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p53 Mutation-Targeting Medications Approved by the FDA and in Clinical Trials

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Abstract

About half of all cancers in humans have mutations in the tumor suppressor p53 (p53), most of which are missense mutations. Not only do p53 mutations impair its ability to suppress drugs, but they also give the missense mutant p53 (mutp53) oncogenic properties that are distinct from those of the wild-type p53. Restoring or stabilizing wtp53 conformation from mutp53, rescuing p53 nonsense mutations, depleting mutp53 proteins and inducing p53 synthetic lethality or targeting vulnerabilities imposed by p53 deficiencies (activated retrotransposons) or mutations (enhanced YAP/TAZ) are some of the approaches that have been taken to develop novel cancer therapies because p53 mutations are specific to cancer. The mechanisms of action and activities of FDA-approved and clinically available drugs that target p53 mutations to stop the progression of cancer are summarized here Cancer spread is aided by mutations in the tumor suppressor p53 (p53).

Keywords: FDA • Drugs • Cancer

Introduction

This is primarily attributable to missense mutant p53's (mutp53) loss of function as a tumor suppressor, dominant-negative activities over wild-type p53 (wtp53) and wtp53-independent oncogenic activities through interactions with other tumor suppressors or oncogenes (gain of function: GOF). P53 mutations are ideal therapeutic targets because they are cancer-specific and occur in less than 50% of human cancers and rarely in normal tissues [1]. Restoration or stabilization of the wtp53 conformation from missense mutp53, rescue of p53 nonsense mutations, depletion or degradation of mutp53 proteins, induction of p53 synthetic lethality and targeting of vulnerabilities imposed by p53 mutations (enhanced YAP/TAZ activities) or deletions (hyperactivated retrotransposons) are all methods used to target p53 mutations. This review article summarizes the p53 mutation-targeting drugs that are currently in clinical trials as well as those that have already been approved by the FDA and focuses on the clinically available drugs.

The majority of clinical studies have been carried out without stratifying the p53 status, despite the growing body of evidence that statins deplete mutp53. However, very few clinical reports have examined the effects of statins on cancer progression or survival by stratifying the p53 mutation status. Statin users with lung adenocarcinoma, for instance, outperformed non-statin users in terms of overall survival when the tumors had p53 mutations, demonstrating the statins' tumor inhibitory effects. Statin use, on the other hand, appears to have no effect on colon cancer, even when patients are divided according to their p53 status [2]. Variations in the dosage of statins, the kinds of statins used and the kinds of p53 mutations found in tumors could be the cause of the disparity. Certainly,showed that using mouse models to induce mutp53 degradation in tumors, a high dose of statins was required.

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Description

Some phase 3 clinical trials on hepatocellular carcinom, gastric cancer and small cell lung cancer investigated the impact of statins on cancer inhibition; However, none of these studies took into account the tumor's p53 status. Furthermore, the addition of statins to standard chemotherapy did not appear to improve survival in any of these trials. Two clinical trials utilizing stratification of tumor p53 mutation status have recently begun [3]. One is a phase evaluating the efficacy of atorvastatin in patients with dominant-negative missense p53 mutations who are at risk for colon cancer and have long-standing ulcerative colitis. The other is a window-of-opportunity trial to see if atorvastatin reduces conformational mutp53 levels in solid tumors and relapsed acute myeloid leukemia. These studies may further demonstrate that tumor p53 status is a crucial factor in determining whether statins inhibit tumors. The aforementioned statins and HSP90 inhibitors are mutp53 depleters [4]. Statins induce CHIP-mediated degradation of mostly conformational mutp53, whereas HSP90 inhibitors cause MDM2- and CHIP-mediated degradation of both DNA contact and conformational mutp53.

Since mutp53 is necessary for the growth and survival of cancers that express mutp53, both drugs take advantage of the addiction of cancer cells to it. However, there are a number of questions that need to be answered in the future, such as how exactly mutp53 depletion suppresses tumors, what cellular context efficiently induces these drugs' tumor inhibitory effects, which p53 mutants respond to these drugs and how much mutp53 depletion is required to stop cancer from growing [3,4]. Proteins or pathways involved in the G2 or M (mitotic) cell cycle checkpoints are frequently inhibited by drugs that induce p53 synthetic lethality [5]. However, it's possible that inhibiting these checkpoint proteins or pathways alone won't be enough to effectively suppress tumors. In point of fact, in p53-deficient cells, the genetic deletion of ATM (mutated ataxia telangiectasia) or ATR (mutated ataxia telangiectasia and Rad3-related ataxia) by itself does not result in cell death.

Conclusion

Therefore, effective strategies for causing cell death in p53-deficient cancer cells must identify the precise mechanisms and cellular contexts of p53 synthetic lethality. Because p53 mutations are specific to cancer, they make excellent molecular targets for targeted cancer therapy that is likely to have few side effects. The p53 mutation has been the target of several drugs. The majority of drugs that target p53 mutations need to be evaluated for their clinical safety and efficacy, despite the fact that biological effects have been demonstrated using

cell culture and mouse models. The precise mechanisms of action and effective strategies to induce cell death specifically in p53-deleted or -mutated cells by these drugs must be elucidated in order to reduce side effects and improve the efficacy of mutp53-targeted therapy.

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