Student Research Conference — Review of The Use of 5-Fluorouracil as a Chemotherapy Drug to Treat Colorectal Adenocarcinoma

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Background: Colorectal Adenocarcinoma

Colorectal Adenocarcinoma is a cancer isolated in the colon and rectum. It is the third most commonly diagnosed cancer in the United States[14]. This cancer does not occur suddenly as it takes years to develop and tends to be caused by changes to the lining of the colon or rectum [4]. The p53 protein, that regulates the cell cycle to prevent mutations, is most commonly effected by colorectal adenocarcinoma by causing mismatch DNA repair sequence. [3]

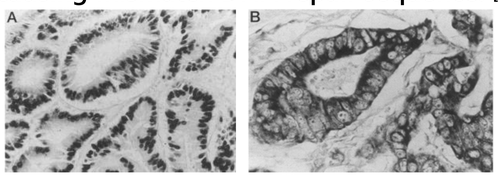


Figure1: A: Carcinoma displaying nuclear p53PAb48ol accumulation. (B) Tumor with cytoplasmic p53cAII accumulation (left panel). [3]

Normal Cell Replication vs. Cancerous Cell Division

For cancer to begin, there has to be a mutation in both a positive and negative cell cycle regulator. Growth factor signals then begin to send growth signals when growth factors aren't present.[7] Thus causing uncontrolled growth resulting in tumors.
Oncogenes are mutated, proto-oncogenes are normal. Mutation of a protein can force oncogenes to stay on, or extra copies of the gene cause the production of too much protein as well. If RAS is stuck on, it demands cell division and proliferation.

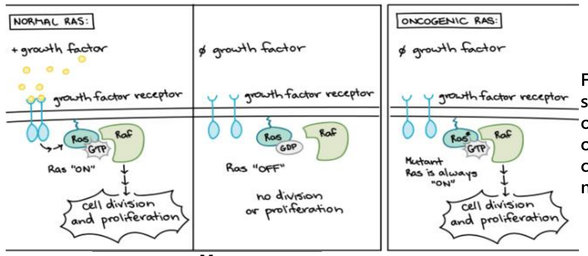


Fig 2. Normal RAS showing an on and off option compared to oncogenic RAS which is constantly on and has no off option [7]

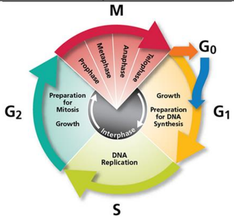


Fig 3. Normal Cell division [8]

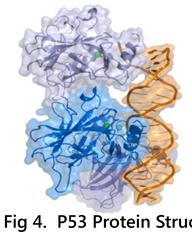


Fig 4. P53 Protein Structure. [8]

Tumor suppressor genes block the cell cycle to prevent the formation of cancerous tumors. Tumors form when tumor suppressors stop working. Tumor protein p53 stops the cell cycle due to DNA damage and acts at the G1 checkpoint.[8] P53 controls G1 to S transition.[8] P53 also activates DNA repair enzymes to fix damaged DNA.[8] P53 induces apoptosis if cell damage is too severe. In cancer cells P53 is usually damaged, missing or mutated.[8]

Introduction

5-Fluorouracil (5-FU) has been known to treat numerous cancers and is administered most commonly by IV to patients. It can also be paired with other drugs based on the patient, type of cancer, and desired outcome. Numerous cancers can be treated by using 5-FU such as Breast, Anal, Stomach, Colon, and some Skin cancers [1]. 5-Fluorouracil has been called one of the most effective and safe medicines in the health system.
5-FU's side effects include inflammation of the mouth, loss of appetite, low blood cell counts, hair loss and skin inflammation [1]

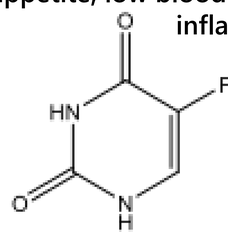
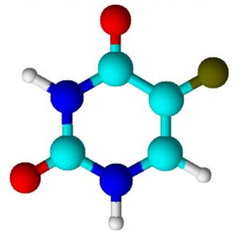


Fig 5. Chemical structure of 5-FU



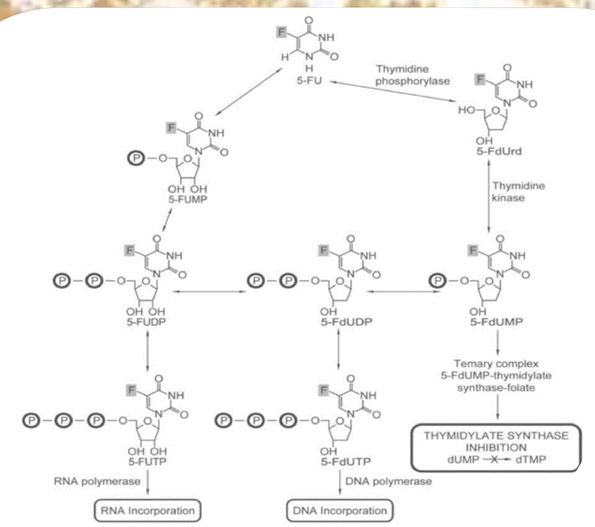
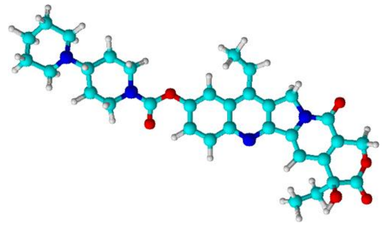


Fig 6. Metabolic pathway of 5-FU to achieve end products that promote thymidylate synthase inhibition, DNA incorporation, or RNA incorporation. [7]

5-Fluorouracil Mode of Action

5-FU blocks the action of thymidylate synthase (TS) and stops the production of DNA.[8] This occurs because the action of blocking TS results in the blockage of the synthesis of primidinethymidine which is required for DNA replication.[8] During the metabolic pathway, Thymidylate Synthase methylates deoxyuridine monophosphate (dUMP) to make thymidine monophosphate dTMP. dTMP is the T base in DNA, with the blocked action of TS, the T nucleotide becomes scarce which causes cancer cells to undergo cell death via thymineless death.[8]

Stage 2 / Stage 3 Research Drug: Irinotecan



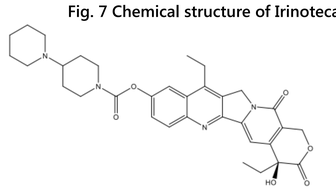


Fig. 7 Chemical structure of Irinotecan

Irinotecan is a semisynthetic derivative of camptothecin, and was first introduced in the late 1980's as a second line of treatment after the failure of 5-FU and Leucovorin[12]. Irinotecan causes S-phase specific cell cytotoxicity by interacting with Topoisomerase I DNA complexes. This causes double-strand DNA breakage and apoptosis[11]. When Irinotecan is used in combination with 5-FU and LV there is a better response rate, prolonged disease progression, and increased survival time[12].

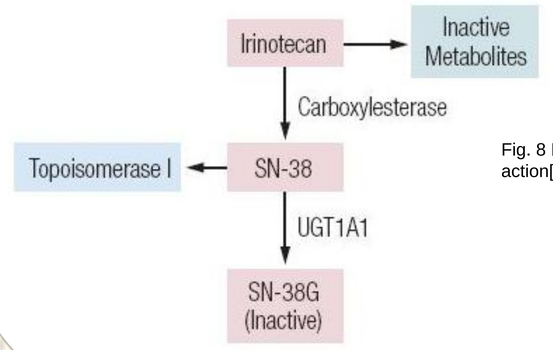


Fig. 8 Irinotecan mechanism of action[15]

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