The Regulation of ATF4/CHOP by c-Myc in NSAID-induced Chemoprevention

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To most-effectively combat the progression of colorectal cancer, the second leading cause of cancer death, chemoprevention is utilized. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have chemopreventive properties that are vital in suppressing tumorigenesis. A loss of the Adenomatous Polyposis Coli (APC) tumor suppressor gene, which initiates tumorigenesis, also triggers NSAID-induced apoptosis associated with endoplasmic reticulum (ER) stress response. Activating Transcription Factor 4 (ATF4) and C/EBP Homologous Transcription Factor (CHOP) are implicated in the ER stress response to culminate in apoptosis. Loss of APC also induces the expression of c-Myc, a regulator gene found to control cell cycle progression and cell proliferation. Past studies suggest that c-Myc could regulate ATF4/CHOP, but specific interactions are unknown. This study aims to examine c-Myc's influence on ATF4/CHOP to improve efficiency of chemopreventive methods, such as specifying drugs to target certain genes/proteins. Protein expression of ATF4, CHOP, and cleaved caspase 3 via the knockdown and overexpression of c-Myc in HCT116 and NCM356 cells were examined through Western blots. Quantifying Reverse Transcription-PCR was utilized to quantify RNA through mRNA fold. c-Myc's regulation of ATF4/CHOP was more evident with knockdown than overexpression. Data indicate that in the synthetic lethal interaction of c-Myc mediated and NSAID-induced apoptosis, c-Myc regulates ATF4/CHOP. c-Myc’s overexpression of ATF4/CHOP induces proapoptotic function for ER stress. Although c-Myc’s knockdown of ATF4/CHOP would promote cell survival signalling, c-Myc’s knockdown is found to inhibit cell proliferation within colon cancer cells. Further examination should be done to identify c-Myc’s targets.

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