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The Role of Mesothelin in Pancreatic Cancer

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1. Introduction

Mesothelin (MSLN) is a glycosylphosphatidylinositol (GPI)-anchored cell surface glycoprotein and differentiation antigen. MSLN gets its name from typically limited expression in the mesothelial lining of the pleural cavity, where it was first identified in 1996 by Chang and Pastan[1]. The human MSLN gene (localized to 16p21)[2] encodes a 71-kDa precursor protein that is cleaved by furin-like proteinases to produce an amino-terminal 31 kDa soluble fragment, termed the megakaryocyte-potentiating factor (MPF), which is released to the extracellular fluid, and a carboxy-terminal 40 kDa membrane-bound fragment[1,3,4].

The normal function of MSLN has remained elusive. Following the initial report of megakaryocyte colony-forming activity[5], a mutant mouse model generated by homologous recombination showed that platelet numbers in both wild-type and MSLN null mice, were not changed, which suggested that MSLN is not required for megakaryocyte growth and differentiation *in vivo*[6]. These mice also showed no discernable phenotype, indicating that either MSLN does not play a significant role *in vivo* or that other molecules may be filling in for MSLN by playing a similar role in normal tissues. MSLN is predicted to have a superhelical structure made of ARM-type helical repeats, and is thereby predicted to function as superhelical lectins that bind the extracellular carbohydrate moiety of glycoproteins[7]. Supporting a potential role in cell-to-cell adhesion, it has been shown that MSLN interacts with mucin MUC16 to enhance cell-cell binding, which can play a role in leading to peritoneal metastatic dissemination of tumors[8].

Where the importance of MSLN is evident in the progression of cancers. MSLN is overexpressed in a variety of cancers, including mesotheliomas, stomach, and endometrial cancers, as well as in squamous cell carcinomas of the esophagus, lung, and cervix[9,10]. In addition, several studies have reported the overexpression of MSLN in virtually all human pancreatic ductal adenocarcinomas[11]. In tumors, MSLN may function as a mediator of cell survival under anchorage-independent conditions, where it facilitates anchorage-independent growth and confers resistance to anoikis[12].

2. Mesothelin in pancreatic cancers

Despite the fact that it is only the tenth most common type of cancer and accounts for only 6% of new cancer cases in North America, pancreatic cancer is the deadliest cancer, with the

worst prognosis of all solid tumors[13]. Due to its highly aggressive nature characterized by invasive growth and early metastasis, and compounded by late diagnosis and lack of effective therapies for treatment, pancreatic cancer remains the fourth leading cause of cancer-related deaths, 35,000 deaths from 42,000 new cases per year[3,14] and a 5 year survival rate of less than 5%[13,14].

In addition to its role in other cancers, MSLN is increasingly becoming established as a key factor in human pancreatic adenocarcinomas. The soluble fragment of MSLN, MPF, was first detected in the supernatant of the HPC-Y5 human pancreatic cell line in 1994 [5]. In fact, HPC-Y5 had the highest MPF activity of 64 cancer cell lines tested, implicating MPF as an important factor in pancreatic anomalies. The latest research confirms the MPF is in fact responsible for increased phosphorylation of ERK1/2, leading to a decreased rate of cell death and an increase in cell number[15].

MSLN expression has since been assessed in pancreatic cancers, where it is found to be overexpressed in a majority of pancreatic ductal adenocarcinomas[4,9,16], with little expression in normal pancreas and chronic pancreatitis[11]. In their studies, for instance, Argani *et al.* used serial analysis of gene expression (SAGE) as well as *in situ* hybridization, RT-PCR, and immunohistochemistry to show that MSLN is consistently overexpressed in 60 of 60 pancreatic tumors. Meanwhile, MSLN does not seem to be expressed in normal pancreatic tissues [4,17,18]. Recently, for instance, Glass *et al.* showed that MSLN 24 of 42 (57%) adenocarcinomas stained for MSLN, while only 0 of 16 non-carcinomas (0%) did so[19].

Exactly what the molecular mechanisms are which give rise to MSLN overexpression are not well documented. However, a recent study attributed MSLN overexpression in pancreatic cancers to an upstream enhancer element containing a transcription enhancer factor (TEF-1) dependent MCAT motif termed Canscript[2], although the presence of this factor was required but not sufficient for MSLN expression. The oncogenic transcription co-factor YAP1, normally phosphorylated and inactivated by the Hippo-YAP1 pathway, has been implicated in the activation of MSLN expression through the regulation of Canscript activity. Knocking down YAP1 expression in HeLa cells dramatically reduced endogenous MSLN expression and suppressed Canscript reporter activity; yet overexpression of YAP1 in HEK293 cells did not turn on MSLN expression, indicating that YAP1 may be necessary but not sufficient for MSLN overexpression[20]. Another study analyzed the methylation state of several pancreatic cancer-associated genes, and found that MSLN was hypomethylated in adenocarcinoma compared to its methylated state in normal pancreatic tissues, indicating an epigenetic event trigger is involved in MSLN overexpression[21].

Pancreatic cancer studies have revealed roles for MSLN in increasing aggressiveness of tumor cells, including enhancement of proliferation and migration. Li *et al.* found that overexpression of MSLN is also associated with an increased S-phase cell population in a cell cycle analysis. This resulted in a 90% increase in proliferation for MIA-PaCa2 cells overexpressing MSLN compared to vector controls[16]. Subsequent studies by Bharadwaj *et al.* elucidated a mechanism through which MSLN promotes proliferation of pancreatic cancer cells through alteration of Cyclin E as a result of constitutive activation of Signal Transducer and Activator of Transcription protein 3 (STAT3)[3]. Bharadwaj *et al.* have further shown that MSLN overexpression results in upregulation of growth/survival pathways through autocrine production of growth factors such as IL-6[22]. MSLN also induces in an increase in

NF-κB activation which leads to resistance to TNF-α-induced apoptosis[23], indicating a mechanism through which MSLN may help to increase survival of tumor cells in the highly inflammatory milieu evident in pancreatic cancer through Akt/PI3K/NF-κB Activation and IL-6 overexpression. MSLN overexpression results in secretion of high levels of IL-6, which could in turn be responsible for the cells' increased viability and proliferation under serum-reduced conditions through a IL-6/soluble IL-6R (sIL-6R) trans-signaling mechanism and the induction of the IL-6-STAT3 pathway[3,22].

MSLN overexpression has also been associated with increased metastatic potential in pancreatic cancers. *In vitro* experiments showed that MSLN increases pancreatic cancer cell migration by 300%, while *in vivo* results showed and increase in local and liver metastases following orthotopic injection, with control cells without MSLN expression showing no metastases[16]. Cancer antigen-125 (CA125), the circulating antigen encoded by the *MUC16* gene, has been identified as a marker for differential diagnosis of pancreatic mass lesions with an 88.2% positive predictive value for diagnosis of pancreatic tumors[24]. Taking into account that the high affinity of mesothelin-CA125 interaction might be the cause of intracavitary tumor metastasis[8,25], a recent study by Einama *et al.* determined that co-expression of these two factors plays a significant role in the acquisition of aggressive clinical behavior of pancreatic tumors, finding that co-expression of MSLN and CA125 correlated with unfavorable patient survival outcome [25].

3. Advances in diagnosis and treatment of mesothelin-overexpressing pancreatic cancers

MSLN is an attractive candidate for targeted therapy given its limited expression on normal tissues and high expression in tumors and the fact that it is expressed on the surface of cells. Immunostaining against MSLN has been demonstrated to be an effective adjunct to cytology for diagnosis of pancreatic adenocarcinoma[26], with a 90% accuracy rate in diagnosing pancreatic malignancies. In addition, the release of the MPF from the cell surface following furin cleavage makes it an attractive target for diagnostic detection.

Elevated circulating MSLN levels have been detected in patients with pancreatic disease[27]. Using ELISA, 73 of 74 (99%) patients with pancreatic adenocarcinoma were found to have elevated circulating levels of MSLN compared with none of 5 healthy controls[27]. Other approaches, including using multiplexed Proximity Ligation Assay (PLA) have been used to effectively detect levels of mesothelin-MUC16 complex in serum and plasma levels[28]. MSLN has also been used as a biomarker to test the efficacy of new technologies for early, minimally invasive diagnosis of pancreatic adenocarcinoma. In a study involving minimally invasive fine needle aspirations MSLN has helped to differentiate pancreatic adenocarcinomas from chronic pancreatitis with near 100% accuracy[29]. Another study utilized acoustic wave device-based immunosensors in molecular cancer biomarker detection in real-time, and effectively identified MSLN expression in three different pancreatic cancer cell supernatants, although further study is needed with this technology to determine its effectiveness in patient tissues[30].

Most recently, ELISA has been used not just to test for MSLN circulation in patients with advanced tumors, but for attempted early detection of pancreatic anomalies. A pancreatic ductal carcinoma transgenic animal model was established in rats using a Cre/loxP

controlled human K*ras* oncogene [13]. Using this system, Fukamachi *et al.* demonstrated that the rat homolog of human MSLN, *Erc* (expressed in renal carcinoma), could be detected in the serum of pre-symptomatic, pre-malignant pancreas lesions, opening the door to potential early diagnosis of mesothelin-induced pancreatic malignancies, as well as testing of early stage chemotherapeutic intervention to prevent progression of malignancies.

Potential treatments focusing on MSLN are already undergoing clinical trials. One example is use of a mouse-human chimeric antibody (MORAb-009), an IgG1kappa monoclonal antibody with an affinity of 1.5 nM for human MSLN containing the murine SS1 Fv for MSLN, which is currently being examined in a Phase II clinical trial[31,32]. This antibody prevents adhesion of mesothelin-bearing tumor cells to MUC16 positive cells and also elicits cell-mediated cytotoxicity on mesothelin-bearing tumor cells. A newer study using phage display has shown successful isolation of HN1, a human scFv, which recognizes a conformation-sensitive epitope of MSLN on cancer cells and promotes apoptosis by acting as an immunotoxin[31]. While this particular study focused on ovarian cancer treatment, it stands to reason that pancreatic cancer would make an effective target for future treatments with this antibody. MSLN has also been used as a targeting factor for pancreatic tumors in conjunction with quantum dot (QD) technology. QDs are semi-conductor nanocrystals which, when encapsulated in carboxyl-functionalized amphiphilic polymers form stable, micelle-like structures which form a potential platform for visualization and drug delivery to tumors[33]. Ding *et al.* conjugated MSLN-specific Ab to QD micelles and used them for effective targeted delivery to pancreatic cancer sites *in vitro* and *in vivo*[33]. The high level of overexpression of MSLN in pancreatic cancer cells and tumors compared to normal tissues allowed for selective targeting of QDs, indicating the potential of MSLN-targeted QDs or other MSLN-conjugated vehicles to serve as agents for tumor diagnosis, imaging, and treatment through drug delivery.

Another approach for MSLN focused therapy comes from studies involving SS1P (SS1(dsFv)PE38), a recombinant anti-mesothelin immunotoxin. SS1P was developed consisting of an anti-mesothelin Fv (SS1) fused to PE38, a 38-kDa portion of Pseudomonas exotoxin A[34,35], which kills cells upon internalization following binding to MSLN on the cell surface. A phase I study was conducted involving 34 patients, 2 of which had pancreatic adenocarcinoma[35]. The patients tolerated the doses given, indicating a potential for progressing to additional studies. Although results were encouraging in patients with ovarian cancer or mesotheliomas, no response was seen in the 2 pancreatic cancer patients. A second Phase I trial, this time involving continuous infusion of SS1P, was more recently conducted[36] to measure toxicity tolerance, also with promising results. Newer studies by the same group are currently examining methods for improving the efficacy of SS1P therapy by combining treatement with Taxol, which appears to limit the binding of SS1P with shed MSLN in the extracellular fluid rather than on the cell surface, thereby increasing the effectiveness of SS1P internalization and the killing of tumor cells[37]. Yet another toxin insertion approach used a a biodegradable nanoparticulate delivery system targeted specifically to mesothelin-overxpressing cell lines to deliver diphtheria toxin DNA, which effectively inhibited protein translation of targeted cells *in vitro*[38].

Finally, approaches using pancreatic cancer vaccines show that MSLN has great potential as an immunotherapeutic targets[10,39]. Johnston *et al.* showed that mesothelin-specific T cells can be induced in patients with pancreatic cancer. Their results indicated that mesothelin-

specific CD4+ and CD8+ T cells were generated from peripheral blood lymphocytes of 50% of patients with pancreatic cancer, up from only 20% of healthy individuals[27], and another study showed consistent induction of CD8+ T cell responses to multiple MSLN epitopes in a small number of patients[40]. A study by Yokokawa *et al.* sought to define additional MSLN epitotpes capable of more efficiently activating T cells to lyse tumors[10]. Jaffee *et al.* carried out a phase I trial in patients with surgically resected adenocarcinoma of the pancreas was conducted using an allogeneic granulocyte-macrophage colony-stimulating factor (GM-CSF)-secreting tumor vaccines[39]. In a phase II trial, these results were confirmed through induction of mesothelin-specific CD8+ T cell responses following exposure to different MSLN epitopes, leading to a correlation of the posttreatment induction of mesothelin-specific T cell responses with improved overall response [41].

The latest attempts at immunotherapy with MSLN involved vaccination with virus-like particles (VLPs) to induce protective antiviral immune responses against MSLN, yielding promising results. Li *et al.* investigated the effect and mechanism of chimeric VLPs that contain human MSLN (VLP-hMSLN) as a candidate vaccine for controlling pancreatic cancer progression in an orthotopic pancreatic cancer mouse model[16]. In the study, VLP-hMSLN vaccination inhibited tumor progression in C57BL/6J mice, and increased mesothelin-specific antibodies and CTL activity and decreased regulatory T cells, resulting in reduced tumor progression and prolonged survival. Most recently, dendritic cells transduced with full-length MSLN cDNA-encoding adenoviral vectors have been shown to elicit mesothelin-specific cytotoxicity against pancreatic cancer cells *in vitro*, through activation of both CD8+ T cells and CD4+ helper T cells[42], suggesting the therapeutic potential of using MSLN-targeted DC vaccines in future clinical applications.

4. Conclusion

MSLN is an important molecule overexpressed in a variety of cancerous human malignancies, and in particular has been identified as a biomarker of pancreatic cancers. The high expression of MSLN in pancreatic tumors compared with its limited expression in normal tissues makes it an interesting candidate for targeted therapies and diagnostic screening. In addition, MSLN has been shown to play important roles in proliferation, survival, and metastatic potential of pancreatic tumors where it is overexpressed. While much progress has been made in understanding the molecular mechanisms that give rise to MSLN-associated pancreatic cancer pathogenesis, further studies are needed to truly elucidate the functions and effects of this molecule with regards to what still remains the deadliest of human cancers.

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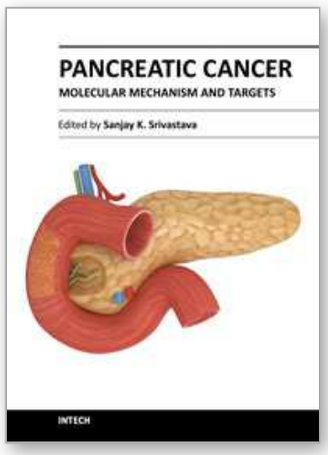
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This book provides the reader with an overall understanding of the biology of pancreatic cancer, hereditary, complex signaling pathways and alternative therapies. The book explains nutrigenomics and epigenetics mechanisms such as DNA methylation, which may explain the etiology or progression of pancreatic cancer. Book also summarizes the molecular control of oncogenic pathways such as K-Ras and KLF4. Since pancreatic cancer metastasizes to vital organs resulting in poor prognosis, special emphasis is given to the mechanism of tumor cell invasion and metastasis. Role of nitric oxide and Syk kinase in tumor metastasis is discussed in detail. Prevention strategies for pancreatic cancer are also described. The molecular mechanisms of the anti-cancer effects of curcumin, benzyl isothiocyante and vitamin D are discussed in detail. Furthermore, this book covers the basic mechanisms of resistance of pancreatic cancer to chemotherapy drugs such as gemcitabine and 5-flourouracil.

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