Contribution of p53, p63, and p73 to the developmental diseases and cancer
Minireview

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Tumor suppressor TP53 gene is one of the most mutated genes in human genome. Inactivating somatic mutations and disruption of p53 protein have been described in almost all human malignancies. Its inactivation by germline mutation leads to the rare but severe familial precancerosis termed Li-Fraumeni syndrome. This syndrome is characterized by the early onset of different types of cancers including soft-tissue sarcomas, breast and brain cancers, leukemias, lung, laryngeal cancers, and adrenocortical carcinomas. The key role of p53 in tumor suppression has been confirmed in animal models as well. The p53 -knock-out and knock-in animals were born alive but were tumor prone. In late nineties, two genes with high homology with TP53 were discovered, TP73 and TP63, respectively. Animal models showed that p73 is an important player in neurogenesis, sensory pathways and homeostatic control. The p63 is critical for the development of stratified epithelial tissues such as epidermis, breast, and prostate. Despite the structural similarities with p53, the function of these proteins in tumorigenesis is controversial. On one hand, there are evidences that both, p63 and p73-deficient animals are not tumor prone, on the other hand, there is evidence that such animals develop tumors later during their life. Unlike in TP53 gene, mutations in TP63 and TP73 genes are rare, however, germline mutations in TP63 are linked to the human developmental diseases. In this minireview, we describe the contribution of the p53, p63, and p73 to human pathology with emphasis on their different roles in development and tumorigenesis.

Key words: p53, p63, p73, tumor suppression, tumorigenesis, germline mutation

p53. The linkage between p53 and human pathology has been known for a long time. The TP53 is mapped in the short arm of the chromosome 17 (17p13.1) [1, 2, 3]. This locus is often deleted and affected by loss of heterozygosity found in number of human tumors including breast [4], ovarian [5], lung [6], and brain [7]. In the cell, p53 protein predominantly exists as a single isoform [8].

TP53 gene is found to be mutated on somatic as well as on germline level, respectively. According to the IARC TP53 mutation database [9], more than 75% of all p53 gene mutations on both levels are missense single base substitutions, while deletions of TP53 gene represent less than 0.5%. This situation is more typical for oncogene than for tumor suppressor and points to the oncogenic feature of mutated p53, mainly by dominant-negative effect. There is couple of hotspot mutations described for p53 including codons 175, 245, 248, 273, and 337 [10]. It is apparent that these mutations affect mainly the central DNA-binding region of p53 protein. Such a protein is stable, accumulates in the nucleus of tumor cells but it lacks its specific DNA-binding activity and transactivating properties [11, 12].

More than half of human tumors bear inactivating mutations. The already mentioned IARC database and other works show wide range of tumors with identified TP53 gene mutations including tumors of colorectum, lung, breast, and leukemias [9, 10]. On the other hand, kidney tumors show very small percentage of all mutations identified [11].

Germline mutations of TP53 are linked with early onset of breast carcinomas, soft-tissue sarcomas, osteosarcomas, leukemias, brain tumors, and adrenocortical carcinomas [9]. Together, these types of cancers are characteristic for a rare autosomal dominantly inherited disorder termed Li-Fraumeni syndrome [13, 14, 15]. It is characterized by the early onset of aforementioned cancers in individuals from affected families. Families, in which classic phenotype of syndrome is not ex-

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pressed completely, are termed Li-Fraumeni syndrome-like and are represented by many different features. Occurrence of a variety of cancers is common to all of these families. In our laboratory, we have found a germline p53 mutation in combination with the germline mutation in APC gene in a family severely affected by different types of cancer including colorectal and breast cancers [16].

To study the function of mutant TP53 in living organism, knock-out and knock-in mice have been prepared [17, 18]. The knock-out mouse lacking both copies of TP53 is assured of developing some form of malignant growth within 2 to 10 months after birth. Most commonly, these animals die from thymic lymphomas, although a significant number of animals develop a range of sarcomas [17]. Unlike null mice, heterozygotes lacking one allele develop a greater number of mesenchymal cancers including fibrosarcomas, osteosarcomas, and hemangiosarcomas [18]. Interestingly, both p53 null and heterozygotes, develop low percentage of carcinomas, or epithelial cancers. This is not in agreement with the situation in man where, for example in colorectal cancer, loss of p53 is very often associated with transition of benign adenoma to a malignant carcinoma [19]. This discrepancy might be explained by the differences between human and mouse genetic background, including different length of telomeres [20].

The knock-in animals are generated by the introduction of altered form of p53 into its endogenous genomic locus. Such p53 constructs bear mutations commonly found in human tumors, including the most frequent missense point substitutions. These p53 heterozygote animals express high percentage of carcinomas, including lung adenocarcinomas and squamous cell carcinomas what is phenotype similar to that of Li-Fraumeni syndrome patients [21, 22].

In addition, the p53 functions may be affected by single nucleotide polymorphisms. The well known p53 polymorphisms are BstUI in exon 4 and MspI in intron 6 which are both studied in connection with different type of cancers, including breast cancer [23].

p73. The TP73 gene is localized at chromosome 1p36 which is a region frequently deleted in neuroblastoma, colon cancer, melanoma, and breast cancer [24, 25]. The p73 is found in numerous isoforms in cell, including TA isoform expressed with transactivation domain, and ΔN without this domain [26]. In addition, C-terminal region splicing gives a rise to at least seven isoforms of p73 (α, β, γ, δ, ε, ζ, and η) [8, 26, 27].

Based on structural similarities, it has been hypothesized that p73 could be a new tumor suppressor. However, there was no germline mutation found in TP73 and also somatic p73 mutations were rare in human tumors [28, 29].

In contrast with the p53-deficient mice, which exhibit increased susceptibility to spontaneous tumorigenesis, initial experiments using p73 deficient mice did not confirm its role in tumor suppression [30]. These mice exhibited neurological, pheromonal and inflammatory defects but did not develop tumor phenotype. The p73 knock-out mice survived birth but often died after 4 to 6 weeks of chronic infections. These findings indicated the role of p73 as an important factor in development of the central nervous system, sensory pathways and homeostatic control but did not suggest its role in tumor suppression [30]. These observations led to the speculation that despite its structural homology with p53, the p73 might not be tumor suppressor as its counterpart p53.

In contrary, the p73 seems to have an oncogenic potential what was underlined by the observations of increased expression of variety of p73 isoforms in primary tumors and tumor cell lines. A number of human malignancies have been reported to express high levels of p73 including neuroblastomas [31], lung [32], breast carcinoma [33], bladder cancer [34], ovarian cancer [35], gastric cancer [36], esophageal carcinoma [37] and in other malignancies. Moreover, patients with overall higher expression of p73 isoforms have a poorer prognosis than those with undetectable level [38, 39].

More recently, using antibodies or RT-PCR for specific isoforms of p73 enables to elucidate the function of p73 isoforms more precisely. It is evident that the TA isoform has similar properties as a wild type p53, so, it has the ability to transactivate p53 responsible genes. Thus TA isoform is likely to play a tumor suppressor role in human tumors [40]. On the other hand, the ΔN isoform is thought to play a role in blocking the transactivation of both, p53 and TA isoform target genes such as p21, Bax, MDM2 or 14-3-3σ and it is considered to be a dominant-negative transcriptional inhibitor of p73 [41, 42]. There are evidences that some tumors do have increased expression of ΔN isoform, including malignant gynecological tumors, breast cancers, gastric, and esophageal adenocarcinomas [41, 43, 44]. In gastric and esophageal cancer-derived cell lines, ΔNp73 is specifically overexpressed, which leads to suppression of p73 transcriptional and apoptotic activity, as well as to increase of β-catenin protein levels and activation of TCF-dependent transcription [43]. However, it is worth to note, that overexpression of proapoptotic TA isoform has been also described in these cells [43].

The function of p73 in tumor suppression is after recent findings of Flores et al. [45] even more controversial. Unlike the results of Yang et al. [30], Flores and coworkers used mice with deleted p73 DNA-binding domain. In these experiments, ten percent of $p73^{+/-}$ mice developed lung adenocarcinomas, 12.5% developed thymic lymphoma and the same percent developed hemangiosarcomas by the age of two years. Together with the observation of loss of heterozygosity in $p73^{+/-}$ tumors, these data support the tumor suppressive functions of p73 and its prominent role in suppression of tumorigenesis [45]. The exact mechanism of p73 in tumor suppression remains to clarify.

p63. The TP63 gene is localized at chromosome 3q27 [46]. Like the p73, the p63 protein is found in numerous isoforms as well. The TA isoform is expressed with transactivation domain, whereas ΔN is expressed without this domain [46]. In addition, C-terminal region splicing leads to creation of at least three isoforms of p63 (α, β, and γ) [46].

Unlike the TP73 gene, the germline mutations have been found in the TP63 gene and are linked with several human syndromes such as EEC, LMS, SHFM4, AEC/Hay-Wells, RHS, and ADULT. The EEC syndrome is characterized by the presence of malformation of hands and feet (ectrodactyly), ectodermal dysplasia, and clefting of the lip and palate [47]. The LMS (limb-mammary) syndrome was described as a disorder with presence of severe hand and/or foot anomalies, and hypoplasia/aplasia of the mammary gland and nipple [48]. The SHFM4 (split-hand/split foot malformation) syndrome also expresses developmental abnormalities of limbs with syndactyly, median clefts of the hands and feet, and aplasia and/or hypoplasia of the phalanges, metacarpals, and metatarsals. Some SHFM4 patients have been found to have mental retardation, ectodermal findings, and orofacial clefting [49]. The AEC (ankyloblepharon-ectodermal defects-cleft lip/palate) and RHS (Rapp-Hodgkin) syndromes are probably the same genetic disorder with variable manifestation. It is characterized by the presence of different abnormalities including congenital ectodermal dysplasia with coarse, wiry, sparse hair, dystrophic nails, slight hypohydrosis, scalp infection, hypodontia, maxillary hypoplasia and cleft lip/palate [50]. The ADULT syndrome phenotypically overlaps all mentioned disorders. Affected patients show defects of hands and fingers, hypoplastic breast and nipples, loss of permanent teeth, atrophic dry, photosensitive skin, dermatitis, thin, sparse blond hair etc. [51].

There is an evident correlation between certain p63 mutations and the phenotype of these syndromes. The mutations in codons 204, 227, 279, 280, and 304 lead to the amino acid substitution and are present in about 75% of all EEC patients. These mutations affect DNA binding domain of p63 protein [52]. The p63 gene mutations were initially detected in eight AEC families and all were missense mutations in SAM domain [53]. As well as AEC patients, the RHS patients display SAM localized mutations in p63 gene which support the idea that these two syndromes are the variants of the same genetic disorder [50]. Patients with LMS syndrome showed frameshift mutations in exon 13. The location of these mutations is probably the factor which causes slightly different phenotype than EEC, especially missing hair and skin defects in LMS [52]. In ADULT syndrome, the missense mutations in TA domain as well as in DNA binding domain were described [54]. To date, eight p63 gene mutations have been described in SHFM patients what counts about 10% of all SHFM cases. These mutations were dispersed along the p63 gene [55].

The p63 plays a key function in development. This is clearly demonstrated in $p63^{-/-}$ mice which show different developmental defects including the complete lack of all stratified squamous epithelia and their derivates, such as epidermal appendages and mammary, lacrimal, and salivary glands. Due to the lack of an epidermal barrier, these mice dehydrate and die shortly after birth. In addition, these mice develop craniofacial abnormalities including cleft lip and palate and a lack of teeth [56, 57]. These phenotypes clearly correspond with those of human developmental syndromes with p63 mutations.

Like in the case of p73, role of p63 as a tumor suppressor in tumorigenesis is controversial. On one hand, the $p63^{+/-}$ mice were not tumor prone and mice heterozygous for p63 and p53 had fewer tumors than $p53^{+/-}$ mice alone [58]. On the other hand, there is opposing evidence, that $p63^{+/-}$ mice did develop tumors at the age of approximately 12 months . Ten percent of these mice developed squamous cell carcinomas, and 20% developed histiocytic sarcomas. In addition, mice heterozygous for p63 and p53, and for p73 and p53 develop a more severe phenotype with higher tumor burden and metastases [45].

It is apparent that p63 plays a role in human tumorigenesis as well. In tumors, predominant isoform is ΔNp63 which was shown to be overexpressed in different malignancies including lung cancer cells [59], head and neck squamous cell carcinomas [60], bladder carcinomas [61] and others. The contribution of ΔNp63 to tumorigenesis may be associated with its function as a critical inhibitor of proapoptotic TAp73 isoform [62]. However, it still remains to be determined whether apoptosis is the sole function of TAp63 and TAp73 that is essential for their proposed tumor-suppressive property [63].

Conclusion

The tumor suppressor gene TP53 is one of the most studied genes in the human genome. The mutations in this gene signify the increased risk of cancer development in affected persons. Moreover, the germline mutation leads to the expression of severe Li-Fraumeni syndrome characterized by the early onset of different type of cancers. Such a situation is also well documented in animal models.

One would expect that p63 and p73 will have similar roles in cell biology and thus they would contribute to pathogenesis in the similar manner than p53 does. However, this is not the case. Despite their structural similarities with p53, these two members of the p53 family do not seem to be classic tumor suppressors as their counterpart p53. While p73 is an important player in neurogenesis, sensory pathways and homeostatic control, p63 is critical for the development of stratified epithelial tissues such as epidermis, breast, and prostate. However, increased or decreased expression of p63 and p73 in some tumors clearly point to the fact that these proteins do imply in cancer, moreover, in tissue specific manner. The exact mechanism of how they contribute to the human cancer remains an open question. It is apparent that to answer this question will need to understand the role of all isoforms in the interaction network which members of p53 protein family create.

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