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Commentary

Wild-type p53 in cancer cells: When a guardian turns into a blackguard

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ABSTRACT

The tumor suppressor p53 controls a broad range of cellular responses. Induction of a transient (cell cycle arrest) or a permanent (senescence) block of cell proliferation, or the activation of cell death pathways in response to genotoxic stress comprise the major arms of the survival-death axis governed by p53. Due to these biological properties, inactivation of p53 is a crucial step in tumor development and progression, reflected by the high incidence of *TP53* mutations in different types of human cancers. The remarkable potency of p53 in suppressing tumorigenic outgrowth has promoted the expectation that tumor cells expressing wild-type p53 (wtp53) should be more prone to elimination by cytotoxic treatments than tumor cells expressing mutant p53 (mutp53) with defunct wtp53 activities. However, recent findings yielded somewhat unexpected insights concerning the preponderance of the survival-promoting effects of wtp53 in cancer cells, a rather undesired property from the therapeutic point of view. In this commentary we will discuss the possibility that the developmentally established distinct patterns of wtp53 mediated responses in different tissues are an important factor in determining the ultimate outcome of cellular responses mediated by wtp53 in different types of tumor cells, with a particular focus on the divergent impact of wtp53 in malignant tumors of the central nervous system. We infer that a selective gain of pro-survival functions of wtp53 in cancer cells will confer a survival advantage that counteracts tumor therapy.

1. Functional diversification of wtp53 and cell specification

The remarkable functional dichotomy of wtp53, which can either promote cell survival or commit cells to a suicidal path, has been recognized since a long time and is manifested both during normal development and in the response of different types of embryonic and homeostatic tissues to DNA damage [1–3]. The palette of survival-promoting activities of wtp53 is much broader than previously thought, covering a broad range

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Abbreviations: wtp53, wild-type p53; mutp53, mutant p53; CNS, central nervous system; BTISC, brain tumor initiating stem-like cells; GBM, glioblastoma multiforme; ClQ, chloroquine.

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of cellular responses including regulation of the cell cycle, facilitation of DNA repair pathways by both transcriptional and non-transcriptional mechanisms, maintenance of low levels of reactive oxygen species, and a direct activation of genes with anti-apoptotic activities. A schematic diagram of p53's diverse roles as "guardian of the genome" is shown in Fig. 1. An overview of the complex network of pro-survival and apoptotic responses mediated by wtp53, and of their underlying mechanisms can be found in recent reviews [4–6]. In this commentary we will discuss the possibility that pro-survival functions of wtp53 in some types of cancer cells may contribute to their overall survival potential and thus counteract cytotoxic effects of tumor therapies targeting DNA damage pathways.

The spatio-temporal diversification of wtp53 functions during development is determined both at the level of p53 expression [7,8,1] and of modulation of p53 transcriptional activity, primarily through the Mdm2 inhibitory feedback loop [9,10]. Studies with mice carrying a hypomorphic allele of *mdm2* have been instrumental in revealing that p53 responses undergo a diversification during development, resulting in distinct effects in different tissues expressing comparable levels of wtp53: while triggering a strong apoptotic response in epithelial cells of the small intestine and in cells of the hematopoietic lineage even in the absence of DNA damage, a merely elevated wtp53 level does not lead to apoptosis in other tissues [11,12]. Studies with $p53^{515C/515C}Mdm^{-/-}$ mice expressing the transcriptionally active mutant $p53^{R172P}$ in an *mdm2*-null background revealed that the proliferation inhibiting function of p53 is also influenced by the cellular context [13]. The $p53^{R172P}$ protein is deficient for apoptosis-inducing functions, but has retained the ability to inhibit proliferation [13]. A tissue-comparative assessment of the expression of p21, a canonical transcriptional target of p53 that induces cell cycle arrest, revealed that responsiveness of the *p21* promoter to $p53^{R172P}$ varies among different tissues: whereas $p53^{R172P}$ activated *p21* in the bone marrow and in the proliferating compartment of the developing brain, *p21* was not induced in proliferating epithelial cells of the skin and dental epithelium [13]. Assuming that the tissue-specific transcriptional pattern of the $p53^{R172P}$ mutant reflects that of wtp53, these findings indicate that in different tissues the transcriptional potential of p53 might not be implemented uniformly, thereby establishing a framework for the functional diversification of p53 responses.

The inherent functional dichotomy of wtp53 is also manifested in distinct cell types within a given tissue. The different impact of p53 on different cell types of the central nervous system (CNS) constitutes a prominent example. p53 is a major regulator of developmental and DNA damage-induced apoptosis during embryogenesis [14,15,1,2]. In the developing CNS, p53-dependent apoptosis plays an essential role in the death response to genotoxic and non-genotoxic insults in neural precursor cells [16,17]. In the adult brain, p53 expression is confined to the neurogenic niche in the lateral ventricle, where p53 controls self-renewal of adult neural stem cells

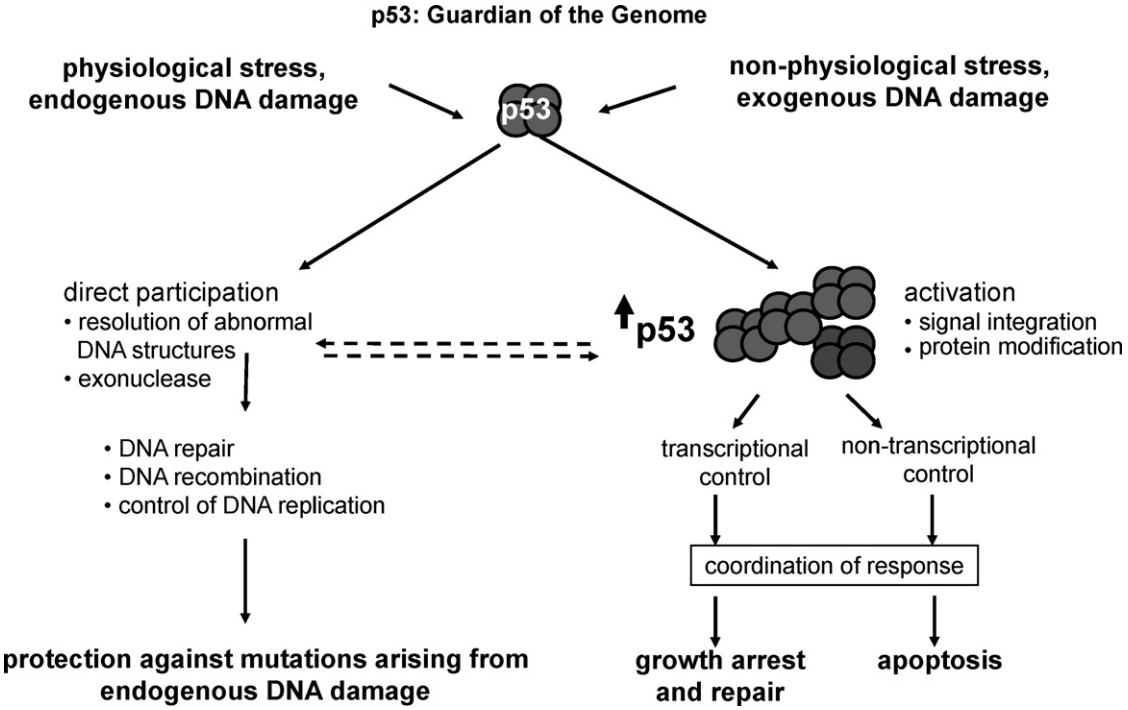

Fig. 1 – Diverse roles of p53 in its function as "guardian of the genome". p53 protects the genome under physiological and non-physiological stress conditions. Depending on stress levels, p53 will accumulate to different levels. p53 can directly participate in repair processes by binding to DNA and resolving abnormal DNA structures, by its exonuclease activity, or induce a transcriptional response by activating p53 target gene expression. In addition, p53 is able to mediate non-transcriptional responses, e.g. apoptosis induction via direct activation of the mitochondrial apoptosis pathway. Various activities of p53 might be performed simultaneously, as p53 exists in various subpopulations, which might perform different functions.