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Review Article

The *p53* gene with emphasis on its paralogues in mosquitoes

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Abstract The *p53* gene is highly important in human cancers, as it serves as a tumor-suppressor gene. Subsequently, two p53 homologues, *i.e.*, p73 and p63, with high identity of amino acids were identified, leading to construction of the p53 family. The *p53* gene is highly important in human cancer because it usually transcribes genes that function by causing apoptosis in mammalian cells. In contrast, p63 and p73 tend to be more important in modulating development than inducing cell death, even though they share similar protein structures. Relatively recently, p53 was also identified in mosquitoes and many other insect species. Uniquely, its structure lacks the sterile alpha motif domain which is a putative protein-protein interaction domain and exclusively exists at the C-terminal region in p73 and p63 in mammals. A phylogenetic analysis revealed that the *p53* gene derived from mosquitoes is composed of two paralogues, p53-1 and p53-2. Of these, only p53-2 is responsively up-regulated by dengue 2 virus (DENV2) in C6/36 cells which usually survive the infection. This indicates that the *p53* gene is closely related to DENV infection in mosquito cells. The specific significance of p53-2's involvement in cell survival from virus-induced stress is described and briefly discussed in this report.

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Background

The eukaryotic cell cycle is normally divided into four distinct phases, G_1, S, G_2, and M; its progression can be downregulated through a p53-depedent pathway when stress-induced DNA damage occurs.[1] The *p53* gene in mammal cells was demonstrated to be a critical mediator of the apoptotic response to DNA double-strand (ds) breaks via the transcriptional activation of proapoptotic genes.[2] Therefore, the genomic integrity of a cell population or organism can be maintained. Mutation of the *p53* gene and/or a functional defect in the p53 pathway usually results in ineffectiveness in causing apoptosis which was found in most human tumor cells.[3] About 50% of cancer cases are estimated to possess a mutation of the *p53* gene, and almost all cancers exhibit inactivity of p53.[4] p53 is genetically conserved in a broad spectrum from mammals to lower invertebrates.[5] Two more homologs, *i.e.*, p63 and p73, were subsequently discovered as additional members of the p53 family.[6] The common ancestor gene of p53 family members is supposed to be the first gene that duplicated to produce a p53 gene and a p63/p73 ancestor in cartilaginous fish.[7] Bony fish and higher vertebrates contain all three genes with diverse functions despite their possessing preserved structural features.[8]

The p53 family

The basic structure of p53 is composed of four conserved domains (Fig. 1), including an amino-terminal transactivation domain (TAD) consisting of a proline-rich domain (PR), a central DNA-binding domain (DBD), and a carboxy-terminal oligomerization domain (OD).[9] The TAD is highly associated with the cell fate, presumably governing genes involved in cellular senescence, DNA editing, and repair pathways.[10] The DBD is located in the central region and is the target of most p53 mutations found in human cancers.[9] The OD contains a nuclear export signal (NES) and contributes to form a dimer of two dimers of p53 in structure.[9] The sterile alpha motif (SAM) is a putative protein-protein interaction domain that exclusively exists in the C-terminal region of p63 and p73.[11] The SAM domain is necessary to stabilize the OD structure in both p63 and p73.[11] In many proteins, the SAM domain is involved in signaling and transcription, providing a structure which appropriately binds phosphotyrosine phosphatase and initiates downstream signaling events.[12]

It was reported that p53 independently duplicates, and therefore, it is a divergent ancestral gene from p63 and p73, although they have shared structural identities to each other.[13] Comparing gene compositions, p63 and p73 are more similar to each other than each of them is to p53.[7] As a result, p63 and p73 are thought to have more-ancient roots and are likely to be the ancestors of p53.[6] However, there is increasing evidence showing that they have shared, overlapping functions. For instance, they may commonly induce cell-cycle arrest and apoptosis in cells.[14] Nevertheless, distinct functions among them are also reported, such as involvement in regulating stress responses to suppress tumors, ectoderm development, and both.[15] DNA damage usually activates p53 but not p63 or p73[14], further revealing the existence of different physiological functions among members of the p53 family. In a study using p63 and p73 knockout in mice, developmental abnormalities but not cancer susceptibility were observed.[16] Another study also showed that the combined loss of p63 and p73 caused failure of apoptosis in cells containing functional p53 in response to DNA damage.[17] Mutations of p63 and p73 rarely being found in human cancers reflects that p63 and p73 are more important in modulating development than in inducing cancer.[4] Nevertheless, p53, p73, and p63 may interact with each other, as p53 mutants with loss of the tumor-suppressing capacity were reported to inactivate p73.[15,18] Studies on their interactions are required for further clarification of relationships among them.[10]

In a cell in a resting status, p53 is localized in the cytoplasm, while it accumulates in the nucleus following stress and functions as a transcription factor.[19] According to a genome-wide investigation, 149 putative new p53 target genes were highly associated with cancer.[20] Another study further revealed that at least 125 protein-coding genes and noncoding RNAs are transcriptional targets directly regulated by p53 under a wide range of stress signals in cells.[21] These results suggest that p53 is responsive to various stresses induced by chemical mutagens, irradiation, viral infections, etc.[1] In addition, diverse transcriptional co-regulators may be recruited to regulate cellular RNA

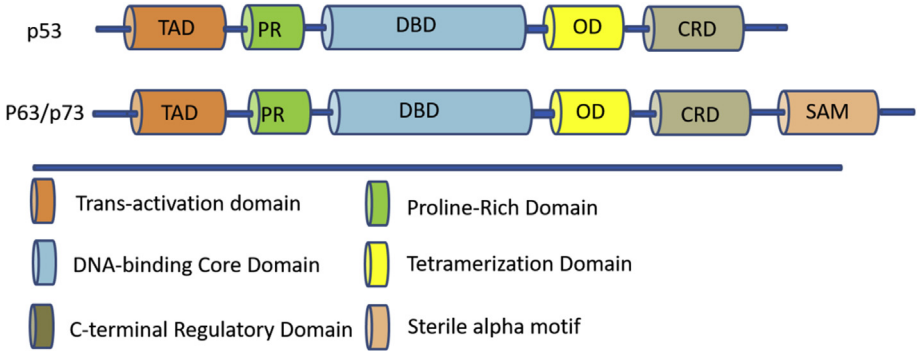

Fig. 1. Schematic structures of p53 and p63/p73 members of the p53 family. All of them are composed of a transactivation domain (TAD), proline-rich domain (PR), DNA-binding core domain (DBD), oligomerization domain (OD), and C-terminal regulatory domain (CRD) while an additional sterile alpha motif (SAM) exclusively exists at the C-terminus of p63 and p73.

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