p63 – an Important Player in Epidermal and Tumour Development

p63 – důležitý hráč ve vývoji epidermálních struktur a nádorových onemocnění

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Summary

p63 is a transcription factor which plays an important role in epidermal development, differentiation and tumourigenesis. p63 belongs to the p53 protein family and at least six isoforms were identified to date. p63 isoforms play contrary roles during the development and formation of the epidermis as well as in cancer. p63 participates in epithelial development, where it affects proliferation and differentiation of epidermal cells. Inherited mutations in the *TP63* gene generate different developmental defects and p63 knockout in mice results in the absence of epidermis. Another important role of p63 is the control of cell-cell adhesion, where it regulates desmosomes. The loss of proliferation and cell-cell adhesion control are important for tumourigenesis and overexpression of p63 can enhance tumour growth and inhibit apoptosis. This review briefly summarises the roles of p63 in epithelial development, cellular proliferation, adhesion and migration and reveals its share in tumourigenesis and metastasis.

Key words

p63 – cell development – cell proliferation – cell adhesion – tumourigenesis – epidermis

Souhrn

Protein p63 je transkripční faktor, který má významnou funkci ve vývoji a diferenciaci epidermálních struktur a v průběhu tumorigeneze. Je členem rodiny nádorového supresoru p53 a vyskytuje se minimálně v počtu šesti izoforem, které mají během vývoje epidermis a při vzniku a progresi nádorů opačné funkce. Protein p63 ovlivňuje proliferaci a diferenciaci epidermálních buněk v průběhu ontogeneze: vrozené mutace v genu *TP63* vedou k různým vývojovým deformacím a odstranění tohoto genu u myší má za následek ztrátu epidermis. Protein p63 také ovlivňuje buněčnou adhezi prostřednictvím regulace desmozomů. Ztráta kontroly proliferace buněk a mezibuněčné adheze je přitom důležitou událostí při vývoji nádorů a vysoká hladina p63 podporuje růst nádorů a brání apoptóze nádorových buněk. Tento přehledový článek stručně shrnuje úlohy proteinu p63 ve vývoji epitelů, buněčné proliferaci, adhezi a migraci a poodhaluje jeho význam při vzniku nádorových onemocnění a tvorbě metastáz.

Klíčová slova

p63 – epidermální vývoj – buněčná proliferace – buněčná adheze – vývoj nádorového onemocnění – epidermis

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Introduction

The epidermis is a peripheral skin layer that provides the human body with a natural physical protection from dehydration and pathogens. It is composed of proliferating basal and differentiated suprabasal keratinocytes [1]. The self-renewing ability of the epidermis requires an appropriate proliferation and differentiation program in the basal layer [2]. Basal stem cells proliferate to produce daughter transit amplifying cells whose proliferative capacity is more limited compared with basal stem cells. After the set of cellular divisions, TA cells migrate through the epidermis layers and begin the process of differentiation towards the formation of external skin components [3]. Recent studies have established an important developmental role for p63 in stratified tissue formation. p63 regulates transcription of multiple genes which encode transcription factors, adhesion and signalling molecules, proteins involved in the cell cycle, apoptosis and also tissue specific proteins such as keratins, involucrin and loricrin [4]. The importance of p63 in skin development was mainly supported by observations in knockout mice, that after birth lacked multilayered epithelia and any skin appendages, such as teeth, hair follicles and mammary glands which indicates that p63 defines the stem cell compartment for this tissue [5]. In this article we would like to summarise the role of p63 in the development of epidermis and demonstrate the link between p63 expression and tumourigenesis.

p63 Isoforms and Their Transactivation Properties

p63 protein is one of the most significant transcription factors engaged in the growth of keratinocytes and skin development (Fig. 1) [6,7]. Protein p63 belongs to the p53 family [8,9] and like the other family members it contains three typical domains: amino-terminal transactivation domain (TA), DNA-binding domain and carboxy-terminal oligomerisation domain (OD) (Fig. 2) [8]. p63 is encoded by the *TP63* gene. The expression of *TP63* is directed from two distinct promoters, resulting in protein isoforms either containing (TA) or lacking (ΔN) the N-terminal transactivation domain [8]. Furthermore, these transcripts can then be subjected to alternative splicing to generate at least three different C-terminal isoforms termed α, β and γ [10] and newly described δ and ε isoforms [11]. Only the α isoforms possess a sterile alpha motif (SAM) – a protein-protein interaction domain – and a transcription inhibitory domain (TI) (Fig. 2) [12,13]. ΔNp63 isoforms are recognised as a dominant negative inhibitor of TAp63 isoforms and other p53 family members [8]. Despite the fact that ΔNp63 lacks the transactivation domain prevalent in TA isoforms, it can demonstrate transactivation through the transactivation domain present in its N-terminal end [14].

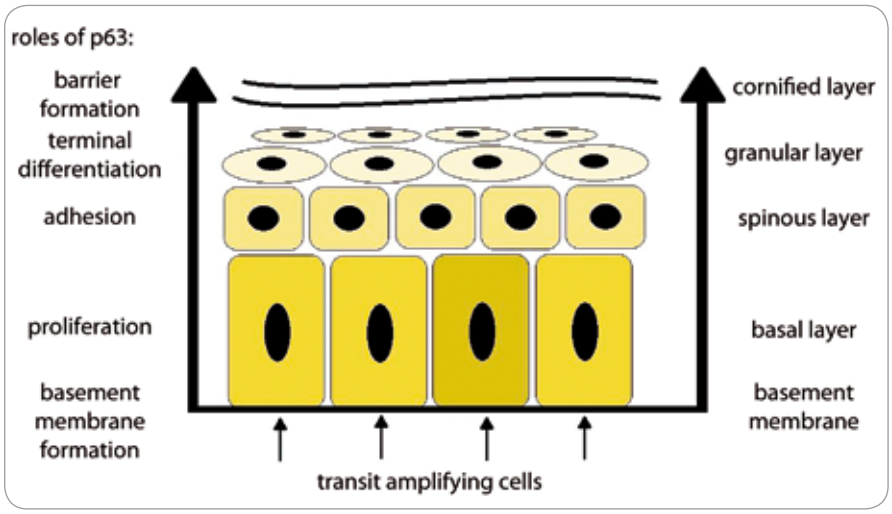

Fig. 1. Roles of p63 in epidermis formation. Epidermis consists of keratinocyte layers. Stem cells located in the basal layer divide and produce transit amplifying stem cells, which are located in the basal layer. Transit amplifying stem cells initiate terminal differentiation and form spinous layer. Continuation of this process gives rise to granular and cornified layers. p63 is engaged during the whole process of formation of the epidermis.

The Role of p63 in Proliferation and Differentiation Processes in Epidermal Cells

Though TAp63 isoforms appear earlier than ΔNp63 during embryogenesis, ΔNp63 is much more abundant in the embryo [15,16]. Transgenic mice with overexpressed TAp63α in the epidermis revealed hyperplasia and inhibited differentiation [15] indicating that the correct development of epidermis needs an adequate balance between TA and ΔN isoform levels.

p63 with its' transactivation and inhibition capacities is required for the proliferation of epidermal cells [17] and the level strictly correlates with the proliferative abilities of keratinocytes *in vitro* [18]. Experiments on developing zebrafish embryos with down-regulated ΔNp63 displayed a total loss of epidermal proliferation. Later studies in p63 knockdown epidermis showed that most of the cells ceased in G1 phase followed by an additional decrease of cells in S and G2/M phase. This phenomenon was accompanied by a reduced level of the proliferation marker Ki67 and by increased levels of cell cycle inhibitors such as WAF1 or p16. These findings thus clearly indicate that p63 knockdown cells are growth-arrested [17].

Besides playing roles in cellular proliferation processes, p63 performs an important function in the regulation of differentiation. Epidermis created from pan-p63 knockdown keratinocytes showed defects in stratification and differentiation and the expression of characteristic differentiation markers was not observed in the absence of p63. On the contrary, the loss of p63 led to the expression of markers of simple epithelium (keratins 8 and 18) which normally are not present in stratified tissues [17]. A proposed model for p63 function in the differentiation process is based on

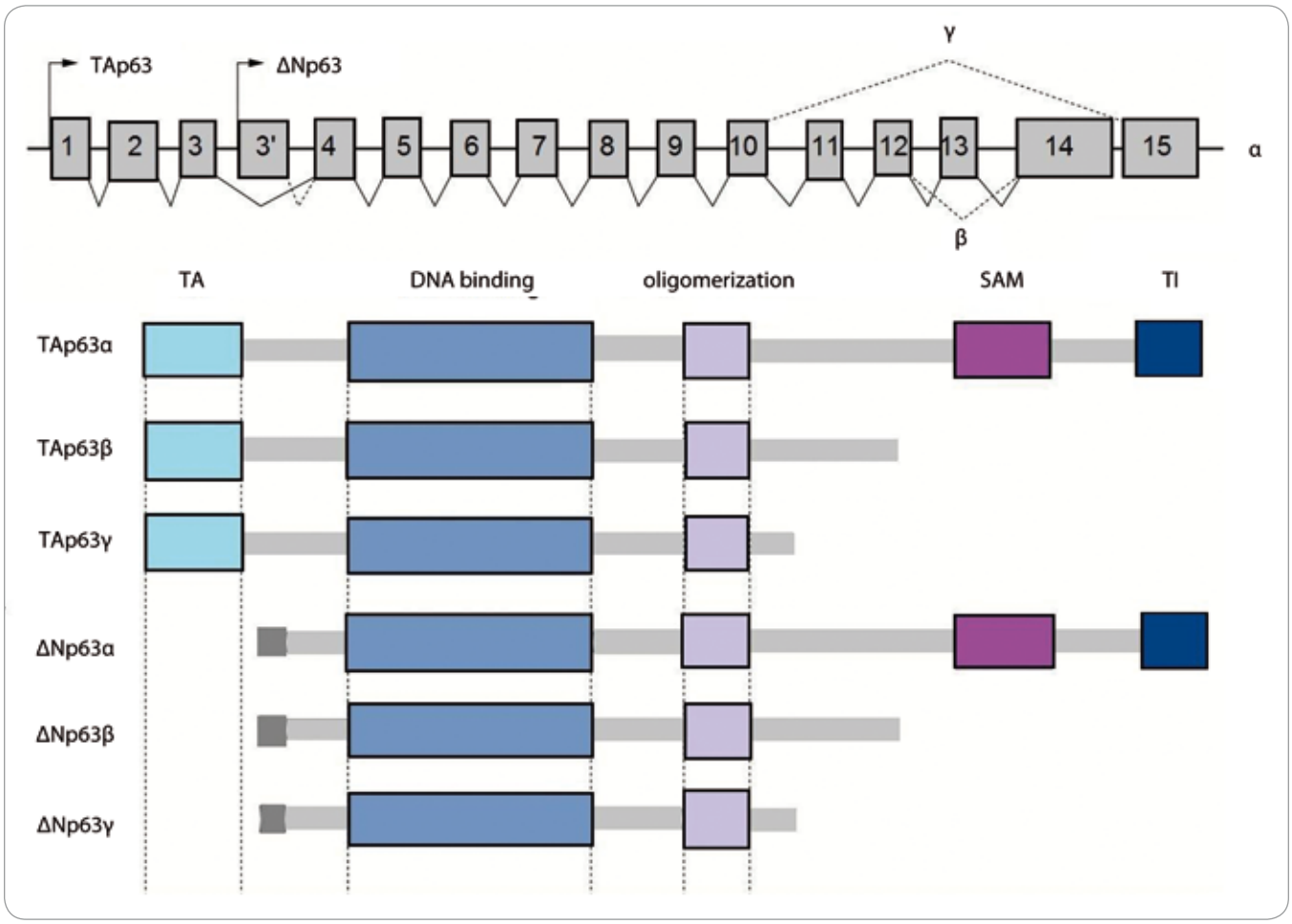

Fig. 2. Structure of the *TP63* gene and p63 protein isoforms. Depending on the promoter there are two distinct N-terminal isoforms: TAp63 – full-length and ΔNp63 – N-terminally truncated. Due to alternative splicing at the 3' end, TAp63 transcripts can produce three different C-terminal isoforms termed α, β, γ. p63 protein comprises DNA binding domain, oligomerization domain and N-terminal transactivation (TA) domain (only TA isoforms), α isoforms possess also a sterile alpha motif (SAM) and a transcription inhibitory domain (TI).

the correct balance between protein levels of p63 isoforms [15]. In the basal layers of the epidermis, ΔNp63 is the predominantly expressed isoform, but its abundance is reduced in the suprabasal layer of stratified epithelium. In contrast, increased levels of TAp63 can be observed in the upper parts of the epithelium inhibiting terminal differentiation [8,15]. While ΔNp63 seems to play a major role in stratification as well as in differentiation of epithelium, TAp63 appears to be important in its' late differentiation [17].

Recent studies revealed that differentiation of epidermal cells begins through asymmetric cell division in the basal layer [19]. This process was not observed in p63-null keratinocytes. In addition, p63 activity has been related to many genes significant in differentiation such as Notch, inhibitor of nuclear factor kappa-B kinase subunit alpha (IKKα) [20] or keratin 14 which are only expressed in basal cells within stratified epithelia [21]. IKKα plays an important role in the proliferation and differentiation process and mice with IKKα deletion displayed incorrect proliferation and differentiation of skin cells. p63 isoforms can directly transactivate IKKα by attaching to the p53-like sequence on its promoter or *via* transcription factor protein C-ets1 (Ets-1) [20,22].

Notch signalling is a major pathway that fosters stem cells to begin the process of differentiation towards keratinocytes [23,24]. One of the ligands for Notch receptor is jagged 1 protein (JAG-1), which was found to be a p63 target [25]. Notch activation can suppress p63 expression in keratinocytes while permanent p63 function inhibits the ability of Notch receptor to induce cell cycle arrest. Moreover, promoting cell cycle arrest by Notch signalling involves induction of WAF1 protein, which can be controlled by p63 [24].

The differentiation program is based on the cooperation between specific sets of genes being part of the epidermal differentiation complex (EDC) within mouse chromosome 3 and encoding components of the cornified layer [26]. Chromatin architecture within the tissue-specific EDC locus can be remodelled by special AT-rich sequence-binding protein-1 (Satb1). Satb1 functions as a genome organiser, directing chromatin-remodelling enzymes and transcription factors and therefore playing

an important role in the regulation of tissue-specific gene expression programs [27,28]. It was shown that Satb1 stimulates the differentiation of progenitor cells in the basal layer towards keratinocytes and can be directly regulated by p63 [26]. Satb1 is co-expressed with p63 in basal cells during embryonic and postnatal development and mice that have lost expression of p63 exhibited severely decreased levels of Satb1 and also loricrin (a marker of differentiated keratinocytes). Additionally, Satb1 knockout mice showed diminished epidermal cell proliferation and their skin appeared to be much thinner in comparison with wild-type Satb1 mice [29].

p63 and Skin Appendages Development

Skin appendages which include teeth, hairs and glands are derived from ectodermal and mesodermal tissues [30]. The first step of skin appendage formation is very similar for all types, when the placodes start to form a bud. However, the following events differ among them and depend on the kind of skin derivative [30,31]. Genes which control the development of skin derivatives are highly conserved across species [31]. The essential role of p63 in skin appendage development was observed in the p63-knockout mice where animals lacking p63 expression died perinatally and demonstrated a dramatic phenotype. Their epithelium stayed single-layered and lacked all the appendages such as hair follicles, teeth, whiskers and glands [5]. Analogically, mutations in p63 are related to such phenotype in humans as ectrodactyly, ectodermal dysplasia and cleft lip/palate syndrome (EEC), limb-mammary syndrome (LMS), ankyloblepharon-ectodermal defects-cleft lip/palate syndrome (AEC), acro-dermato-ungual-lacrimal-tooth syndrome (ADULT) or Rapp-Hodgkin syndrome (RHS) [32]. When developing hair, teeth and vibrissae during embryogenesis, p63 is initially expressed throughout the epithelium. With the progressive development the level of p63 decreases within the inner layers [16,33]. At the beginning, as well as during the whole process of ectoderm development, only ΔN isoforms were detected, whereas the expression of TA isoforms was observed at later stages [16]. Research in zebrafish revealed ΔNp63α to be the most abundantly expressed isoform during embryonic development [34] and mutations in p63-associated syndromes are mostly found within regions specific for the α isoform [35]. These observations suggest that ΔNp63α is the essential isoform participating in the development of skin and skin appendages.

Role of p63 in Cellular Adhesion

Among other things, p63 plays an important role in the regulation of processes mediating cell-cell adhesion within the epidermis. Reduced p63 expression in cultured mammary cells caused impaired cell adhesion and decreased expression of desmosomal components [36,37]. Furthermore, p63 was stated to directly regulate the expression of membrane protein Perp – one of the most important elements for desmosome development [38]. Desmosomes are cell to cell junction protein complexes, necessary to provide skin with the strength needed to withstand mechanical stress. They attach cell surface proteins to the intermediate cytoskeletal filaments [39,40]. Beaudry et al showed that Perp-deficient mouse epithelium had a decreased number of desmosomes and was filled with blisters leading to postnatal lethality [41]. Furthermore, they revealed that Perp acts as a significant tumour suppressor in UVB-induced squamous cell carcinoma (SCC). It plays an important role as a mediator of p53-induced apoptosis. *In vivo* experiments performed in mice confirmed that loss of Perp protein promotes tumourigenesis and contributes to tumour progression.

Studies in squamous cell carcinoma of head and neck (SCCHN) cell lines, revealed that p63 regulates genes responsible for cellular adhesion which plays a crucial role in cell invasiveness and metastatic potential of this cancer type [42] and the loss of p63 results in increased cell migration [43].

p63 in Tumourigenesis

p63 participates in the cellular signalling processes following DNA damage by controlling cell cycle arrest and apoptosis and therefore it is also important in cancer development. Probably, it does not function as a basic tumour suppressor because it is rarely mutated in human cancers. In most cases, tumours maintain p63 expression and moreover the *TP63* locus is sometimes amplified and thus p63 is overexpressed [9,44]. High level of p63 was found in more than 80% of SCCHN and other squamous epithelial malignancies [45,46]. As ΔNp63 induces proliferation it can also enhance tumour growth [47,48]. ΔNp63 binds to and suppresses p73 activity that results in the inhibition of apoptosis [45,49] and also functions as a transcriptional repressor of Bcl-2 family members, as it was found to bind to their promoters [49,50]. p63 is a key survival factor for SCC, because its inhibition by interfering RNA induces apoptosis. It is also degraded after cisplatin treatment in SCC, which seems to be an important chemotherapy response [49,51]. What is more, it was found that ΔNp63 is a novel ATM regulator, which controls p53 serine-15 phosphorylation through transcription of the ATM kinase. This research proved that, loss of ΔNp63 results in reduction of ATM-dependent phosphorylation and inversely overexpressed ΔNp63 stimulates ATM signalling. These observations suggest that ΔNp63 isoform may play a significant role in response to DNA damage [52]. Regarding TAp63 isoforms, they are expressed in some malignant lymphomas, while ΔNp63 isoform is not present [53]. However, the role of particular isoforms of p63 in cancer is still not clear and needs further investigation.

As mentioned above, p63 can regulate expression of desmosomes components. Some studies suggest that a decrease in desmosomes components occurs during cancer progression in humans and can be correlated with tumour metastasis [54,55]. Furthermore, the loss of Perp expression, a direct p63 target, can promote tumour initiation [41].

Barbieri et al showed that disruption of p63 expression in squamous cell lines led to a decrease of transcripts specific for squamous tissues and significant modifications in keratinocytes differentiation. Furthermore, it resulted in the

upregulation of non-epithelial tissues markers, where many of these proteins were associated with an increased invasiveness and metastatic potential in tumour cells [43]. Nevertheless, the role of p63 in tumourigenesis is not fully elucidated to date and remains the subject of promising cancer research.

Future Perspectives

Animal models and cell culture studies indicate that p63 plays an important role in epithelial formation, especially in the control of proliferation, differentiation and adhesion of basal stem cells. It also plays an important role in cancer progression through cell cycle arrest and the regulation of apoptosis. TAp63 and ΔNp63 isoforms may collaborate together to maintain the program of stratification and differentiation, with ΔNp63 apparently predominant in the regeneration process. Further studies into the role of p63 are crucial for better understanding of epidermis creation and cancer cell development.

References

1. Candi E, Schmidt R, Melino G. The cornified envelope: a model of cell death in the skin. Nat Rev Mol Cell Biol 2005; 6(4): 328–340.
2. Fuchs E, Raghavan S. Getting under the skin of epidermal morphogenesis. Nat Rev Genet 2002; 3(3): 199–209.
3. Koster MI. p63 in skin development and ectodermal dysplasias. J Invest Dermatol 2010; 130(10): 2352–2358.
4. Vigano MA, Mantovani R. Hitting the numbers: the emerging network of p63 targets. Cell Cycle 2007; 6(3): 233–239.
5. McKeon F. p63 and the epithelial stem cell: more than status quo? Genes Dev 2004; 18(5): 465–469.
6. Candi E, Dinsdale D, Rufini A et al. TAp63 and DeltaNp63 in cancer and epidermal development. Cell Cycle 2007; 6(3): 274–285.
7. Koster MI, Roop DR. Mechanisms regulating epithelial stratification. Annu Rev Cell Dev Biol 2007; 23: 93–113.
8. Yang A, Kaghad M, Wang Y et al. p63, a p53 homolog at 3q27-29, encodes multiple products with transactivating, death-inducing, and dominant-negative activities. Mol Cell 1998; 2(3): 305–316.
9. Murray-Zmijewski F, Lane DP, Bourdon JC. p53/p63/p73 isoforms: an orchestra of isoforms to harmonise cell differentiation and response to stress. Cell Death Differ 2006; 13(6): 962–972.
10. Barbieri CE, Pietenpol JA. p63 and epithelial biology. Exp Cell Res 2006; 312(6): 695–706.
11. Mangiulli M, Valletti A, Caratozzolo MF et al. Identification and functional characterization of two new transcriptional variants of the human p63 gene. Nucleic Acids Res 2009; 37(18): 6092–6104.
12. Ghioni P, Bolognese F, Duijf PH et al. Complex transcriptional effects of p63 isoforms: identification of novel activation and repression domains. Mol Cell Biol 2002; 22(24): 8659–8668.
13. Serber Z, Lai HC, Yang A et al. A C-terminal inhibitory domain controls the activity of p63 by an intramolecular mechanism. Mol Cell Biol 2002; 22(24): 8601–8611.
14. Helton ES, Zhu J, Chen X. The unique NH2-terminally deleted (DeltaN) residues, the PXXP motif, and the PPXY motif are required for the transcriptional activity of the DeltaN variant of p63. J Biol Chem 2006; 281(5): 2533–2542.
15. Koster MI, Kim S, Mills AA et al. p63 is the molecular switch for initiation of an epithelial stratification program. Genes Dev 2004; 18(2): 126–131.
16. Laurikkala J, Mikkola ML, James M et al. p63 regulates multiple signalling pathways required for ectodermal organogenesis and differentiation. Development 2006; 133(8): 1553–1563.
17. Truong AB, Kretz M, Ridky TW et al. p63 regulates proliferation and differentiation of developmentally mature keratinocytes. Genes Dev 2006; 20(22): 3185–3197.
18. Pellegrini G, Dellambra E, Golisano O et al. p63 identifies keratinocyte stem cells. Proc Natl Acad Sci USA 2001; 98(6): 3156–3161.
19. Lechler T, Fuchs E. Asymmetric cell divisions promote stratification and differentiation of mammalian skin. Nature 2005; 437(7056): 275–280.
20. Candi E, Terrinoni A, Rufini A et al. p63 is upstream of IKK alpha in epidermal development. J Cell Sci 2006; 119(Pt 22): 4617–4622.
21. Herfs M, Hubert P, Delvenne P. Epithelial metaplasia: adult stem cell reprogramming and (pre)neoplastic transformation mediated by inflammation? Trends Mol Med 2009; 15(6): 245–253.
22. Gu L, Zhu N, Findley HW et al. Identification and characterization of the IKKalpha promoter: positive and negative regulation by ETS-1 and p53, respectively. J Biol Chem 2004; 279(50): 52141–52149.
23. Dotto GP. Crosstalk of Notch with p53 and p63 in cancer growth control. Nat Rev Cancer 2009; 9(8): 587–595.
24. Rangarajan A, Talora C, Okuyama R et al. Notch signaling is a direct determinant of keratinocyte growth arrest and entry into differentiation. EMBO J 2001; 20(13): 3427–3436.
25. Nguyen BC, Lefort K, Mandinova A et al. Cross-regulation between Notch and p63 in keratinocyte commitment to differentiation. Genes Dev 2006; 20(8): 1028–1042.
26. Martin N, Patel S, Segre JA. Long-range comparison of human and mouse Sprr loci to identify conserved non-coding sequences involved in coordinate regulation. Genome Res 2004; 14(12): 2430–2438.
27. Cai S, Lee CC, Kohwi-Shigematsu T. SATB1 packages densely looped, transcriptionally active chromatin for coordinated expression of cytokine genes. Nat Genet 2006; 38(11): 1278–1288.
28. Pavan Kumar P, Purbey PK, Sinha CK et al. Phosphorylation of SATB1, a global gene regulator, acts as a molecular switch regulating its transcriptional activity in vivo. Mol Cell 2006; 22(2): 231–243.
29. Fessing MY, Mardaryev AN, Gdula MR et al. p63 regulates Satb1 to control tissue-specific chromatin remodeling during development of the epidermis. J Cell Biol 2011; 194(6): 825–839.
30. Millar SE. Molecular mechanisms regulating hair follicle development. J Invest Dermatol 2002; 118(2): 216–225.
31. Mikkola ML, Millar SE. The mammary bud as a skin appendage: unique and shared aspects of development. J Mammary Gland Biol Neoplasia 2006; 11(3–4): 187–203.
32. Celik TH, Buyukcam A, Simsek-Kiper PO et al. A newborn with overlapping features of AEC and EEC syndromes. Am J Med Genet A 2011; 155A(12): 3100–3103.
33. Rufini A, Weil M, McKeon F et al. p63 protein is essential for the embryonic development of vibrissae and teeth. Biochem Biophys Res Commun 2006; 340(3): 737–741.
34. Bakkers J, Hild M, Kramer C et al. Zebrafish DeltaNp63 is a direct target of Bmp signaling and encodes a transcriptional repressor blocking neural specification in the ventral ectoderm. Dev Cell 2002; 2(5): 617–627.
35. Rinne T, Hamel B, van Bokhoven H et al. Pattern of p63 mutations and their phenotypes-update. Am J Med Genet A 2006; 140(13): 1396–1406.
36. Carroll DK, Carroll JS, Leong CO et al. p63 regulates an adhesion programme and cell survival in epithelial cells. Nat Cell Biol 2006; 8(6): 551–561.
37. Cheng X, Koch PJ. In vivo function of desmosomes. J Dermatol 2004; 31(3): 171–187.
38. Ihrie RA, Marques MR, Nguyen BT et al. Perp is a p63-regulated gene essential for epithelial integrity. Cell 2005; 120(6): 843–856.
39. Green KJ, Gaudry CA. Are desmosomes more than tethers for intermediate filaments? Nat Rev Mol Cell Biol 2000; 1(3): 208–216.
40. Yin T, Green KJ. Regulation of desmosome assembly and adhesion. Semin Cell Dev Biol 2004; 15(6): 665–677.
41. Beaudry VG, Jiang D, Dusek RL et al. Loss of the p53/p63 regulated desmosomal protein Perp promotes tumorigenesis. PLoS Genet 2010; 6(10): e1001168.
42. Gu X, Coates PJ, Boldrup L et al. p63 contributes to cell invasion and migration in squamous cell carcinoma of the head and neck. Cancer Lett 2008; 263(1): 26–34.
43. Barbieri CE, Tang LJ, Brown KA et al. Loss of p63 leads to increased cell migration and up-regulation of genes involved in invasion and metastasis. Cancer Res 2006; 66(15): 7589–7597.
44. Mills AA. p63: oncogene or tumor suppressor? Curr Opin Genet Dev 2006; 16(1): 38–44.
45. DeYoung MP, Johannessen CM, Leong CO et al. Tumor-specific p73 up-regulation mediates p63 dependence in squamous cell carcinoma. Cancer Res 2006; 66(19): 9362–9368.
46. Sniezek JC, Matheny KE, Westfall MD, et al. Dominant negative p63 isoform expression in head and neck squamous cell carcinoma. Laryngoscope 2004; 114(12): 2063–2072.
47. Hibi K, Trink B, Patturajan M et al. AIS is an oncogene amplified in squamous cell carcinoma. Proc Natl Acad Sci USA 2000; 97(10): 5462–5467.
48. Massion PP, Taflan PM, Jamshedur Rahman SM et al. Significance of p63 amplification and overexpression in lung cancer development and prognosis. Cancer Res 2003; 63(21): 7113–7121.
49. Rocco JW, Leong CO, Kuperwasser N et al. p63 mediates survival in squamous cell carcinoma by suppression of p73-dependent apoptosis. Cancer Cell 2006; 9(1): 45–56.
50. Chung J, Lau J, Cheng LS et al. SATB2 augments DeltaNp63alpha in head and neck squamous cell carcinoma. EMBO Rep 2010; 11(10): 777–783.
51. Li Y, Zhou Z, Chen C. WW domain-containing E3 ubiquitin protein ligase 1 targets p63 transcription factor for ubiquitin-mediated proteasomal degradation and regulates apoptosis. Cell Death Differ 2008; 15(12): 1941–1951.
52. Craig AL, Holcakova J, Finlan LE et al. DeltaNp63 transcriptionally regulates ATM to control p53 Serine-15 phosphorylation. Mol Cancer 2010; 9: 195.
53. Pruneri G, Fabris S, Dell'Orto P et al. The transactivating isoforms of p63 are overexpressed in high-grade follicular lymphomas independent of the occurrence of p63 gene amplification. J Pathol 2005; 206(3): 337–345.
54. Yashiro M, Nishioka N, Hirakawa K. Decreased expression of the adhesion molecule desmoglein-2 is associated with diffuse-type gastric carcinoma. Eur J Cancer 2006; 42(14): 2397–2403.
55. Papagerakis S, Shabana AH, Pollock BH et al. Altered desmoplakin expression at transcriptional and protein levels provides prognostic information in human oropharyngeal cancer. Hum Pathol 2009; 40(9): 1320–1329.