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Camptothecin Promotes ROS-Mediated G2/M Phase Cell Cycle Arrest, Resulting from Autophagy-Mediated Cytoprotection

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Abstract : Camptothecin (CPT) is a quinolone alkaloid which inhibits DNA topoisomerase I that induces cytotoxicity in a variety of cancer cell lines. We previously showed that CPT effectively inhibited invasion of prostate cancer cells and also combined treatment with subtoxic doses of CPT and TNF-related apoptosis-inducing ligand (TRAIL) potentially enhanced apoptosis in a caspase-dependent manner in hepatoma cancer cells. Here, we found that treatment with CPT caused an irreversible cell cycle arrest in the G2/M phase. CPT-induced cell cycle arrest was associated with a decrease in protein levels of cell division cycle 25C (Cdc25C) and increased the level of cyclin B and p21. The CPT-induced decrease in Cdc25C was blocked in the presence of proteasome inhibitor MG132, thus reversed the cell cycle arrest. In addition to that treatment of CPT-increased phosphorylation of Cdc25C was the resulted of activation of checkpoint kinase 2 (Chk2), which was associated with phosphorylation of ataxia telangiectasia-mutated. Interestingly CPT induced G2/M phase of the cell cycle arrest is reactive oxygen species (ROS) dependent where ROS inhibitors NAC and GSH reversed the CPT-induced cell cycle arrest. These results further confirm by using transient knockdown of nuclear factor-erythroid 2-related factor 2 (Nrf2) since it regulates the production of ROS. Our data reveal that treatment of siNrf2 increased the ROS level as well as further increased the CPT induce G2/M phase cell cycle arrest. Our data also indicate CPT-enhanced cell cycle arrest through the extracellular signal-regulated kinase (ERK) and the c-Jun N-terminal kinase (JNK) pathway. Inhibitors of ERK and JNK more decreased the Cdc25C expression and protein expression of p21 and cyclin B. These findings indicate that Chk2-mediated phosphorylation of Cdc25C plays a major role in G2/M arrest by CPT.

Keywords : camptothecin, cell cycle, checkpoint kinase 2, nuclear factor-erythroid 2-related factor 2, reactive oxygen species
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