysplasia phenotypes. This mini-review underlines a few venues of investigations about the key role for TP63 in skin biology and pathology.

INTRODUCTION

Multiple molecular mechanisms are underlying the skin cell proliferation and differentiation, while the master gene involved in genetic and epigenetic regulation of skin-specific genes, tumor protein (TP)-p63 is being investigated for the last decade [1-4]. *TP63* gene encoding transcription factors with the transactivation domain (TA-) and without it (ΔN-), is rarely mutated in cancer, however is often mutated in heritable skin disorders, such as ectodermal dysplasia [3,4]. *TP63* mutations can cause several different disorders: ectrodactyly, ectodermal dysplasia and cleft lip/palate syndrome (EEC), ankyloblepharon-ectodermal defects-cleft lip/palate syndrome (AEC), limb mammary syndrome (LMS), Acro-Dermato-Ungual-Lacrimal-Tooth syndrome (ADULT), Rapp- Hodgkin syndrome (RHS), and split hand/foot malformation (SHFM4) [1,3,4]. Each group of mutations affects specific functions of TP63 protein, such its ability to bind TP63 responsive elements in gene promoters (DNA-binding domain), to be properly ubiquitinated (TI-domain), and to form protein/protein complexes with other regulatory components (SAM domain), as reviewed in [5-10].

The key studies show that *tp63* null mice display single-layered and translucent skin, with an altered stratified epithelia leading to a breakage of the epidermal barrier formation that protects against dehydration [11,12]. Homozygous ΔNp63 null mice show under-developed stratified epidermis with clusters of disorganized epithelial cells exhibiting a premature expression of terminal differentiation markers [13]. However, ΔNp63α expressing transgenic mice show an abnormal hair follicle development and altered cell fate of follicular keratinocytes [14].

TP63 proteins exert their functions through the transcriptional regulation (activation of repression) by binding to the specific downstream gene targets, many of them involved in the direct control of the skin epithelial sheet architecture, stem cell renewal, cell cycle arrest, apoptosis, senescence, autophagy, skin aging, cellular response to ultraviolet (UV)- irradiation, and epigenetic controls of thereof via enzymes and microRNAs, thereby contributing to the molecular pathogenesis of several genetic diseases of skin and epithelial tissues [15-26]. Among TP63 responsive gene targets are the following genes implicated in skin development and functions: *ALOX12B, AQP3, BPAG1, CASP14, CDH1, CLDN1, DLX3, 5 and 6, DSG, DSP, EVL, HBP1, IKK, IVL, IRF6, KRT5, and 14, LSH, PPL, PERP, SATB1, TPRG1,* and *ZNF750* [17,20,21,27-37].

TP63 also engages in numerous protein-protein interactions that contribute to chromatin remodeling, RNA transcription, RNA splicing, protein degradation, and signaling [6-8,10,38-40]. TP63 associates with many proteins involved in a fine-tuned regulation of gene expression. For example, the AEC-derived *TP63* mutations altered the ability for TP63 to physically associate with mRNA processing/splicing proteins (e.g. ABBP1, SRA4) leading to a deregulated splicing of FGFR2 receptor responsible for epithelial/mesenchymal transition (EMT) [6,8]. AEC-derived mutations in *TP63* were also found to alter the TP63 binding to SATB2, which has been implicated in the development of cleft palate, and down regulation of PERP [38,39].

TP63 is over expressed in multiple human epithelial cancers, including head and neck, esophagus and lung cancers, cervix and breast tumors [40]. Accumulating evidence shows that TP63

and especially its ΔN isoforms play a critical role in head and neck squamous cell carcinomas (HNSCC). ΔNp63a, the most predominantly expressed isoform in HNSCC, is over expressed and sometimes amplified in HNSCC tumors [41].

Role of autophagy in cutaneous functions and TP63

First indication of autophagy in skin cells was produced almost thirty years ago showing the melanin macro globule (MMG), formerly called "macromelanosome," a cytoplasmic spherical granule formed in the melanocyte [42]. MMG are retained within melanocytes or transferred to keratinocytes and Langerhans cells in the epidermis, and macrophages in the dermis, where they can fuse with other heterolysosomes [41]. Cutaneous malignant melanomas often exhibit pigmented regions that are darker than the surrounding skin [43]. While melanoma cells are the original source of the melanin, keratinocytes and melanophages also contribute to the tumor color because they contain melanin obtained from melanoma cells [42]. Moreover, autophagy appears to be a common trait of invasive melanoma cells in the dermis [42]. Strikingly, the Caucasian skin keratinocytes exhibit higher autophagic activity than those from African American skin [42]. Melanosome accumulation in keratinocytes was accelerated by treatment with lysosomal inhibitors or with small interfering RNAs specific for autophagy-related proteins, which are essential for autophagy supporting its pivotal role in skin color determination, as well as in chemo- or immuno- therapeutic treatment of melanoma patients [43-45].

UVB, a major cause of skin damage, which accompanies complex alterations in irradiated skin cells (e.g. DNA lesions, oxidative stress, inflammation and caspase activation), was also shown to induce macroautophagy and mitochondrial autophagy [46,47]. Furthermore, the epidermal expression of SQSTM1, the key regulator of autophagy, is found to be significantly higher in psoriatic skin than in skin affected by atopic dermatitis or from healthy controls, suggesting the role for autophagy in cutaneous inflammation [48]. Both UVA- and UVA-oxidized phospholipids induced autophagy in epidermal keratinocytes leading to a massive accumulation of high-molecular-weight protein aggregates containing the autophagy-adaptor protein SQSTM1 in ATG7-/- keratinocytes [49].

Squamous cell carcinoma (SCC) cells exposed to cisplatin displayed a dramatic ATM-dependent phosphorylation of ΔNp63α leading to a transcriptional regulation of downstream mRNA and microRNA gene targets in SCC cells [26,49]. Phosphorylated ΔNp63α was shown to regulate autophagic gene expression (e.g. *ATG1/ULK1, ATG3, ATG4A, ATG5, ATG6/BECN1, ATG7, ATG9A* and *ATG10*) in cisplatin-treated SCC cells through both transcriptional and post-transcriptional mechanisms [26,50].

Epigenetics, skin cell malfunction, and TP63

Epigenetic regulation mediates genomic adaption to the environment and epigenetic alterations (heritable changes in gene function that occur without any change in DNA sequence through changes in chromatin structure) can contribute to the development of disease phenotypes, as can mutations [50]. The epigenetic molecular mechanisms include DNA methylation, modifications of histones, histone code, chromatin and polycomb remodeling complexes, noncoding microRNAs implicated in regulation of RNA transcription and RNA processing [50].

Accumulating evidence shows that epigenetic mechanisms are involved in the control of epidermal development and terminal keratinocyte differentiation [51]. Multiple elements of epigenetic machinery (e.g. DNMT1, JMJD3, SETD8, HDAC1 and 2, EHMT1 and 2, BRG1, CHD1, 3, and 4, BMI1, CBX2, 4, and 6, EZH2, JARID2, and SATB1) were implicated in molecular mechanisms underlying epidermal differentiation programs, as reviewed in [51]. In the epidermis of p63-null mice the expression of a large number of genes involved in the control of nuclear/chromatin assembly and remodeling is significantly changed compared to wild-type controls [39]. On one hand, TP63 directly controls the SATB1 transcription and promotes establishing of specific higher-order chromatin structure in central domain of the epidermal differentiation complex required for maintenance of the proper balance of gene expression during terminal keratinocyte differentiation [39]. On the other hand, TP63 expression in keratinocytes is regulated by histone methyltransferase SETD8, which, in turn, is a target of c-Myc transcription factor and mediates its effects on epidermal differentiation [52]. Another TP63 transcriptional target LSH, an SNF2-like chromatin remodeling ATPase encoded by the *HELLS* gene, is essential for normal levels of DNA methylation and to drive skin stem cell proliferation and tumorigenesis [40]. LSH acts as an efficient transcriptional repressor by cooperating with the DNMT1, DNMT3B, HDAC1 and HDAC2 to silence gene transcription [40]. TP63 was shown to play a critical role in regulation of various epigenetic enzymes and accessory proteins by activating or repressing their transcription, as well as modulating their levels by TP63-dependent microRNAs [53], Ratovitski, in preparation].

TP63 and microRNAs in skin proliferation and differentiation

Essential role of microRNAs in governing a self-renewal and migration of skin stem cells supported by the function of Argonaute (AGO) proteins as essential components of the RNA-induced silencing complex [54]. When both *AGO1* and *2* are ablated in the skin, the global expression of microRNAs is significantly compromised and causes severe defects in skin morphogenesis [54]. The overall profound impact of microRNAs on epidermal and hair development was demonstrated by generating mice with skin-specific targeting of the two major components of the microRNA processing machinery, DICER and DGCR8. Keratinocyte-specific deletion of *DICER* and *DGCR8* resulted in dramatic and similar skin phenotypes affecting the follicular epithelium and inter-follicular epidermis [55,56]. Intriguingly, both TAp63 and ΔNp63 directly regulate transcription of *DICER*, while directly repressing the expression of miR-34 encoding genes [57-60].

Inhibition of miR-34a and miR-34c activity restored keratinocyte cell cycle progression and the expression of several cell cycle regulators, CCND1 and CDK4 [60]. TP63 expression is modulated by miR-720 and miR-574-3p in the suprabasal layers of the epidermis [56]. MiR-205 is broadly expressed in the epidermis, including the basal, suprabasal and superficial layers and skin stem cells [60]. Genetic deletion of miR-205 causes neonatal lethality with severely compromised epidermal

and hair follicle growth [60]. In the miR-205 knockout skin cells, phospho-AKT is significantly down regulated, while cells prematurely exit the cell cycle and become quiescent [60]. MiR-205 targets negative regulators of PI(3)K signaling that mediate the repression of phospho-AKT and restrict the proliferation of skin cells [59]. Moreover, the loss of miR-205 is associated with melanoma progression [61]. MiR-205 was also reported to promote keratinocyte migration through downregulation of lipid phosphatase INPPL1 and modulating AKT signaling [62]. MiR-31 is highly expressed in 'activated' skin conditions (e.g. wound healing, carcinogenesis, and psoriasis), and elevated miR-31 levels in a transgenic mouse model results in aberrant wound healing and hair loss [56,63]. MiR-31 is also present in anagen hair follicles and exerts inhibitory effects on hair follicle growth by targeting multiple genes [56,63].

MiR-200a, miR-200b, miR-200c, miR-141, miR-429, miR-19b, miR-20, miR-17-5p, and miR-93 are preferentially expressed in the epidermis, while miR-199a, and miR-199b are exclusively expressed in the hair follicle, as reviewed in [56]. The skin-specific miR-203 is abundantly expressed in differentiating cells of the epidermis, hair follicle and sebaceous gland in mice, as well as in the suprabasal epidermal layer in human skin [64]. By targeting ΔNp63, miR-203 may control 'stemness' and act as a molecular switch between proliferative basal cells and terminally differentiated suprabasal keratinocytes [65].

Accumulating evidence supports that microRNAs, whose transcription regulated by TP53 family factors (TP53, TP63, and TP73), could contribute in multiple signaling pathways involved in cell cycle arrest, apoptosis, autophagy, metabolism and epigenetic transcriptional regulation, thereby potentially underlying the mechanisms leading to epithelial cell maintenance, and tumor development and chemoresistance [50]. As a member of the TP53 family, TP63 transcription factor is likely to play its decisive role in transcriptional and post-transcriptional regulation of microRNAs in epithelial cancers, epithelial differentiation and EMT [50]. ΔNp63α was shown to inhibit miR-138, -181a, -181b, and -130b expression by binding directly to TP63-responsive elements located in close proximity to the genomic loci of these microRNAs in primary keratinocytes [66].

The AEC syndrome and TP63

The most severe cutaneous manifestation of the AEC is the long-lasting skin fragility with severe skin erosions after birth [67-69]. Additionally, the skin of the AEC patients shows an impaired expression of differentiation markers involved in cell adhesion and barrier formation, as well as a dysregulated cell cycle regulation [67,68]. The new knock-in mouse AEC models were recently offered for investigation of the molecular mechanisms underlying the AEC, as well as providing potential therapeutic approaches [67-69]. These models show the skin fragility associated with microscopic blistering between the basal and suprabasal compartments of the epidermis and reduced desmosomal contacts [69]. Expression of desmosomal CDH and DSP was strongly reduced in knock-in mouse AEC mutant keratinocytes and in newborn epidermis similarly to human keratinocytes isolated from AEC patients, in TP63-depleted keratinocytes and in p63 null embryonic skin, indicating that *TP63* mutations causative of AEC syndrome have a dominant-negative effect on the wild-type TP63 protein [69]. The AEC *TP63* mutations exert a selective dominant-negative function on wild-type TP63 associated with impairment of fibroblast growth factor signaling resulting from reduced expression of *FGFR2* and *3*, direct TP63 target genes [68]. In summary, the *in vitro* and *in vivo* studies of the potential biological treatments modulating the effect of AEC-derived *TP63* mutations on *FGFR2b* splicing needed to shed a light on the AEC pathogenesis.

AEC mouse models also display a deregulation of the TP63 transcriptional target ZNF750, which is associated with familial psoriasis [36,70]. ZNF750 is reported to induce KLF4, which is essential for the barrier function of skin [70]. *TP63* with AEC mutations prevented the transcriptional induction of ZNF750 in an organotypic human tissue model, while the forced expression of ZNF750 rescued impaired epidermal differentiation resulting from AEC mutants suggesting the existence of a p63–ZNF750–KLF4 network in human epidermal development and homeostasis [36,70]. Among the genes that deregulated in AEC are those implicated in epidermal adhesion, skin barrier formation and hair follicle biology (e.g. *FRAS1, COL7A, CDH3, SPRR1A and 4, LCE5A, HRNR, ALOX12B, GATA3, KRT 25, 27, 33B, 34, 35, 81 and 85, and PERP*), some of them are controlled directly or indirectly by TP63 [70-72].

FUTURE STUDIES

Among the ninety genes associated with the genetic skin disorders, several functional pathways were defined to play a role in epidermal differentiation, including NOTCH, TGFβ, IKK, MAPK, PI3K, TP63, and WNT), as reviewed in [70]. In general, TP63 exerts its function through a transcriptional regulation of downstream gene targets. For example, the deregulation of *KRT1, 5, 10, 14,* and *PLEC1* is implicated in epidermolysis bullosa simplex or epidermolytic ichthyosis altering the basement membrane zone adhesion and hemidesmosomes and causing epidermal blistering [70]. Deregulation of *ALOX12B* was shown to cause lamellar ichthyosis affecting cholesterol metabolism [70], while *CLDN1* is involved in neonatal ichthyosis sclerosing cholangitis syndrome showing ichthyosis, hypotrichosis, and dental abnormalities [70]. *KRT1, 9, 16* and *17* are implicated in palmoplantar keratoderma and pachyonychia congenital showing alteration if desmosomes affecting palms, soles, and hair and causing nail dystrophy [70]. Mutations in the TP63-regulated *CDH3* cause hypotrichosis with juvenile macular dystrophy and ectodermal dysplasia, ectrodactyly, macular dystrophy altering development of the hair and retina [71-73]. Interestingly, that TP63, as well as miR-203, miR-21 and miR-125b implicated in the regulation of TP63 or TP53, has been suggested in the pathogenesis of psoriasis [74-77].

Disrupted skin barrier due to altered keratinocyte differentiation is common in pathologic conditions such as atopic dermatitis, ichthyosis and psoriasis [78]. The dominant mutation in the TP63 target *ZNF750* leads to a clinical phenotype reminiscent of psoriasis and seborrheic dermatitis [78]. Furthermore, the deregulation of the TP63/hedgehog cross talk was reported to underlie the pathogenesis of basal cell carcinoma of the skin through regulation of *SUFU* expression [78]. Evidently, the additional studies needed to define the molecular pathways underlying the role for TP63 transcriptional

targets in the pathogenesis of the above-mentioned high morbidity skin abnormalities that could be targeted as potential fields of intervention using TP63-related biomolecules or reagents [50,56,63,66,79]. Finally, the TP63 antibodies have been proven to be useful tool in the diagnosis of a primary cutaneous carcinosarcoma, spindle cell SCC, and in distinguishing sclerosing cutaneous tumors [79-82].

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