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The role of p53 and MDM2 in tumor formation and its therapeutic potential

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Tumor formation is a complicated process that involves the dysfunction of major cell cycle regulation genes. Due to the variety of pathways to forming various cancers, researchers are striving to find out how major tumor suppressor genes are inactivated. The inactivation of the p53 protein has been identified in over half of cancers, leading to questions regarding its role in the aggregation of cancer cells. Studies have shown that too much p53 expression could contribute to cancer progression which makes activation of p53 by itself may not have therapeutic potential. This information has given rise to an important area of study in which activation of p53 occurs in proper quantities by inhibiting its negative regulator protein, MDM2 (Murine Double Minute 2). The following study identifies multiple pharmaceutical compounds which target MDM2 inhibition, releasing the p53 in an active state to induce apoptosis.

Introduction

Cancerous tumors form through various genetic mutations that accumulate over time. Mutations in certain cell growth regulation genes will cause a cancerous growth in one individual but may not form a tumor in another individual with an identical genotype. However, the most common mutation among all cancers works by inactivating the p53 tumor suppressor protein; it is seen in over half of cancers, making it a prominent area of study (Yin et al., 2015). The mechanisms of its inactivation are still relatively unknown, but researchers are looking into the interactions between p53 and its negative regulator, MDM2. If the expression of MDM2 is decreased, researchers predict this will allow p53 to flourish (Hayashi et al., 2019). Would the activation of the tumor suppressor p53 gene in tumor cells pose as a potential new cancer treatment? What mode of activation will provide the most robust tumor resistance? The following review will explore the methods p53 can be activated in tumors where it has previously been shut off and the role of MDM2 expression in repressing p53 activation.

Recent Progress

Before delving into p53's therapeutic effects, scientists must understand what makes it so dangerous. Are there certain arrangements of inactive p53 that make tumors more life-threatening or likely to metastasize? De Smit and colleagues argue the aggregation of inactive p53 proteins enclosed in nuclear inclusion bodies (nIBs) is the most common type of protein accumulation among 6 different cancers (2016). Researchers analyzed 370 tumors with cell lines to quantify p53 aggregates; they found that the incorporation of p53-containing nIBs within tumors led to more severe prognosis and decreased tumor suppression mechanisms (De Smit et al., 2016). Interestingly, the team discovered that the aggregates of p53 contained both wild-type and mutant p53 genes, but both still had the same damaging effects on tumor regulation. However, most aggregates containing nIBs held mutant-p53. This led to the hypothesis that wild-type p53 can enclose themselves in protective inclusion bodies when the body is undergoing a state of stress, such as cancer development (De Smit et al., 2016). This study demonstrates that p53 aggregation within inclusion bodies can be just as harmful to cancer development as completely inactive p53 (De Smit et al., 2016).

Other oncologists are attempting to find pharmaceutical therapies for cancer patients with inactive p53 before it can develop into dangerous nuclear inclusion bodies. The main compounds in current clinical trials are biological inhibitors of MDM2 and its biological counterparts. Research has illustrated that p53 is activated when its negative regulators, most commonly MDM2, are suppressed (Hayashi et al., 2019). Trials utilizing MDM2 inhibitors were successful in increasing the transcriptional

activity of p53. This increased expression, in turn, enhances the immune system to fight invading cancer cells (Hayashi et al., 2019; Zhou et al. 2021; Liu et al., 2012). ALRN-6924, a potential MDM2 inhibition therapy, is an improved version of the successful inhibitor ATSP-7041 (Kocik et al., 2019; Zhou et al., 2021). ALRN-6924 works by mimicking the viral pathway of the endogenous retroviruses (ERVs) that constitute 30% of the genomic receptors for p53 in melanoma cells (Zhou et al., 2021). This mimicry signals to the body that tumors are developing, and immune cells must invade the area (Zhou et al., 2021). The study of ALRN-6924's efficacy showed the inhibitor successfully mimicked the ERV pathway, initiating a state of stress that triggered the upregulation of dsRNA creation. The dsRNA formation signals stress to the body which activates the interferon (IFN) immunity pathway to the targeted tissue (Zhou et al., 2021). The results showed that ALRN-6924 upregulated cytotoxic T-cells to the tumor and the epigenetic suppression of repetitive sequences (Zhou et al., 2021). With both mice and human trials proving to be successful, ALRN-6924 may be a step in the right direction toward activating p53.

Some researchers are having difficulties finding a drug that will not cause a relapse of protein activity quickly. Previous studies have found that one out of three patients with Acute Myeloid Leukemia (AML) have higher expression levels of the p53-inhibitor, MDM2. Hayashi and colleagues proposed that the therapeutic effects of the MDM2 inhibitor DS-5272 would increase p53 activity (2019). Their trials proved successful during the application stages. In both mice and human models, individuals experienced higher levels of inflammation and expression of interferon genes, illustrating an increased immune response (Hayashi et al., 2019). Unfortunately, some groups lacked response to the treatments, and all responsive mice had relapsed within 2 weeks post-treatment (Hayashi et al., 2019). Hayashi's team deduced that DS-5272 is successful in prompting cell cycle arrest and apoptosis only during treatment – therefore, it is not a proper treatment for long-term survival (2019).

Another MDM2 antagonist studied is RG-7388 which is believed to have better "selectivity and potency" than other first-generation nutlins – a group of common antitumor drugs being researched (Higgins et al., 2014). The team administered the antagonist at 30 mg/kg daily in one group and 50 mg/kg twice per week in the other. The data demonstrated that the groups had similar efficacies in inducing apoptosis both in vivo and in vitro (Higgins et al., 2014). Past research criticized this inhibitor's capability to sustain antitumor function after treatment has finished (Zhang et al., 2013). Higgins argues that the p53 apoptosis activation revealed itself to be nonreversible once it began signaling in SJSA1 cells (2014). The data showed that levels of p53 stayed at a higher level for much longer than the levels of other molecules such as MDM2 and p21 (Higgins et al., 2014). RG-7388 is controversial in its potential for cancer treatment due to its long-term treatment plan but may be a step toward elevating antitumor activity.

While most research is concentrated on pharmaceutical therapies, some scientists are dedicated to finding naturally-derived chemicals for long-term p53 activation. Studies involving endometrial cancer cell lines have shown significant promise for a treatment using SDGE, or steam-distilled ginger extract (Liu et al., 2012). Lui and colleagues remarked on how the effects of SDGE are comparable to the inhibitory effect on MDM2. Inhibition of MDM2 leads to increased p53 activation and induction of apoptosis which is crucial to eliminate cancer cells (Liu et al., 2012). The study isolated 22 terpenoid components with MDM2 inhibition abilities and identified citral as the most effective suppressor of cell proliferation (Liu et al., 2012). Implementing SDGE into tumor cell lines exhibited a 37-42% decrease in cell proliferation which is about the same efficacy as radiation treatment alone (Liu et al., 2012). For comparison, the common chemotherapy drug cisplatin displays a 59-61% decrease in proliferation which is still more effective than the natural compound. Further studies using SDGE and cisplatin in tandem may provide an even higher efficacy in cancer patients (Liu et al., 2012).

To obtain the best MDM2 inhibition, it is also important to study the other naturally-occurring proteins that bind to MDM2 and assist in p53-degradation. Chen and their team analyzed prostate cDNA to find new proteins that inhibit MDM2 (2007). The S7 protein was isolated as a positive regulator of p53 that increases the rate of apoptosis and slows cancerous proliferation (Chen et al., 2007). Other cellular factors assisting in the deactivation of MDM2 include MDM4, L11, P14, and more (Chen et al., 2007). This study leads to a need for finding pharmaceuticals that target the upregulation of the S7 protein. Identifying inhibitory molecules existing within the body will help to create pharmaceuticals targeting multiple cancer-fighting proteins. Properly inhibiting MDM2 requires multiple inhibitors working in tandem on various targets to treat cancer cells (Kocik et al., 2019).

Discussion

In conclusion, scientists have made significant steps towards developing cancer therapies through MDM2 inhibition and activation of p53. Teams of researchers have identified various compounds that decrease tumor cell proliferation and increase immune signaling in the area (Hayashi et al., 2019; Zhou et al., 2021; Higgins et al., 2014). ALRN-6924 proved the most effective overall in the

long-term induction of apoptosis by p53 activation of the IFN pathway (Zhou et al., 2021). Other chemicals such as DS-5272 (Hayashi et al., 2019) and RG-7388 (Higgins et al., 2014) showed limited efficacy as their therapeutic effects tend to wear off a few weeks after treatment terminates. The research made it clear that MDM2 suppression is the best way to treat malignancies caused by insufficient p53 function, and further studies should reveal viable inhibitory cancer therapies. Future studies must delve into the proteins assisting MDM2 inhibition to find an effective treatment for cancer and what pharmaceuticals will cause an appropriate, long-term response in patients. The longevity of therapeutic effects is still the greatest weakness of current MDM2 inhibitors. However, research has made promising leads in activating p53 in the short-term which gives promise to success in further trials.

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