

P62 PROMOTES COLORECTAL CANCER CELL SURVIVAL AND CHEMORESISTANCE

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Colorectal cancer (CRC) is the third most common diagnosed and second leading cause of cancer death worldwide. According to the latest statistical data, the number of new cases of CRC and the mortality rate are expected to increase annually [1]. Advanced CRC is treated with a combination of chemotherapeutic agents 5-fluorouracil (5-FU) and oxaliplatin (OxaPt), which cause DNA damage and induce cell death. During chemotherapy, cancer cells can acquire resistance to chemotherapeutic drugs, which reduces the effectiveness of cancer treatment [2]. The underlying mechanisms of chemoresistance, including the role of specific factors and proteins, are poorly understood.

One possible cause of chemoresistance is the multifunctional protein selective autophagy receptor p62. Higher levels of p62 protein are detected in the cancerous tissues of CRC patients compared to healthy tissues. Increased levels of p62 in CRC patients predict poor survival prognosis [3]. p62 is an autophagic receptor that targets ubiquitinated organelles or proteins to autophagosomes for degradation. Also, p62 plays a role in tumorigenesis by regulating NF-κB signalling pathways, inflammation, cell proliferation, viability, survival, angiogenesis, and cytokine expression in the tumour environment [4]. The impact of p62 on the molecular causes of chemoresistance in CRC cells is insufficiently analysed.

The aim of our study was to investigate the role of p62 in resistance to 5-FU and OxaPt in human CRC cell lines. As an *in vitro* model, we used colorectal carcinoma cell line HCT116 and its chemoresistant sublines HCT116/FU and HCT116/OXA, which had acquired resistance to 5-FU and OxaPt. Cells were transfected with p62-specific siRNA and they were treated with 5-FU or OxaPt. Then, we evaluated the effects of p62 silencing on cell viability (crystal violet test), apoptosis (flow cytometry), active caspase-3 levels (western blot) and cytokine interleukin-8 (IL-8) (ELISA) amount in HCT116 cells and their chemoresistant sublines. Our data revealed that the silencing of p62 decreased HCT116, HCT116/FU and HCT116/OXA cells viability, and increased their sensitivity to 5-FU and OxaPt treatment. The downregulation of p62 reduced the activation of caspase-3 and did not affect the fraction of apoptotic cells but reduced the amount of IL-8 protein.

Our results revealed that p62 is an important factor in chemoresistance by stimulating pro-survival molecules.

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