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Molecular mechanisms involved in acquired chemotherapeutic drug resistance to 5-FU in colorectal cancer

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Colorectal cancer (CRC) is the third and second most common cancer in males and females respectively and has the third highest mortality rate reported worldwide. In patients with metastatic CRC, chemotherapy is the current approach taken to treat the patients. The most common drug used for the treatment is 5-Fluorouracil (5-FU) by itself or in combination with other drugs. However, the cells develop resistance to the drugs resulting in treatment failure. Even though the molecular mechanisms regulating chemoresistance is critical, it is poorly understood. Here, to study the mechanisms involved in chemoresistance, a panel of 7 CRC cells resistant to 5-FU was generated by continuously growing the CRC cells in the presence of the drug. Parental and 5-FU resistant CRC cells were assayed for regulators of acquired chemoresistance to 5-FU using quantitative proteomics, DNA methylation, and biochemical experiments. The assays revealed several mechanisms contributing to acquired drug resistance including epithelial-to-mesenchymal transition (EMT), deregulated apoptotic and signaling pathways, senescence and increased survival autophagy. With the aim to target proteins involved in these mechanisms, a combination of inhibitors and CRISPR based gene knockout techniques were used to sensitize the 5-FU resistant cells. Among these, inhibitors to late autophagy could sensitize the 5-FU resistant cells while the other mechanisms including EMT were observed to be by-stander effects which did not affect the sensitivity of the resistant cells. Hence, inhibiting autophagy in combination with 5-FU can be a potential treatment avenue for CRC patients exhibiting resistance to chemotherapy, thereby aiding in overcoming chemoresistance and improving their survival rates.

Biography

Nidhi has completed her Master's in Biotechnology and Bioinformatics from La Trobe University, Melbourne, Australia and is currently in her final year of PhD. She also has experience of 3 years as a Research Assistant in National AIND Research Institute (NARI), India.

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