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Colon Cancer Stem Cell Models for Drug Discovery

Abstract:

Pharmacological chemotherapeutic agents represent mainstream treatment options for colon cancer. Conventional and targeted therapeutics are associated with systemic toxicity, acquired therapy resistance and chemo-resistant cancer initiating stem cells. These limitations emphasize identification of stem cell targeting bioactive agents as testable drug candidates. Natural products exhibit low toxicity, preclinical efficacy and are unlikely to be associated with phenotypic resistance. These agents may represent new drug candidates. Reliable drug-resistant cancer stem cell models facilitate investigations to identify potential drug candidates. Cellular models for genetically predisposed early onset colon cancer provided a means to isolate and characterize drug-resistant phenotypes for familial adenomatous polyposis and hereditary non-polyposis colon cancer subtypes, respectively. Treatment with non-steroidal anti-inflammatory agent sulindac (SUL) and DNA synthesis inhibitor fluoro-uracil (FU) selected SUL resistant 850MIN COL and FU-resistant Mlh1/1638N COL tumorigenic colonic epithelial cells, respectively. Drug resistant cells exhibited increased tumor spheroid formation and upregulated expression of CD44, CD133 and c-Myc, representing cancer stem cell markers. Treatment of SUL-R cells with mechanistically distinct dietary phytochemicals inhibited tumor spheroid formation. Treatment with curcumin, a bioactive agent from turmeric, inhibited tumor spheroid formation and downregulated CD44, CD133, and c-Myc expression. Collectively, these data provide mechanistic leads for future investigations to examine the effects of bioactive agents on Apc and DNA mismatch repair gene expression, cancer stem cell specific telomerase expression, epigenetic modification and epithelial-mesenchymal transition. These future research directions also provide a basis for future investigations on patient derived tumor explants and organoids to extend clinically relevant translational potential of the preclinical evidence.

Biography

Telang is the research director at palindrome liaisons consultants. He earned Ph.D. Degree in 1974, and obtained post-doctoral training at university of Nebraska, American health foundation, New York and memorial Sloan Kettering cancer center, New York. Faculty appointments: memorial Sloan Kettering cancer center, New York, Weill Cornell medical college of Cornell university, New York and Strang cancer prevention center, New York. Grant review study sections: us national cancer institute and us department of defense. Editorial boards: oncology reports, international journal of oncology, world academy of sciences journal and international journal of molecular sciences. Awards: national cancer institute first award, department of defense idea award and a.m. marquis lifetime achievement award. Peer-reviewed publications: carcinogenesis, cancer prevention, and cancer stem cell biology. Past funding: us national cancer institute and us department of defense breast cancer research program.