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DNA REPAIR IMBALANCE IS ASSOCIATED WITH TUMOR AGGRESSIVENESS AND MODULATES RESPONSE TO CHEMOTHERAPY IN COLORECTAL CANCER

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Inappropriate DNA repair caused by inefficiency of one of its pathways - such as base excision repair (BER), mismatch repair (MMR), nucleotide excision repair (NER) and translesion synthesis (TLS) - is known to have influence in several cancer clinical and pathological outcomes and to contribute to chemotherapy resistance. In this work, we characterized the main DNA repair pathways expression profiles in colorectal tumors and its association with clinical and pathological features. In addition, we also exploited, in vitro, the possible mechanisms behind tumor aggressiveness and response to chemotherapy (5-fluouracil (5-FU) and temozolomide (TMZ)). This study design included two arms: (1) clinical: Seventy pairs of sporadic colorectal tumours and matched adjacent mucosal specimens were assessed for BER (MPG, OGG1, APE1, Polβ, XRCC1), MMR (MLH1 and MSH2), NER (CSB, XPA, XPD, XPG, ERCC1) and TLS (DNA polymerases eta, theta and kappa) gene (qPCR) and protein expression (immunohistochemistry) and its association with pathological and clinical features commonly used for patient staging and treatment approaches. (2) In vitro: MMR-deficient colon cancer cells overexpressing MPG and XRCC1 and treated with 5-FU and TMZ were evaluated for viability and energy metabolism. Our results demonstrated that DNA repair pathways have a heterogeneous expression pattern and plenty of associations with poor clinical and pathological outcomes. However, BER gene and protein changes in expression levels seem to lead to a pathway imbalance, which may be exploited as a tool for a more accurate therapy design. Since the overexpression of a BER upstream (MPG), but not downstream (XRCC1), component is associated with higher sensitivity to 5-FU and TMZ in colon cancer cells due to ATP depletion and lactate accumulation, we suggest that the levels of both MPG and XRCC1 in colorectal tumors might be used to predict 5-FU effectiveness in MMR-deficient neoplasms.

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