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Deregulation of EMT genes induced by hypoxia and inflammation independent of DNA methylation changes in human PDAC cell lines

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Background & Aim: The 5-year survival rate in pancreatic ductal adenocarcinoma (PDAC) is less than 5%. Inflammation is a key mediator of PDAC development and inducer of epithelial-to-mesenchymal transition (EMT), which reversibility can be explained by epigenetic plasticity. We investigated mechanisms connecting inflammation and hypoxia with EMT, focusing on EMT-associated DNA methylation changes.

Materials and Methods: We established a fibro-inflammatory pancreatic cancer model by indirect co-cultivation of PDAC cell lines with activated stromal fibroblasts. The BxPC-3, MIA PaCa-2, and SU.86.86 cells were cultivated with or without conditioned media for 48 hours and six days in normoxic or hypoxic (1% O2) conditions. The expression pattern of inflammatory and EMT genes was assessed using the RT² Profiler PCR Arrays. DNA methylation of 15 top-ranked genes was evaluated by pyrosequencing. DNA methyltransferase inhibitor decitabine was used to confirm the epigenetic regulation of studied genes.

Results: Inflammation, mainly combined with hypoxia, induced a significant shift in gene expression, BxPC-3 cells being the most sensitive, with significant deregulation of 44 inflammatory and 41 EMT-associated genes. The highest changes were found in VIM, ITGA5, BMP2, and FN1 expression. However, these changes were only rarely associated with corresponding DNA methylation changes.

Conclusion: Although short-term cultivation under inflammatory and hypoxic conditions altered EMT-associated genes' expression, these changes did not correlate with corresponding DNA methylation. We hypothesize that other mechanisms, rather than DNA methylation alone or additional epigenetic modifications occurring in malignant cells, may contribute to detected gene expression regulation changes.

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