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Nanoparticle mediated LCS-1 delivery for the targeted therapy of BLM-deficient colorectal cancer cells

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Statement of the Problem: Targeted cancer therapy using synthetic lethality approach is a promising strategy for specifically killing cancer cells by exploiting somatic mutations in cancer cells. Targeting the colorectal cancer (CRCs) cells using LCS-1 (SOD1 inhibitor) by exploiting the reported synthetic lethal interaction between SOD1 and BLM, LCS-1 drug shows very low water solubility due to hydrophobic in nature. The study aimed to develop a nanocarrier for LCS-1 delivery.

Methodology & Theoretical Orientation: We developed magnetic nanoparticle containing iron oxide as a core and conjugated three layers of polymers onto iron oxide core viz., aminocellulose (AC), dendron (upto generation-2) and PEG.

Findings: VSM analysis exhibited those nanoparticles after layers of polymers still retain the superparamagnetic behavior. Cytocompatibility study showed no sign of cytotoxicity on normal cells (HEK293) and exerted mainly by AC. Dendron layer due to branching having pockets for LCS-1 encapsulation while PEG prevents nanoparticles aggregation and imparts hydrophilicity. LCS-1 loaded nanocarrier showed high selectivity about 104 times to BLM-deficient HCT116 cells as compared to BLM-proficient HCT116 cells. LCS-1 loaded nanocarrier induced persistent DNA damage as demonstrated by DNA double strand break markers (γH2AX and 53BP1) and ultimately apoptotic cell death preferentially in BLM-deficient HCT116 cells.

Conclusion & Significance: Customized polymeric nanoparticles for the effective delivery of LCS-1 were synthesized and characterized for selective targeting of colorectal cancer cells. These nanoparticles were cytocompatible and they enhanced the efficacy of LCS-1 as shown by enhanced killing of BLM-defective CRC cells as compared to free LCS-1.

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