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ROLE OF VIMENTIN IN CANCER AND ITS EXPRESSION ON THE SURFACE OF PANCREATIC TUMOR CELLS WITH EPITHELIAL MESENCHYMAL TRANSITION.

Biological Science

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ABSTRACT

Vimentin is widely expressed and highly conserved and is constitutively expressed in mesenchymal cells. Because of this, Vimentin is often used as a marker of mesenchymally-derived cells or cells undergoing an epithelial-to-mesenchymal transition (EMT) during both normal development and metastatic progression. Increased vimentin expression has been observed in various cancers including the pancreatic tumor. Vimentin's over-expression in cancer correlates well with increased tumor growth . Vimentin has an importance as a marker for epithelial-mesenchymal transition (EMT). cells undergoing EMT appear to acquire stem-like features, indicating the crucial role of EMT in CSC generation. CSCs, a small subgroup of tumorigenic cells within tumors, can self-renew, differentiate, survive under stress, and metastasize. Its over-expression in a large number of cancers and its role in mediating various tumorigenic events, vimentin serves as an attractive target for cancer therapy. Although EMT is associated with several tumorigenic events, vimentin's role in the underlying events mediating these processes remains unknown. By virtue of its overexpression in cancer and its association with tumor growth and metastasis, vimentin serves as an attractive potential target for cancer therapy.
In this review we summarize the role of vimentin in cancer and its expression on the surface of pancreatic tumor cells with mesenchymal transition.

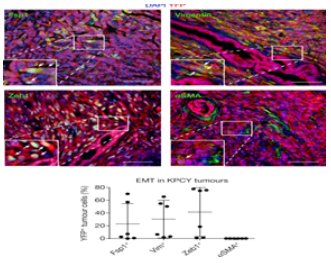
KEYWORDS

Epithelial-mesenchymal transition, tumorigenic cells , CSCs , Over-expression

INTRODUCTION

Vimentin plays a vital role in the progression and prognosis of cancer via the EMT and the corresponding signaling pathways, which contributes to the tumorigenesis, metastasis, invasion, and therapeutic resistance of various tumors . The vimentin overexpression stimulates the metastasis and invasion of colorectal cancer . However, its prognostic significance remains unclarified. Vimentin could be a promising predictive marker for patients with stage III colorectal cancer , whereas a recent study indicated that vimentin was of no prognostic value for these patients. Epithelial to mesenchymal transition (EMT) is one of the earliest events in cancer cell metastasis. EMT can be viewed as a preparatory mechanism where the cells acquire the mesenchymal phenotype, by undergoing cytoskeletal rearrangements, to gain motility for further metastasis–1. Intermediate filaments (IF) play a vital role during EMT progression by maintaining cellular stiffness. Out of the six major IFs, Vimentin (type 3 IFs) is considered as the most important facilitator for mesenchymal cellular stiffness. Vimentin gets expressed in epithelial cells only when EMT is activated otherwise they solitary express keratin as a major IF. Apart from its cytoskeletal role, phosphorylated counterpart of Vimentin acts as signaling agent during EMT and interacts with numerous proteins to execute strong cellular survival responses. The identification of circulating tumor cells (CTCs) relies on epithelial tumor cell markers. In the present study, we aimed to determine whether cell-surface vimentin could be a biomarker to isolate CTCs in pancreatic ductal adenocarcinoma (PDAC). Vimentin was identified as highly expressed on the surface of mesenchymal-phenotype pancreatic tumor cells. Vimentin+ CTCs were detected in 76% of patients with PDAC (76/100) using CTCs enriched via a microfluidic assay. A cut-off value of two vimentin+ CTCs distinguished patients with PDAC from healthy individuals.

In this review, we discuss the roles of EMT in the dissemination and metastasis of pancreatic cancer and the role of Vimentin in cancer and its expression on the surface of pancreatic tumor cells with epithelial mesenchymal phenotype.



2 . Expression on the surface of pancreatic tumor cells with epithelial mesenchymal phenotype:

Cells undergoing EMT appear to acquire stem-like features, indicating the crucial role of EMT in CSC generation. CSCs, a small subgroup of tumorigenic cells within tumors, can self-renew, differentiate, survive under stress, and metastasize. CSCs are often identified using a number of cell surface markers, including CD44, CD24, and CD133, which are essential for detecting CSCs in a cluster undergoing EMT . CSCs, which express traits of both stem cells and cancer cells, have been identified in tumors [53], and based on cell division symmetry and gene expression alterations, CSCs differ from other cells within the tumor . These findings emphasize the crucial role of EMT in cancer recurrence and metastasis. Pancreatic CSCs are defined as a CD24+/CD44+ subpopulation.

EMT is regulated by a complex network involving epigenetic modifications, transcriptional control, alternative splicing, protein stability, and subcellular localization . Some pathways might be crucial for a given EMT event during tumor progression such as differentiation, metastasis, and tumorigenesis. Members of the transforming growth factor-β (TGF-β) superfamily have been implicated as major EMT induction signals during almost all morphogenetic events, including tumorigenesis and metastasis . EMT-TFs, such as SNAIL, ZEB, and Twist, are considered master regulators of these complex networks . In addition, multiple miRNAs, including miR-200 and miR-34, establish a negative feedback loop to maintain epithelial and mesenchymal homeostasis.

2.1 Cancer Stem Cells Undergo EMT in Pancreatic Cancer:

Cells undergoing EMT appear to acquire stem-like features, indicating the crucial role of EMT in CSC generation. CSCs, a small subgroup of tumorigenic cells within tumors, can self-renew, differentiate, survive under stress, and metastasize. CSCs are often identified using a number of cell surface markers, including CD44, CD24, and CD133, which are essential for detecting CSCs in a cluster undergoing EMT . CSCs, which express traits of both stem cells and cancer cells, have been identified in tumors, and based on cell division symmetry and gene expression alterations, CSCs differ from other cells within the tumor . These findings emphasize the crucial role of EMT in cancer recurrence and metastasis.

EMT-TFs, including members of the SNAIL and ZEB families, play crucial roles in the gland-reconstituting activity of stem cells as master regulators . ZEB1 is described as an EMT inducer and transcriptional repressor that in particular represses stemness-inhibiting miR-203 and miR-200 family members. Downstream miR-200 family members, including Sox2 (sex determining region Y-Box 2) and Klf4 (Kruppel-like factor 1), are also stem cell factors. Additionally, the correlation between ZEB1 and stemness is measured by the extent of sphere formation in undifferentiated pancreatic cancer cells . For example, ZEB1 knockdown results in poor initiation of sphere formation and a further reduction in sphere number after in vitro migration, indicating that ZEB1 is necessary for self-renewal. Pancreatic CSCs are defined as a CD24+/CD44+ subpopulation , and decreased CD24 expression in ZEB1-knockdown cells has been confirmed. However, Snail1 mediates a shift from asymmetric (one stem cell, one differentiating

cell) to symmetric (two stem cells) cell divisions, showing that EMT has a role increasing CSC numbers in the tumor stem cell reservoir TGF-β is defined as the main and crucial EMT inducer during cancer pathogenesis progression and dramatically enhances the program by which cancer-associated fibroblasts (CAFs) increase the frequency of tumor-initiating cells in cancer patients.

CONCLUSION:

From all the above studies, it is evident that vimentin is a multifunctional protein and in majority of the cancers vimentin is over-expressed and studies link its expression to the aggressiveness of the cancer. Importantly, expression of vimentin is mainly associated with metastatic phenotype and poor prognosis of the disease outcome. Understanding the mechanism of vimentin gene regulation and the role of extracellular/cell surface vimentin can contribute to the better understanding of cancer and control the invasiveness of the cancer cells. Though all findings indicate a future significance of vimentin as a biomarker and has a significant roles of EMT in the dissemination and metastasis of pancreatic cancer and its expression on the surface of pancreatic tumor cells with epithelial mesenchymal phenotype.

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