Review of Tumor Suppressor Gene P53

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Abstract: **Background:** During tumorigenesis, cells proliferate unchecked, altering tissue homeostasis and leading to subsequent hyperplasia. This process parallels the recovery of cell cycle, abnormal DNA repair, and the passivation of apoptotic programs in response to DNA damage. In most human cancers, these processes are associated with dysfunctions of the tumor suppressor p53. As a key transcription factor, the evolutionarily conserved tumor suppressor p53 (encoded by TP53) plays a central role in response to various cellular stresses. A variety of biological processes are regulated by p53 such as cell cycle arrest, apoptosis, senescence and metabolism. Besides these well-known roles of p53, accumulating evidence show that p53 also regulates innate immune and adaptive immune responses. p53 influences the innate immune system by secreted factors that modulate macrophage function to suppress tumourigenesis. Dysfunction of p53 in cancer affects the activity and recruitment of T and myeloid cells, resulting in immune evasion. p53 can also activate key regulators in immune signaling pathways which support or impede tumor development[1]. Hence, it seems that the tumor suppressor p53 exerts its tumor suppressive effect to a considerable extent by modulating the immune response. In this review, we concisely discuss the emerging connections between p53 and immune responses, and their impact on tumor progression. Understanding the role of p53 in regulation of immunity will help to developing more effective anti-tumor immunotherapies for patients with TP53 mutation or depletion.

Keywords: P53; Tumor Suppressor Genes; Tumor; Cancer

1. Introduction

As a well-studied protein, p53's reputation largely stems from its role as a tumor suppressor, which is activated in response to stress signals such as genotoxic injury or nutrient deprivation [2]. Mutations in p53 are always accompanied by dysregulation of metabolism, migration and invasion, all of which ultimately lead to the development of clinical tumors and more aggressive malignancies [3]. Cancer cells can be recognized and destroyed by innate and adaptive immune effector cells, a process known as cancer immune surveillance [4]. In recent years, various studies have shown that p53 can also control tumor-immune system crosstalk. Loss of p53 in tumors causes changes in myeloid and T cell responses. Specifically, p53 deletion increases myeloid infiltration by enhancing cytokine secretion [5]. Furthermore, p53 dysfunction in some cases reprograms components of the tumor microenvironment, leading to changes in the immune milieu that exacerbate tumor progression. In addition to its ability to control cellular homeostasis to suppress tumorigenesis, accumulating observations suggest that p53 also plays a role in the inflammatory response [6]. Chronic inflammation creates potentially cancer-promoting conditions. In inflamed tissues, cytokines or inflammatory mediators can activate a variety of transcription factors, such as NF-κB and signal transducer and activator of transcription 3, which are critical for the promotion of cancer. Activation of NF-κB and STAT pathways leads to the enrichment of ROS in the TME, ultimately leading to chronic inflammation [7]. Growing evidence strongly suggests that p53 dysfunction in tumors enhances chronic inflammation, which in turn promotes tumor progression.

2. P53 and signal sensors and activators of transcriptional pathways

The signal sensors and activators of the transcription family are a group of transcription factors that regulate cytokine-dependent inflammation and immunity. Constitutive activation of STATs, especially STAT3, induces and maintains the primary inflammatory microenvironment to stimulate the initiation and survival of malignant cells. p53 regulates inflammatory responses through STAT3 activated by the inflammatory factor IL-6. Furthermore, loss of p53 in pancreatic cancer resulted in activated STAT3 phosphorylation, which was initiated by IL-6. Like NF-κB, STAT3 directly binds to the p53 promoter to repress p53 transcription, limiting its typical tumor suppressor function. Blocking STAT3 activates p53 expression, resulting in p53-dependent tumor cell apoptosis [8]. Studies have shown that tumor cells that rely on long-term STAT3 signaling are more sensitive to STAT3 inhibitors than normal cells. Therefore, STAT3 protein can be used as a new type of cancer treatment drug, and more effective and selective STAT inhibitors are expected to be developed in the future. Emerging studies have shown that the tumor microenvironment (TME) significantly affects tumor cell growth and invasion. The TME contains not only cells but also signaling molecules, extracellular matrix and mechanical signals. The immune landscape of the TME is composed of all these cells and molecules that support tumor transformation, protect cancer cells from host immunity, and provide a niche for metastasis. In addition to the cell-autonomous effects of p53, emerging evidence suggests that p53 can also exert effects on neighboring cells, namely the non-cell-autonomous activities of p53. Therefore, a better understanding of the function of p53 in the TME may be helpful for those with p53 mutations of cancer patients tailor-made personalized treatment.

3. Mutant p53 as a tumor antigen

Cancer cells are always accompanied by unstable genetic changes and produce new antigens to differentiate cancer cells from normal cells. The accumulation of p53 hotspot mutations in tumors is considered an immunocompetent neoantigen for immunotherapy. However, progress in this field has been limited by the efficiency of p53 mutant antigen recognition in cells [9]. A recent clinical trial in metastatic ovarian cancer showed that p53 hotspot mutations lead to infiltration of mutation-reactive T cells into ovarian cancer metastases. TIL and TCR genetically engineered T cells recognize tumor cell lines that endogenously express these p53 neoantigens. These results highlight the potential of p53 mutations as targets for T-cell immunity and gene therapy. Furthermore, increased p53 protein levels associated with p53 mutations were associated with the production of anti-p53 autoantibodies, reinforcing the potential role of p53 in regulating tumor antigenicity. While mutant p53 has shown promise in the field of immunotherapy, in some cases induction of specific antitumor responses can trigger immune evasion. Recent studies have shown that broad-spectrum vaccines generated from dendritic cell/tumor cell fusions can potentially prevent adaptive immune escape [10].

As a tumor suppressor, p53 has been extensively studied for its cell-autonomous inhibition of malignant tumors. Recently, increasing evidence has suggested a potential link between p53 and immune function, and p53 dysfunction is also associated with inflammation. Dysfunction of p53 in tumors not only regulates immune recognition, but also affects the interstitial compartment and plays an important role in controlling tumor progression. There are still many uncharacterized issues that may have broad implications for immunity and inflammation, which may ultimately lead to tumor development. For example, how exactly p53 dysregulation affects the immune response to various external or internal stimuli, and the role of p53 in immune cell development. Furthermore, loss or mutation of p53 may reprogram the microenvironment, especially the extracellular components of tumors, but the molecular regulatory mechanisms involved remain largely unknown. P53 mutations can promote tumor cell metastasis. During this process, how immune regulation and responses are altered, and in particular which immune cell functions are altered. In addition, the role of p53 in remote regulation and communication between different tissues or organs will also be a highly anticipated research direction.

4. P53 as a tumor suppressor

Genetic instability is one of the most prominent features of malignant tumors. There are very sophisticated systems for detecting DNA damage and repairing the genome. P53 plays an important role in this "guardian" system. When p53 responds to DNA damage, it causes cell cycle arrest or apoptosis [11]. A study in 1991 showed that wild-type p53 induced apoptosis in leukemia cells [12]. MDM2 is an E3 ubiquitin ligase that controls the degradation of p53. Many tumors overexpress MDM2, even those without p53 mutations. Targeting MDM2 to stabilize p53 seems promising, so many reports on targeting MDM2 or MDM2-p53 have been published. MI-219 is a small molecule that inhibits the MDM2-p53 interaction. MI-219 can also activate the p53 pathway in wild-type p53 cells. Apoptosis and cell cycle arrest were observed in xenograft tumors, resulting in tumor regression. However, MDM2 inhibition and p53 activation in normal tissues may be detrimental. Ringshausen et al. found that p53 is spontaneously activated in many tissues of mdm2-deficient mice. Furthermore, p53 triggers lethal lesions, including ablation of typically radiosensitive tissues [13].

5. P53 Cancer Treatment

Inhibition of p53 protects normal cells during genotoxic chemotherapy or radiotherapy. The side effects of genotoxic treatment of cancer are mainly caused by p53-mediated apoptosis. Small molecules can block p53-dependent transcriptional activity and protect mice from lethal side effects associated with anticancer treatments. If we can avoid the dose-limiting genotoxic pressure on normal cells during cancer chemotherapy or radiotherapy, higher doses may be available for those patients who have an inadequate response to conventional chemotherapy [14].

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