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p63 the guardian of human reproduction

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p63 is a transcriptional factor implicated in cancer and development. The presence in *TP63* gene of alternative promoters allows expression of one isoform containing the N-terminal transactivation domain (TA isoform) and one N-terminal truncated isoform (ΔN isoform). Complete ablation of all p63 isoforms produced mice with fatal developmental abnormalities, including lack of epidermal barrier, limbs and other epidermal appendages. Specific TAp63-null mice, although they developed normally, failed to undergo in DNA damage-induced apoptosis during primordial follicle meiotic arrest, suggesting a p63 involvement in maternal reproduction. Recent findings have elucidated the role in DNA damage response of a novel Hominidae p63 isoform, GTAp63, specifically expressed in human spermatic precursors. Thus, these findings suggest a unique strategy of p63 gene, to evolve in order to preserve the species as a guardian of reproduction. Elucidation of the biological basis of p63 function in reproduction may provide novel approaches to the control of human fertility.

Introduction

p63 is the most ancient member of p53 family of gene, in which is included, besides p53, also p73. p63, like the other two members, uses an alternative promoter at the 5' end of the gene to allow the expression of two different N-terminal isoforms, one containing the N-terminal transactivation domain (TA isoform) and an N-terminal truncated isoform (ΔN isoform) that lacks this domain.[1] Moreover, the C-terminal sequence undergoes alternative splicing that gives rise to a wide range of TA and ΔN isoforms with different C-terminal organization.[2-4] The DNA binding domain (DBD) in the p53 family is the region with the highest degree of conservation among the different protein members and throughout the evolutionary lineage, and, therefore, all family members bind to conserved p53 response elements (p53RE) in promoter DNA. However, there may also be some subtle preferences in the precise nucleotide sequence in the RE recognized by different family members.

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The importance of the p53 family is highlighted by the global impact that these three genes have on cellular function. p53, the first family member to be identified, mainly acts as a tumor suppressor[5-10] and plays a key role in maintaining the integrity of somatic cells in the vertebrate genome.[11-15] Following DNA damage, activation of p53[16-19] leads to cell cycle arrest,[20-22] apoptosis,[23-29] induction of senescence or differentiation.[30-39] p63 partially shares common functions in the DNA damage response with p53.[40] After inactivating mutations of the p53 gene, found in more than 50% of human cancers,[41-44] p63 and p73 can at least partially compensate for the functional loss of p53.[45-55] However, p63 has its own very distinct roles. The first p63-knockout mouse models, independently generated by two groups in 1999, revealed a fundamental role for p63 in epidermal development. p63-null mice die shortly after birth due to the lack of an epidermal barrier and consequent dehydration. They also show additional developmental defects, including lack of limbs and other epidermal appendages. This phenotype led to two different interpretations: lack of proper epidermal stratification and commitment of epidermal embryonic precursors, or a failure in the maintenance of the full repertoire of epidermal stem cells, despite normal commitment and differentiation capabilities.[56-62] However, accumulating data favor the hypothesis that ΔNp63, the dominant isoform in the skin, is crucial for the maintenance of the epidermal stem cell niche and for the proliferation of committed precursors.[34,63-67] Conditional ΔNp63-null mice showed some patches of keratinocytes, which were able to stratify and undergo a program of terminal differentiation, as shown by the expression of loricrin, filaggrin and involucrin in the isolated clusters of disorganized epithelial cells.[68] This finding supports the hypothesis that the absence of p63 results in progenitor cell exhaustion of skin keratinocytes. The ΔNp63-null largely phenocopies the full p63-null (lacking all p63 isoforms) exhibiting severe developmental abnormalities including truncated forelimbs, absence of hind limbs and stratified epidermis.[68] In contrast, the role of TAp63 isoforms in specifying epidermal development has been controversial. The TAp63-null mice developed by McKeon's group did not show any evident morphological defects,[69] while the TAp63-null mouse engineered in Flores's lab, despite normal development, showed accelerated aging, blisters, skin ulcerations, senescence of hair follicles and alopecia.[69] This complex phenotype is dependent on defective proliferation and senescence of dermal and epidermal precursors, and suggests that TAp63

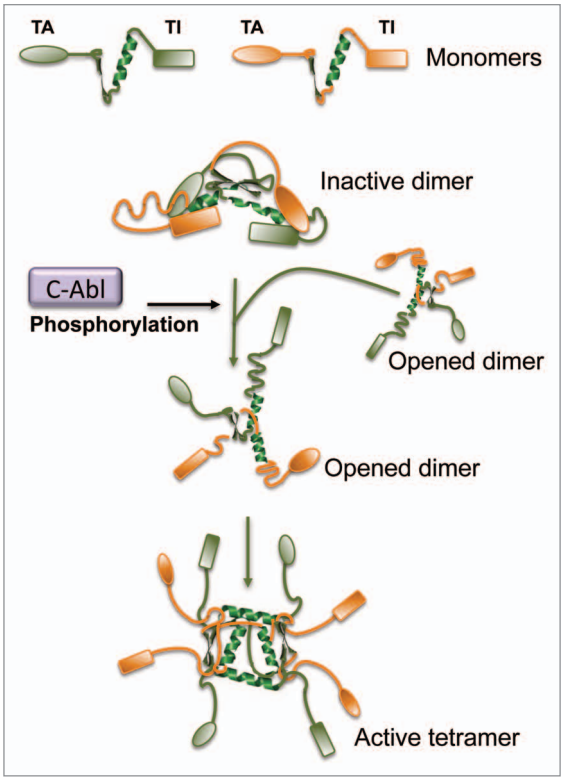

Figure 1. Schematic representation of TAp63a's switch from an inactive dimer to an active tetramer. Interactions within the TAp63a dimer maintain the transcriptional factor in an inactive form: the TA domain from one monomer respectively interacts with TI domain from opposite monomer. Phosphorylation is required to open dimers and allows interaction for tetramerizion. C-Abl is one of the kinases able to trigger activating phosphorylation. TA, transactivation domain; TI, transactivation inhibitory domain.

may also have a role in maintenance of skin stem cells. However, McKeon's work clearly showed that TA isoforms, encoded by p63 gene, are strongly expressed in oocyte nuclei and are responsible for the protection of the female germ line during meiotic arrest.[69] In this review we will discuss the mechanism of p63 function in germ line protection, and we will analyze some aspects concerning the evolutionary pressure which p63 has been undergone to refine its function.

p63 in Protection of Female Germ Line

Preservation of genomic integrity in somatic cells derives from evolution of mechanisms for germ line protection; this last process, indeed, has been fundamental for maintenance of the species during the evolution. Cells from female germ line undergo meiosis in order to generate haploid cells necessary for sexual division. Meiosis is a multiple steps process that starts during embryonic development and temporarily stops when cells reach a tetraploid state. This time window, in female germ line, is extraordinary extended for a long time period, until the specific hormone signaling induces the maturation of oocytes during the ovulation. The extended length of this phase (more than 1 y in mice and decades in humans) places the immature oocytes in a potentially vulnerable state; therefore, effective mechanisms are required for genomic integrity maintenance and the preservation of related species.

Although p63 appears to be completely dispensable for oogenesis, primordial and primary follicles show strong expression of TAp63. The high amount of TAp63 is maintained in an inactive status by the inhibited dimer form, which presents a very low DNA binding affinity. Phosphorylation triggers a conformation change, which releases the inhibitory interaction within the dimer and allows TAp63 tertramerization, increasing the affinity for DNA and transcriptional machinery (**Fig. 1**).[70-72] This tight control of p63 is necessary for the crucial function that TAp63 exerts in controlling oocyte death. TAp63, indeed, is phosphorylated and activated following DNA double-strand breaks (DSBs), induced by ionized radiation or cisplatin treatment.[73] Oocytes from TAp63-null mice showed resistance to high doses of gamma irradiation, while WT oocytes or p53-null oocytes are completely killed.[69] Phosphorylation appeared to irreversibly trigger TAp63 tetrameric state. Treatment with λ-phosphatase, though, leads to complete dephosphorylation of p63, does not affect tetramer conformation, preserving DNA binding affinity of TAp63. However, in contrast to the dimer, this active form shows high susceptibly to degradation. Consistently it has been shown that efficient degradation requires TA domain accessibility.[74-77] Therefore, E3 ligase ITCH[78] or MDM2[79-82] can control intracellular concentration of TAp63 active form, while dimers, hiding the ammino acid consensus for E3 ligases,[16,83] preserve higher protein stability. These biochemical characteristics guarantee a constant high level of inactive TAp63, in a ready but inactive status that can be recruited when necessary. At the same time, this allows a short half-life for the active TAp63 to finely tune the oocyte death regulation, once the pathway has been irreversibly triggered. Recently, BH3-only proapototic BCL-2 family members, PUMA[84-89] and NOXA,[90-94] have been identified as critical downstream targets of DNA damage-induced,[90] TAp63-mediated oocytes apoptosis.[95,96] Primordial follicle oocytes from TAp63-null mice, indeed, failed to show induction of PUMA and NOXA following γ-irradiation. Consistently, PUMA or NOXA-null mice are protected from γ-irradiation-induced apoptosis and produce healthy offspring, resembling TAp63-null mouse.[97]

In *C. elegans*, CEP-1[98,99] and from *D. melanogaster,* Dmp53[100] are the only p53 members present, and they are both exclusively required for germ line fidelity. It seems very likely that mammalian TAp63 in DNA damage-induced apoptosis resembles their function. Moreover, considering the p53-independence of this function invertebrate, Mckeon proposed a model, whereby p63 represents the ancestral member of p53 family. Therefore, while p63 conserves the ancestral function of maintenance of female germ line, p53 has acquired the "modern" role of genomic stability control in somatic cells of vertebrate organisms.

Who Pulls the Trigger for TAp63 Activation?

Phosphorylation of TAp63 appears to be the critical step for activation of DNA damage response in oocytes. The tyrosin kinase c-Abl[101,102] has been reported by Gonfloni et al. to be at least one

of the upstream factors responsible for p63 phosphorylation. Gonfloni and collegues showed that upon cisplatin treatment, in postnatal day 5 (P5) mice, TAp63 was stabilized and phosphorylated (on tyrosine residues Tyr149, Tyr171, Tyr289) consistently with c-Abl nuclear accumulation, leading to oocytes death (**Fig. 2**). Inhibition of c-Abl, by imatinib,[103] a BCR-ABL inhibitor designed and used for clinical treatment of CML (chronic myelogenous leukemia), abolished TAp63 activation and protected mouse oocytes from cysplatin chemotherapy.[73,104,105] This observation underlined the central role of c-Abl in regulation of primordial oocytes cell death and also partially clarified the molecular pathway involved in TAp63 recruitment during oocyte DNA damage response. Moreover, this would imply important medical considerations: inhibition of c-Abl/TAp63 axis, using, for example, imatinib, would open novel options to counteract oocytes cell death to prevent female infertility during cancer chemotherapy. However, it is still controverted whether damage oocytes should die; preventing infertility to result in fetal malformation would be not feasible. On the contrary, a recent report has suggested caution about the possible application of anti-Abl treatment to prevent cysplatin-induced infertility. In a correspondence to *Nature Medicine* editor, Kerr and colleagues showed how in their hands-on co-administration of imatinib and cysplatin in two different mouse strains (CD1 and C57BL6) did not rescue the primordial follicle depletion.[24] Moreover, they showed that administration of imatinib alone increased the number of apoptotic oocytes, accordingly with a possible imatinib-dependent inhibition of the crucial factor for oocyte survival, c-kit.[106] These results undermine the real indispensability of c-Abl for DNA damage-induced oocytes apoptosis. Furthermore, they raised the question about the low specificity of imatinib, which potentially affects enzymatic activity of some other tyrosin kinases, such as c-kit. Gonfloni and colleagues defended their hypothesis, repeating the crucial experiments by inhibiting c-Abl with an alternative compound, GNF-2, that has no affinity for the tyrosine kinase c-kit.[107,108] With GNF-2, they confirmed the role of c-Abl in TAp63 activation. They explained the discrepancy of imatinib results with a different equivalency in the cysplatin solution used in the other work. Apparently, while Kerr et al. were using hospital-grade cysplatin solution, Gonfloni and colleagues were using cysplatin from Sigma. The difference in preparation may affect solubility of the compound, resulting in a different efficacy at the same concentration. However, the debate remains opened. How crucial is the c-Abl contribution for p63 phosphorylation for DNA damage-induced oocytes apoptosis? Multiple kinases showed ability to phosphorylate p63, including ATM, Cdk2, p70s6K, $p38^{MAPK}$,[109,110] Iκβ, Plk,[111] (**Fig. 2**). May any of them partially overcome c-Abl inhibition? Maybe addressing the questions whether the conditional c-Abl-null oocytes are sensitive to cysplatin-induced apoptosis and whether TAp63 is activated would help to clarify this point.

"GTA" p63 Relieves TAp63 in Protection of Hominoidea Male Germ Lines

Despite the fundamental role as guardian of female germ line, no evidence has been obtained for an involvement of TAp63 in

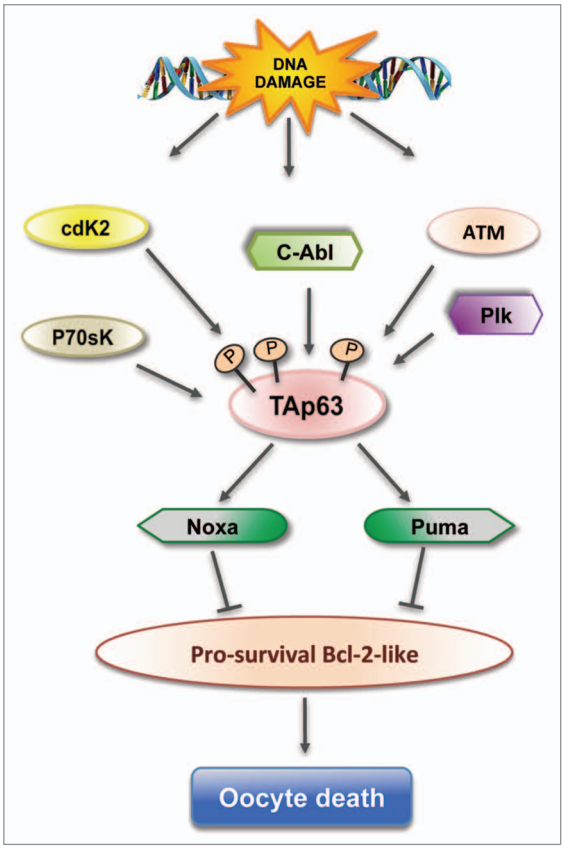

Figure 2. DNA damage actives oocyte death by triggering TAp63 phosphorylation. DNA damage leads to activation of TAp63 inducing its phosphorylation by different kinases. Activated TAp63 mediates the oocyte death by inducing transcription of BH3-only proapoptotic family members, PUMA and NOXA, which can inhibit pro-survival BCL-2 proteins (BCL-2, BCL-w, A1, MCL-1, BCL-XL).

DNA damage response in spermatogenic precursors. Indeed, although TAp63 mRNA has been detected in mouse male germ cells,[112,113] specific antibodies failed to clearly detect protein levels, as shown as for female primordial follicles.[69] Moreover, upon irradiation, mouse $p63^{-/-}$ testis did not show any significant difference in apoptotic response compared with WT.[112,113]

Recently, a novel p63 isoform, unique to Hominoidea (humans and great apes), has been identified in human testis.[114,115] This isoform, termed GTAp63 (germ cell-encoded transactivating p63), rises from a more complex 5' region of human *TP63* gene. Indeed, here three additional upstream exons (U1, U2, U3) that can be fused by alternative splicing with the previous described exon 2, generating different N-terminal splicing variants (**Fig. 3A**). The most abundant splicing variant is originated by fusion of exon U1 with exon 2 and differs from the previous described TAp63 isoforms for a 19-residues long N terminus (**Fig. 3B**). GTAp63 is highly expressed in human male germ cell precursors, while mostly undetectable in all other tissue. Upon genotoxic stress, it shows ability to induces apoptotic p53-responsive genes (PUMA, NOXA, CD95L), thus probably contributing to maintenance of spermatozoa genome integrity. Although protective mechanisms of germ cell genome are generally crucial

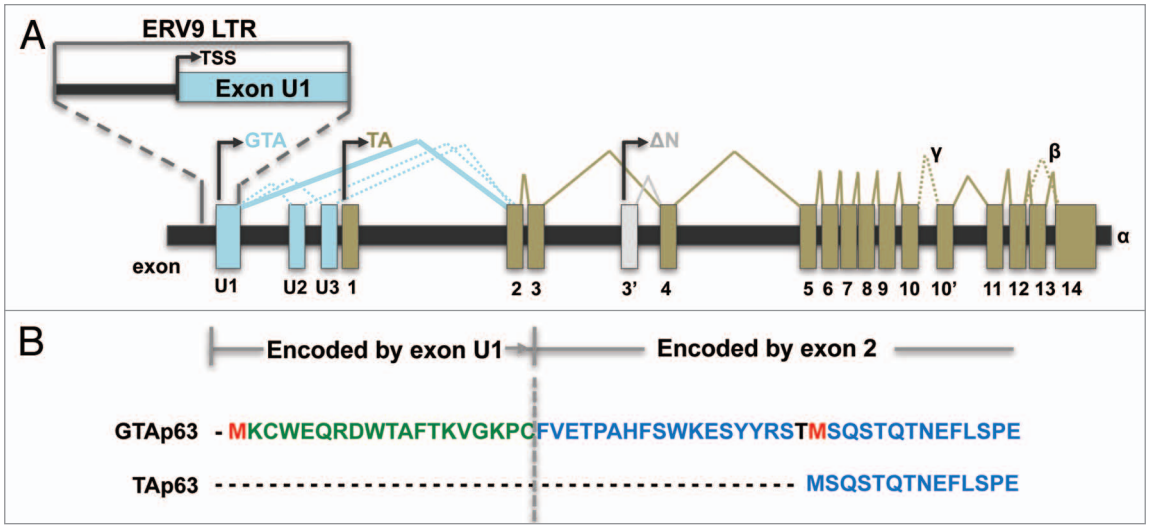

Figure 3. Human testis-specific p63 isoforms are encoded by unique upstream exons. (**A**) Gene architecture of human p63 gene shows presence of unique upstream exons, U1, U2, U3 (sky-blue). The GTAp63 testis-specific isoform is encoded by a direct fusion of exon U1 to exon 2 by premRNA splicing. The black arrows indicate, starting from their first exons, the three transcriptional start sites for GTA (exon U1, sky blues), TA (exon 1, brown) and ΔN (exon 3', gray). The downstream exons 10 and 14 undergo alternative splicing, encoding for the most abundant isoforms α and less abundant β and γ. The ERV9 LTR insert shows the transcriptional start site (TSS) of GTAp63. (**B**) N-terminal amino acid sequences of GTAp63 and TAp63. The 19-amino acidic long N-terminal of GTAp63 encoded by exon U1 is highlighted in green, while in blue is highlighted amino acid sequence codified by exon 2. Red "M" indicates Metionines at translational starts of GTAp63 or TAp63.

for maintenance of all species, this appears particular critical in spermatogenesis of Hominoidea, since humans produce 100 million of spermatozoa per day for a long lifespan. Expression of GTAp63, indeed, was phylogenetically allowed only recently in primate evolution, by insertion of an endogenous retrovirus, ERV9, coinciding with the Hominoidea lineage separation from other primates. The 5' portion of exon U1, indeed, overlaps the LTR sequences of ERV9, which are predominantly transcribed in testis. Therefore, GTAp63 expression is very likely the result of ERV9 LTR promoter activity. This insertion represented a positive event during the evolution, which fortified the expression of a guardian of genome. This has, indeed, enabled a more restrictive surveillance on genome of male germ line, probably coinciding with the requirement a longer fertile lifespan of these species.

Moreover, GTAp63 represents also a potential novel tumor suppressor candidate of testicular tumors. HDAC inhibition restores expression of GTAp63 in testicular carcinomas, where p63 expression is very often lost.[114] Consequently, treatment with HDAC inhibitors,[116,117] like SAHA currently under clinical use,[118] might sinergistically improve anticancer ability of conventional chemotherapeutic compounds,[117,119] like cisplatin, by restoring GTAp63 expression

However, a complete understanding of GTAp63 functions is still far to be clarified. Due to limits of Hominoidea "experimental system," many questions remain elusive. One important issue, for example, concerns the dependence from p53 of DNA damage response in sperm precursors. Does GTAp63 contribute to p53-dependent apoptosis or act completely independent, mimicking TAp63 in oocytes? And does the additional 19-amino acid N-terminal tail allow an at least partial, different promoter responsivity from p53? Further efforts on the study of this novel isoform will be extremely important to completely clarify p63 contribution in human reproduction fidelity.

Concluding Remarks

Many invertebrates, such as *C. elegans* and *Drosophila melanogaster*, have only one p53 family member, which resembles more closely p63 and p73 than p53 from both structural and functional aspects. The p53 members from *C. elegans*, CEP-1,[98,99] and from *D. melanogaster,* Dmp53,[100] are both exclusively required for germ line fidelity. The current most accredited theory, therefore, is that, from germ line fidelity control, p53 members have adapted their function over time in different tissues, controlling different processes, including tumor suppression and development. This is also supported by the fact that from the structural point of view, CEP-1 forms dimers via C-terminal domain, resembling the dimer-tetramer strategy adopted by mammalian TAp63. The ancestral reproduction role has been mainly maintained by p63 as dimer-tetramer, while the subsequent tumor suppression role evolved in p53 as tetramer,[120,121] suggesting a parallel structural-functional evolution.

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