Anticancer activity of DNA methylation inhibitors in colorectal cancer cells

Decitabine and azacytidine are DNA methylation inhibitors used in the treatment of myelodysplastic syndromes and acute myeloblastic leukemia. DNA methylation is a modification that is transmitted to daughter cells during DNA replication, so DNA methylation inhibitors by changing the methylation pattern can potentially affect cell functions in a given population long after treatment. I have shown that decitabine used at a low concentration (≤ 1 μM) demonstrates long-term anticancer activity in colorectal cancer cells - inhibiting cell proliferation and clonogenicity and changing cell morphology. At the same time, decitabine does not affect viability of normal small intestinal epithelial cells. Decitabine induces a number of molecular effects in colorectal cancer cells that last up to 20 days after treatment - increases the expression of the cell cycle regulators p21, p16 and cyclin D1 and interferes with PI3K/Akt signaling pathway. Azacytidine has similar, but weaker than decitabine long-term anticancer effects in colorectal cancer cells. The effectiveness of colorectal cancer treatment is still unsatisfactory due to its molecular and morphological heterogeneity, as well as due to the resistance of cells to chemotherapy. DNA methylation inhibitors, for example by the reexpression of proapoptotic proteins, may lead to sensitization of cancer cells to other chemotherapeutic agents. I have shown that decitabine and azacytidine synergistically increase the toxicity of topoisomerase I and II inhibitors - irinotecan, etoposide, doxorubicin and mitoxantrone - in colorectal cancer cells, regardless of their molecular characteristics. These combinations allow to reduce the concentrations of topoisomerase inhibitors while maintaining or increasing their effectiveness, which translates to fewer side effects in therapy.