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The role of epithelial-mesenchymal transition in the progression of pancreatic and colorectal malignancies

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ABSTRACT

Epithelial-mesenchymal transition (EMT) is a morphologic cellular programme defined as the phenotypic transition from an epithelial to a mesenchymal state. Pathologically hyperactivated EMT is widely described in tumour development and progression. Proteins that orchestrate EMT have been correlated with increasing histologic grade and poor prognosis for several types of carcinomas. Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive solid malignancies, characterized by its insensitivity to the current therapy. Colorectal cancer (CRC) is the second most diagnosed malignancy among females and third among males worldwide. To provide the most effective diagnostic and therapeutic schemes for aforementioned carcinomas, new markers must be discovered and implemented. Various studies suggest that EMT is an indispensable process for PDAC and CDC growth and dissemination. Discovering new molecular models associated with the complex process of carcinogenesis lets us be a one step closer to more personalized diagnostic and treatment schemes for oncological patients. As an example, broaden research on the mechanism of pharmacological miRNA targeting might enable the future implementation of miRNA-based therapeutics into the CRC treatment schemes. On the other hand, proteins or genes related to EMT might become tempting targets for defeating chemo- or radioresistance in patients with PDAC. In addition, EMT inhibition or reversion might overcome acquired resistance to the implemented treatment caused by drug induced-EMT, both in PDAC and CRC patients. This study aims to sum up recent knowledge on the subject concerning epithelial-mesenchymal transition in the pancreatic and colorectal malignancies progression.

INTRODUCTION

Epithelial-mesenchymal transition (EMT) is a morphologic cellular programme defined as the phenotypic transition from an epithelial to a mesenchymal state. Pathologically hyperactivated EMT is widely described in tumour development and progression (Cho, 2019). During this reversible process, epithelial cells lose their cobblestone appearance in monolayer to acquire spindle-shaped mesenchymal morphology (Georgakopoulos-Soares, 2020). The transition is associated with repressing epithelial markers such as E-cadherin and overexpressing markers correlated with mesenchymal state, especially N-cadherin and vimentin. Cancer cells undergoing EMT are suitable for migration, invasion, and proliferation, thereby facilitating tumour progression (Dongre, 2019, Lamouille, 2014). EMT is driven by numerous transcription factors, including SNAIL, TWIST and zinc-finger E-box-binding (ZEB) that repress epithelial marker genes and activate genes associated with the mesenchymal phenotype (Lamouille, 2014). Proteins that orchestrate EMT have been correlated with increasing histologic grade and poor prognosis for several types of carcinomas. Regarding metastasis, numerous studies have shown that most circulating tumour cells express both epithelial and mesenchymal markers, emphasizing the crucial role of EMT during carcinoma dissemination (Ribatti, 2020, Aiello, 2019).

SEARCH STRATEGY AND SELECTION CRITERIA

The aim of the study was to collect up-to-date knowledge on the subject concerning epithelial-mesenchymal transition in the pancreatic and colorectal malignancies progression. To carry on the study, we used the following databases: PubMed, Google Scholar, Web of Science and Medline. The main search concept was to combine keyword "EMT" or "epithelial-mesenchymal transition" with related terms, such as "colorectal cancer", "CRC", "pancreatic cancer" or "PDAC". Particular attention has been concerned to English-language articles from the recent years, encompassing original papers, reviews, and case reports.

EMT IN THE PANCREATIC DUCTAL ADENOCARCINOMA

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive solid malignancies, characterised by its insensitivity to the current therapy (Singhi, 2019). The poor outcomes are mainly associated with the late presentation of the disease. Therefore, the detection of premalignant conditions is essential for early initiated treatment (Mcguigan, 2018). Various studies suggest that EMT is an indispensable process for pancreatic cancer growth and dissemination. EMT might occur even in the premalignant lesions, thus EMT markers might become crucial prognostic indicators (Wang, 2017). In the conducted studies several pancreatic cancer cell lines and surgically resected PDAC samples presented strong EMT characteristics (Cates, 2009, Kyuno, 2014). Immunohistochemical research performed on PDAC specimens indicated that median survival for patients with epithelial tumours was 40.2 months in comparison to 13.7 months for patients with mesenchymal phenotype. What is more, EMT markers status was associated with portal vein invasion and lymph node metastasis (Yamada, 2013).

Malignant tumours, including PDAC, consist of biologically heterogeneous cellular population. A small number of cells possess stem-cell-like characteristics, encompassing the ability to self-renew, which might lead to the tumour recurrence and drug-resistance (Ishiwata, 2018). Recently, the relationship between EMT phenotypes and cancer stem cells (CSCs) has been studied in samples derived from pancreatic cancer. It was proved that cells with EMT phenotype possess molecular characteristics of CSCs, whereas CSCs express an EMT phenotype (Zhou, 2017). Numerous researches confirmed the link between the acquisition of an EMT–like phenotype in cancer cells, CSCs and both chemo- and radioresistance (Niess, 2015; Yin, 2011). In the study conducted by Yin et al. (2011) pancreatic CSCs demonstrated an EMT phenotype, increased motility, and resistance to the gemcitabine-based treatment (Yin, 2011).

The substantial correlation between the epithelial-mesenchymal transition and systemic aggressiveness and drug-resistance has created novel perspectives for therapeutic agents for PDAC (Beuran, 2015). In the study by Polireddy et al. (2016) the induction of EMT resulted in increased drug resistance, metastasis, and elevated number of CSCs. Stem cell markers cannot be used as a markers source due to their limited expression in the very small proportion of cells. Looking for EMT inhibitor brings the possibility for discovering CSC inhibitor and in result overpassing cancer dissemination and drugresistance (Polireddy, 2016). As an example, in the study by Boreddy et al. (2013) deguelin targeted EMT by significant downregulation of the mesenchymal proteins and upregulation of epithelial markers both *in vivo* and *in vitro*. In result, deguelin inhibited metastasis of PDAC along with primary tumour growth (Boreddy, 2013). El Amrani et al. (2019) proved that gemcitabine treatment might induce EMT-like changes that maintain invasion and chemoresistance in PDAC cells (El Amrani, 2019). This discovery was consisted with previous research distinguishing chemosensitive cells with epithelial-like phenotype from more chemoresistant cells with mesenchymal-like phenotype (Kim, 2014).

Another approach concerns targeting tight junctions associated with EMT. In pancreatic cancer samples a few tight junction proteins are proved to be abnormally regulated. Claudin-1, protein kinase C and marvelD3, among others, are involved in EMT of pancreatic cancer cells thus they might become useful biomarkers during disease (Kyuno, 2014). MarvelD3 was proved to be transcriptionally downregulated in poorly differentiated pancreatic cancer cells and during Snail-induced EMT. Depletion of marvelD3 resulted in a decrease in transepithelial electrical resistance and in an increase of permeability (Kojima, 2011). For developing innovative diagnostic and therapeutic schemes via tight junction molecules it seems necessary to investigate the profile and the regulation of tight junctions in pancreatic cancer cells and compare different families, e.g., claudins and MARVEL (Kojima, 2011, Kyuno, 2014).

EMT IN THE COLORECTAL CANCER

Colorectal cancer (CRC) is the second most diagnosed malignancy among females and third among males worldwide (Ghoncheh, 2016). A significant number of patients with CRC undergoing operation unfortunately develop local recurrence or distant metastasis leading to shorter survival. Despite the development of

treatment regimens, there is no effective therapy for advanced CRC (Vu, 2017).

Clinical studies concerning CRC proved that diffuse positivity of the tumour cells for the EMT markers is correlated with unfavourable prognosis. In the study by Shioiri et al. (2006) Slug expression was significantly associated with Dukes stage and distant metastasis. Moreover, E-cadherin expression was significantly correlated with depth of tumour, lymph node metastasis, and Dukes stage (Shioiri, 2006). EMT was linked to the mobility and dissemination of CRC by conferring increased invasiveness and cells metastatic potential (Qi, 2014, Zhang, 2014). In the study by Deng et al. (2016) Twist (a transcription factor regulating EMT) overexpression triggered EMT and a CSC-like phenotype in human colorectal cancer cells and enhanced their migration and invasion. Additionally, Twist-overexpressing CRC cells presented stronger chemoresistance to the oxaliplatin than control samples (Deng, 2016).

A relatively new aspect described in terms of CRC concerns drug induced EMT. Oxaliplatin is suggested to induce the EMT by promoting the release of reactive oxygen species (ROS). Pretreatment with the ROS scavenger N-acetyl-L-cysteine inhibits oxaliplatin-induced EMT and metastasis (Jiao, 2016). On the other hand, another study proved that radiotherapy induces an alteration to a malignant phenotype consistent with EMT in colorectal cancer cells (Kawamoto, 2012). In the research conducted on SW480 CRC cells increased radiation was correlated with mesenchymal phenotype and enhanced migration and invasion abilities (Lin, 2017). However, the radiosensitivity of CRC might be enhanced by Vitamin D via EMT reversing process. Vitamin D inhibits EMT through upregulating cystatin D (the E-cadherin inductor) and plasminogen activator inhibitor-1 and in result intensifies the radiation therapeutic effect on CRC (Yu, 2021).

MicroRNAs (miRNAs) are small endogenous RNAs regulating posttranscriptional silencing of target genes. Therapeutics based on these molecules represent one of the significant areas of scientists' interest because their involvement in carcinogenesis (Fudalej, 2021). The number of miRNAs regulate the epithelial phenotype and EMT by inhibiting the expression of EMT regulators in the cancer cells. Recent studies have demonstrated that the members of the miR-29 and miR-200 families are involved in the CRC progression by regulating epithelial-mesenchymal transition (Chi, 2016). The study by Hur et al. (2013) revealed that restoration of miR-200c inhibits migration and invasion in various CRC cell lines through direct targeting ZEB1, the transcriptional repressor of E-cadherin. It emphasized a pivotal role of miR-200c in the metastatic behaviour of CRC cells and suggests that miR-200c might become a potential diagnostic biomarker and therapeutic target (Hur, 2013). In the *in vitro* studies miR-29c was downregulated in CRC and suppressed EMT. It presented its role in cell migration by negative regulation of the Wnt/β-catenin signalling pathway (Zhang, 2014). On the other hand, increased expression of miR-29a promoted CRC metastasis by E-cadherin inhibition, which highlighted the potential of the miR-29a inhibitor as a novel therapeutic against CRC metastasis (Tang, 2014). Broaden research on the mechanism of pharmacological miRNA targeting might enable the future implementation of miRNA-based therapeutics into the CRC treatment schemes. However, focusing on a single miRNA brings a limited clinical approach, due to the complexity of miRNAs connections involved in the process of carcinogenesis (Dragomir, 2018).

CONCLUSION

Undeniably, EMT plays meaningful role in the growth, proliferation, and dissemination of pancreatic and colorectal malignancies. Selected markers associated with this process might be used in the future to develop and establish personalized diagnosis, risk stratification platform, and treatment algorithm for oncological patients, to improve their survival.

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