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Short Commentary Open Access

Impact of Caffeine on Cancer Signaling Mechanisms: Revisited

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1. Short Commentary

Caffeine is an alkaloid methylxanthine derivative found in coffee, tea, cocoa, and as an additive in many soft drinks and medications. The impact of caffeine on increasing or decreasing the risk of cancer is controversial. Recent studies showed that caffeine, a methylxanthine, potentiates the lethal effects of radiations and toxic agents by overriding of the G2/M checkpoint inducing more cells to die. It does so by inhibiting ATM (ataxia telangiectasia mutated) and ATR (ataxia telangiectasia related). p53, a downstream target of ATM and ATR, is a tumor suppressor protein that functions at G1/S and G2/M checkpoints and is considered as an attractive target for cancer therapy. There is much less override of the G2 block by caffeine in cells with wild-type p53 compared to those with mutant p53. Thus, cancer cells with nonfunctional p53 are more sensitive to radiation. The role of caffeine in sensitizing cells to radiation and genotoxic damage has been well documented in many cell lines. Theophylline, a nonspecific phosphodiesterase inhibitor that has bronchodilator effects, is used for the treatment of asthma and is an effective steroid sparing anti-inflammatory agent. IBMX, also a phoshodiestrase inhibitor, is involved in many signal transduction pathways, including release of Ca2+ from intracellular stores, antagonism of adenosine receptor, and inhibition of phosphodiesterases. DPMX is an antagonist of A2 adenosine receptors that are stimulated by adenylate cyclase in membranes of rat pheochromocytoma PC12 cells. Addition of caffeine to cells will abrogate G2/M checkpoint responses to many genotoxic stresses including UV, gamma radiation and other drugs. Caffeine's method of action is most probably through the metabolism of both purines and pyrimidines, transferring methyl groups to thymidine, adenine, and guanine in de novo synthesis. DNA synthesis takes place through two distinctive pathways depending on the available intracellular pools: a de novo pathway synthesizing nucleic acids from initial precursors and a salvage pathway utilizing purine rings such as xanthine for DNA synthesis. The demethylation of caffeine results in a consequent accumulation of xanthine, altering the balance between purines and pyrimidines, which could account for the inhibition of cell proliferation by caffeine. In conclusion, caffeine can be used therapeutically to induce apoptosis on cancer cells with minimal cytotoxic effect on normal cells and consumption of caffeine-containing beverages and supplements may have protective role against specific cancer types.