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Targeting histones and HDACs to bypass resistance mechanisms in gastric cancers: Relevance for immunogenic cell death and immunotherapy

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Gastric cancer remains a health issue in European countries with an average survival of 10 months due to a late diagnosis and the low efficiency of the standard therapies (e.g. cisplatin) on advanced cancers. One of the causes of cisplatin inefficiency is the high rate of mutation in the tumor suppressor gene p53. This emphasizes the necessity to develop innovative therapeutic strategies. To this end, we investigate the response to cisplatin using whole genome, mi-Rome, and proteome analyses to identify key altered signaling pathways. We identified several epigenetic regulators, including HDACs. Based on these findings, in collaboration with chemists, we developed several strategies to target histones and HDACs to treat gastric cancers. We identified a ruthenium complex that interacts directly with histones and causes alterations in metabolic pathways (e.g. unfolded protein response pathway) to induce immunogenic cell death. This mode of action allows this drug to bypass resistance mechanisms of cisplatin, such as p53 mutations. In parallel, we analyzed the effects of combinatory treatment associating cisplatin with pan or selective HDAC inhibitors. We found that they cooperate to induce synergistic cytotoxicity on gastric cancer cells. Interestingly, the combination of HDAC inhibitors and cisplatin inhibits p53 expression by a transcriptional mechanism. Surprisingly, despite the down-regulation of p53 protein levels, the synergistic induction of apoptosis by the combinatory treatment is dependent upon p53. However, we show that the combination of drugs in cells with p53 mutation is still able to induce a synergistic cytotoxic effect independently of apoptosis but rather through autophagy cell death. Together our work proposed novel and innovative anticancer strategies for gastric cancer allowing to bypass resistance mechanism by targeting epigenetic regulators or histones. By inducing immunogenic cell death, these therapies may cooperate with the most recent immunotherapeutic approaches develop to treat cancers and alleviate some of their limitations.