New Strategies for Improving the Quality of Life of Cancer Survivors: Reversible p53 Inhibition

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Abstract

In recent years, with the improvement of cancer survival through more effective treatment, the emphasis has been in trying to minimize the side-effects caused by chemo- and radiotherapy, to ensure that patients have the best quality of life throughout their cancer journey. The tumor suppressor p53 is widely implicated in a broad range of cancers, and here we summarize its role and the possibilities of its manipulation to improve side effects during active treatment through survivorship.

Keywords: p53 inhibition; Anticancer therapies; Cisplatin

Literature Review

The role of p53 in the consequences of genotoxic stress induced by anticancer therapies

P53 is a tumor suppressor that is either mutated or inactivated in the majority of cancer [1,2]. Abundant evidence indicates that toxicity caused by DNA-damaging anticancer therapies in normal tissues is mainly mediated by p53 [3,4]. P53 accumulates in the cells shortly after anticancer challenges and acts as a nuclear transcription factor that modulates the expression of numerous p53-responsive genes (e.g., p21/Waf-1, 14-3-3-σ, Mdm2, cyclin G, bax). It initiates a cascade of events leading to massive programmed cell death in specific normal tissues during the systemic genotoxic stress associated with chemo- and radiotherapy [3-8]. This makes p53 a target for therapeutic suppression: An approach to reduce side effects associated with treatment of p53-deficient cancers.

The possibility of protecting normal tissues through transient p53 inhibition

Pifithrin-α (PFT), a reversible p53 inhibitor, was initially proposed by Komarova and Gudkov [4] to reduce the side effects induced by anticancer therapies. This small molecule p53 inhibitor has demonstrated a protective capacity in many different tissues, eg., cardiac, inner ear, kidney, bone marrow and gastrointestinal tract [4,8-12]. Benkafadar et al. have shown [13] that the activation of ATM-Chk2-p53 pathway causes cisplatin-induced ototoxicity, and importantly, we showed that targeting this pathway in mice bearing patient-derived triple negative breast cancer, using a genetic approach (5-Fluorouracil, myelosuppressive chemotherapy) reduces the toxicity to normal bone marrow without compromising tumor response to treatment [14].

Potential risk associated with temporary p53 inhibition in anticancer therapy

Safety is an obvious issue in potential clinical applications of p53 inhibitors in cancer treatment. However, the role of p53-dependent apoptosis in the tumor response to therapy is relatively minor, since the majority of tumors with mutated or negative p53 status, even those that retain wild type p53, acquire resistance to apoptosis during their progression. In addition, pharmacological inhibition of p53 through PFT-α has been shown to be transient, and p53 function returns to normal within 12 hours [4,15]. A single intraperitoneal (i.p.) injection of PFT-α immediately before gamma-irradiation protected mice from the lethal genotoxic stress associated with cancer treatment without promoting the formation of tumors or any other pathological lesions within one year of observation [4,5] nor causing a substantial loss in tumour suppressor activity [16]. Our recent study showed that systemic or local administration of PFT-α 30 min before cisplatin and followed by daily injection over 2-5 days was sufficient to protect auditory function [13]. However, an in vitro study has shown that the rescuing effect of PFT-α on p53 wild type cells treated with chemotherapeutic drugs is accompanied by a higher rate of chromosomal abnormalities [17]. Thus, this issue requires further in-depth investigations both in vitro and in vivo. Based on the fact that p53-induced apoptosis mainly results from a mechanism that does not depend on transactivation but instead involves translocation of p53 to mitochondria, to avoid any risk that this might lead to new tumor formation, another small molecule inhibitor named Pifithrin-μ (PFT-μ), has been isolated. PFT-μ inhibits p53-dependent apoptosis but has no effect on p53-dependent transactivation and growth arrest. It has been reported that a single injection of Pifithrin-μ 1 hour before each paclitaxel or cisplatin administration prevents chemotherapy-induced peripheral neuropathy [18].

Conclusion

Finally, in the absence of apoptosis, p53 can turn into a survival factor for tumor cells or tumor stromal cells under genotoxic stress conditions, so reversible p53 inhibition may potentially even influence...
treatment outcome of the p53-deficient tumors through anti-angiogenic mechanism [5,13,19,20], or through attenuation of the increase of autophagy induced by anticancer treatment [13,21,22]. In summary, anticancer treatments cause many severe side effects that are tissue specific and mainly mediated by p53. A short-term inhibition of p53 might avoid side effects, thereby improving quality of life of cancer patients. Thus, these findings are now opening exciting perspectives for reducing side effects of cancer treatment.

References