Targeting Apoptotic Pathways by Regulating Caspase-3 with Chemo-Preventive Agents for Cancer Therapeutics

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Slowing down of apoptosis, a biological process of programmed cell death, is believed to be the leading cause of cancer. Caspase-3 (Cysteine-dependent aspartate-directed protease) enzyme plays a key role in cellular apoptosis induced by various genetic, biochemical & physical factors. The primary goal of this research was to identify chemo-preventive agents and optimal delivery conditions that could enhance the activity of Caspase-3. Resulting activity control can be leveraged towards targeted apoptosis for cancer therapeutics. To quantify the activity of Caspase-3 towards slicing polypeptide segments in protein chains, in-vitro experiments were performed with human Caspase-3 acting on substrate DEVD-pNA (Aspartate-Glutamate-Valine-Aspartate; para-Nitro-Aniline) with different chemo-preventive agents: Curcumin, Ellagic Acid, Sulforaphane, Catechin, and Quercetin. The reaction rate was measured by real-time spectrophotometry. Reaction conditions were varied to understand the effect of pH and ionic concentration on the enzymatic activity. The results from this study demonstrated the effectiveness of chemo-preventive agents in promoting activity of Caspase-3 for DEVD hydroxylation by up to 20 times compared to control. Curcumin provided the strongest promotion. Chemo-preventive agents help in regulation of pro-apoptotic (Bax) or anti-apoptotic (Bcl-2) proteins, and direct activation of Caspase-3 via electrostatic and allosteric interactions with the cysteine active site. Increase in ionic concentration diminishes the electron transfer between peptide chain and enzyme, resulting in the reduction of Caspase activity. Chemo-preventive agents show great potential to promote Caspase activity and can provide effective solution to slow down the spreading of cancer.

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