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Activation of p53 for the Treatment of Cancer

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Tumor suppressor p53 promotes cell death in response to environmental stress signals including DNA damage, hypoxia and aberrant proliferative signals like oncogene activation [Vazquez et al., 2008]. This molecule is important for combating carcinogenesis. A mutation inactivating p53 is found in about 50% of cancer including hepatoma, prostate cancer and lymphoma [Soussi and Wiman, 2007; Petitjean et al., 2007]. In cervical cancer cell line HelaS3, p53 activity is inhibited by human papillomavirus E6 and E7 proteins, which is demonstrated to be critical for the carcinogenesis of cervical cancer [Kessis et al., 1993]. Thus, activation of p53 is an appropriate approach for the treatment of cancers [Vazquez et al., 2008]. We read with great interest the paper "Roscovitine Up-Regulates p53 Protein and Induces Apoptosis in Human HeLaS3 Cervix Carcinoma Cells" published by Wesieska-Gadek et al. in your journal [Wesierska-Gadek et al., 2008]. Roscovitine increases p53 activity in HelaS3 cells through several mechanisms including increased protein expression, decreased degradation and protein activation of p53. The mechanism for the role of activated p53 in cancer treatment involves in both cell cycle arrest and apoptosis. Activation of p53 can increase p21 expression, which in turn inhibits a broad range of CDKs and PCNA-dependent DNA polymerase activity [Warbrick et al., 1997] and thus reduce cell cycle progression. Activation of p53 also causes cell apoptosis through activation of pro-apoptosis pathway and inhibition of IAPs (the inhibitors of apoptosis). Thus, activation of p53 can be used solely for the treatment of cancer.

Roscovitine was compared with cisplatin and proved to be superior because roscovitine has no cytotoxicity. This research provided a new approach to activate p53. The authors showed that roscovitine phosphorylated p53 at Ser46 different from cisplatin which phosphorylated p53 at Ser15. The potency of roscovitine activating p53 is several folds lower than cisplatin. However, cisplatin at high dose causes cytotoxicity, neurotoxicity and nephrotoxicity because it makes DNA mutation. Roscovitine was shown to have no effect on DNA. This is the valuable finding to incorporate non-toxic p53 activator in the cancer treatment regime. Roscovitine may be used in combination with cisplatin to reduce the dose of cisplastin and reduce cytotoxicity while anti-tumor activity is increased. Roscovitine can also be combined with other chemotherapy such as signal pathway inhibitors. Activation of p53 has been used in combination with inhibition of anti-apoptotic pathway such as NF-kB or chemotherapy such as adriamycin [Lowe et al., 1994; Dey et al., 2008]. The components from natural products, which have no cytotoxicity, have also been demonstrated to activate p53 like garlic and mushroom [Peng et al., 2007; Jedinak and Sliva, 2008]. The diallyl disulfide from garlic increases p53 expression markedly at the concentration of 200 μM in colon cancer cell line HT29 [Song et al., 2009]. The extract of mushroom contains major component beta-glucan, which has extensively studied to stimulate immune system to combat cancer [Chen and Seviour, 2007]. Now it is also shown to activate p53. However, it is still needed to confirm how beta-glucan activates p53. Overall, these may provide more potent and safe approaches to activate p53 for cancer treatment.

REFERENCES

Chen J, Seviour R. 2007. Medicinal importance of fungal beta-(1–>3), (1–>6)-glucans. Mycol Res 111:635–652.

Dey A, Tergaonkar V, Lane DP. 2008. Double-edged swords as cancer therapeutics: Simultaneously targeting p53 and NF-kappaB pathways. Nat Rev Drug Discov 7:1031–1040.

Jedinak A, Sliva D. 2008. Pleurotus ostreatus inhibits proliferation of human breast and colon cancer cells through p53-dependent as well as p53-independent pathway. Int J Oncol 33:1307–1313.

Kessis TD, Slebos RJ, Nelson WG, Kastan MB, Plunkett BS, Han SM, Lorincz AT, Hedrick L, Cho KR. 1993. Human papillomavirus 16 E6 expression disrupts the p53-mediated cellular response to DNA damage. Proc Natl Acad Sci USA 90:3988–3992.

Comment on Wesieska-Gadek et al. "Roscovitine Up-Regulates p53 Protein and Induces Apoptosis in Human HeLaS3 Cervix Carcinoma Cells".

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Lowe SW, Bodis S, McClatchey A, Remington L, Ruley HE, Fisher DE, Housman DE, Jacks T. 1994. p53 status and the efficacy of cancer therapy in vivo. Science 266:807–810.

Peng CC, Chen KC, Peng RY, Chyau CC, Su CH, Hsieh-Li HM. 2007. Antrodia camphorata extract induces replicative senescence in superficial TCC, and inhibits the absolute migration capability in invasive bladder carcinoma cells. J Ethnopharmacol 109:93–103.

Petitjean A, Achatz MI, Borresen-Dale AL, Hainaut P, Olivier M. 2007. TP53 mutations in human cancers: Functional selection and impact on cancer prognosis and outcomes. Oncogene 26:2157–2165.

Song JD, Lee SK, Kim KM, Park SE, Park SJ, Kim KH, Ahn SC, Park YC. 2009. Molecular mechanism of diallyl disulfide in cell cycle arrest and apoptosis in HCT-116 colon cancer cells. J Biochem Mol Toxicol 23:71–79.

Soussi T, Wiman KG. 2007. Shaping genetic alterations in human cancer: The p53 mutation paradigm. Cancer Cell 12:303–312.

Vazquez A, Bond EE, Levine AJ, Bond GL. 2008. The genetics of the p53 pathway, apoptosis and cancer therapy. Nat Rev Drug Discov 7:979–987.

Warbrick E, Lane DP, Glover DM, Cox LS. 1997. Homologous regions of Fen1 and p21Cip1 compete for binding to the same site on PCNA: A potential mechanism to co-ordinate DNA replication and repair. Oncogene 14:2313–2321.

Wesierska-Gadek J, Wandl S, Kramer MP, Pickem C, Krystof V, Hajek SB. 2008. Roscovitine up-regulates p53 protein and induces apoptosis in human HeLaS(3) cervix carcinoma cells. J Cell Biochem 105:1161–1171.