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Review

Involvement of stromal p53 in tumor-stroma interactions

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ABSTRACT

p53 is a major tumor-suppressor gene, inactivated by mutations in about half of all human cancer cases, and probably incapacitated by other means in most other cases. Most research regarding the role of p53 in cancer has focused on its ability to elicit apoptosis or growth arrest of cells that are prone to become malignant owing to DNA damage or oncogene activation, i.e. cell-autonomous activities of p53. However, p53 activation within a cell can also exert a variety of effects upon neighboring cells, through secreted factors and paracrine and endocrine mechanisms. Of note, p53 within cancer stromal cells can inhibit tumor growth and malignant progression. Cancer cells that evolve under this inhibitory influence acquire mechanisms to silence stromal p53, either by direct inhibition of p53 within stromal cells, or through pressure for selection of stromal cells with compromised p53 function. Hence, activation of stromal p53 by chemotherapy or radiotherapy might be part of the mechanisms by which these treatments cause cancer regression. However, in certain circumstances, activation of stromal p53 by cytotoxic anti-cancer agents might actually promote treatment resistance, probably through stromal p53-mediated growth arrest of the cancer cells or through protection of the tumor vasculature. Better understanding of the underlying molecular mechanisms is thus required. Hopefully, this will allow their manipulation towards better inhibition of cancer initiation, progression and metastasis.

Contents

Abbreviations: CAF, cancer-associated fibroblast; ECM, extracellular matrix; IL, interleukin; LOH, loss of heterozygosity; MMP, matrix metalloproteinase; SDF-1, stromal derived factor 1; Tsp-1, thrombospondin-1; wt, wild-type.

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1. Introduction

p53 is a major tumor-suppressor gene, mutationally inactivated in about half of all human cancer cases [1]. In most of the other half of cases, which progress with a wild-type (wt) p53 gene, p53 function is probably incapacitated by disruption of the p53 activation pathway or of p53 downstream effectors. In normal, unstressed cells, p53 is largely kept in check through interactions with its major regulator, Mdm2, leading to the rapid proteasomal degradation of p53 [2]. Genotoxic insults, activated oncogenes and a variety of additional stress conditions upregulate p53, usually through disruption of the p53-Mdm2 interaction. Following its activation, the p53 protein undergoes post-translational modifications, causing its stabilization and enhanced nuclear accumulation. In the nucleus, functioning as a transcription factor, p53 orchestrates the concerted response of hundreds of genes [3]. The endpoint of this response is either resolution of the stress that has induced p53 activation (e.g. by repairing the damaged DNA) or induction of apoptosis or cellular senescence of the cell in which p53 has been activated, thus preventing the proliferation of cells that might spawn cancer. Induction of differentiation and accelerated DNA repair are additional p53 activities that conceivably contribute to inhibition of malignant transformation. Remarkably, research in the p53 field has focused predominantly on these cell-autonomous mechanisms [2,4,5].

Yet, several studies over the last decade have highlighted a potential paracrine role for this versatile tumor suppressor. Apparently, p53 activation within a cell affects not only that cell but also its surroundings, by modulating the expression of genes that encode for secreted factors. In the context of tumors, such phenomena would pertain to the stromal component, namely the non-transformed cells of a variety of tissue origins that are usually a major part of any cancerous growth. Specifically, the activity of p53 within these cells could potentially impact upon the growth and viability of neighboring cancer cells. In addition, some reports indicate that p53 activation in a normal tissue could influence not only cells in the immediate neighborhood, but also distantly localized tumors, through endocrine mechanisms. Indeed, p53 induction was shown to induce a significant change in levels of a large number of secreted proteins, and possibly also post-translational modifications in many of them, forming the "p53-secretome" [6]. It can be speculated that some of these factors can affect only nearby cells, while others are stable enough to circulate through the vascular or lymphatic system and impact cancer cells in distant organs.

The cancer microenvironment includes stromal fibroblasts along with extracellular matrix secreted by these fibroblasts, adipocytes, cells belonging to the immune system, blood vessels, muscles and a number of additional cell types. Much of the data about p53 in stromal cells, which will be addressed below, stems from studies on fibroblasts, but p53 might be playing equally important roles also in other types of stromal cells.

In this review, we will focus on the paracrine and endocrine roles of stromal p53. We will summarize the current knowledge about the molecular mechanisms by which these effects might take place, and discuss their impact on the response of tumors to anticancer therapy. We will also address the clinical implications of these relatively new pathways, interconnecting tumors and stroma through the activity of p53.

2. Biological effects of stromal p53

2.1. Effects on tumor growth and cancer cell proliferation

To assess the effect of p53 status of the host upon tumor development, identical tumor cells were inoculated into either p53 knockout mice or wt control mice. Tumor latency was found to be reduced in p53-null hosts relative to their normal controls [7]. Since the predominant type of non-transformed cell in a cancerous growth is usually fibroblasts [8], the authors examined the contribution of the status of p53 specifically in host fibroblasts. An experimental scheme that was repeatedly used to study the role of various fibroblasts in tumor progression is xenograft co-inoculation studies. Potentially tumorigenic tumor cells are inoculated into recipient mice, with or without accompanying fibroblasts. When tumor cells were co-inoculated with p53-null fibroblasts, tumor growth was accelerated relative to the same tumor cells co-inoculated with wt fibroblasts [7]. Furthermore, tumors formed with p53-null fibroblasts demonstrated a higher proliferation rate (based on Ki-67 staining), and less apoptosis (based on TUNEL staining) compared to tumors formed with wt fibroblasts. Although the distinction between fibroblasts and epithelial cells in this study was based on morphological criteria only, the enhanced proliferation and reduced apoptosis appeared to occur mostly in the epithelial component of those tumors. Overall, this study implies that stromal fibroblast p53 inhibits proliferation and enhances apoptosis of xenografted epithelial cancer cells, thereby inhibiting tumor progression [7].

In another study, Komarova et al. treated cancer cells with conditioned medium collected from p53-null cells or from cells carrying wt p53 [9]. Using this system, they could demonstrate *in vitro* paracrine-p53-mediated growth inhibition. In this model, stress-induced p53 activation in the donor cells was required for the conditioned medium to have a cancer-inhibitory effect. It may be speculated that cell–cell contact or cell proximity is required for growth inhibition by basal levels of p53, while following more vigorous p53 activation, higher concentrations of secreted factors can carry this effect over a longer range.

2.2. Effects on angiogenesis

In a seminal study published in 1994, Dameron et al. demonstrated that when fibroblasts derived from Li–Fraumeni patients lose their single wt p53 allele in culture, angiogenic features emerge, implying an anti-angiogenic activity of wt p53 [10]. These researchers went further to demonstrate that this phenotypic switch was due to loss of p53-inducible expression of the anti-angiogenic secreted protein thrombospondin-1 (Tsp-1). Since then, numerous additional p53 target genes were reported that are likely to contribute to an anti-angiogenic effect (see Section 3.2). Activation of tumor p53 was shown to reduce neoangiogenesis in a mouse model, even when only part of the tumor cells harbored wt p53 [11]. This suggests a p53-mediated anti-angiogenic influence of cells on their surroundings. Indeed, in a p53-null fibrosarcoma cell line, exogenous expression of wt p53 did not affect proliferation *in vitro*, but induced tumor dormancy through reduced vascularization *in vivo* [12]. A study by Narendran et al. reported that leukemic bone marrow stromal cells that harbor p53 mutations produce elevated levels of VEGF and support the growth of leukemic cells [13]. However, to the best of our knowledge, formal demonstration of an *in vivo* inhibitory effect of stromal p53 on tumor angiogenesis has not been reported yet.

2.3. Effects on metastasis

As discussed in this review, p53 affects in numerous ways the pattern of proteins secreted by stromal cells. Since some of those secreted proteins have been implicated in metastatic seeding, it is plausible that stromal p53 may also affect metastasis. However, this issue has so far been assessed only indirectly. In particular, Kang et al. reported that elevated expression of prosaposin by tumor cell lines reduces their metastatic potential, without affecting their proliferation rate [14]. Prosaposin is the precursor of saposin, a lipid