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Review

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Biology of Mesothelin and Clinical Implications: A Review of Existing Literature

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Abstract

Since its discovery in 1992, mesothelin (MSLN) has generated significant interest as a therapeutic target. A number of characteristics make it ideal for this purpose. First, it is not expressed on the parenchyma of any vital organs. Second, it is differentially expressed on a number of cancer types that have relatively poor prognosis and lack effective systemic options. Third, it is expressed on the cell membrane making it accessible to large molecule targeted therapies. However, unlike other drug targets that have been exploited for therapeutic benefit, the precise function of MSLN, why it is expressed in certain cancers, and its biological role have not been clearly elucidated. Here the existing literature on the cellular function and expression patterns of MSLN across tumor types is reviewed in order to gain further understanding of this intriguing molecule. In doing so, we conclude that there remains significant ambiguity surrounding its function and role in cellular and tumor biology. Furthermore, the expression of MSLN and its relation of prognosis seems to depend on the type of tumor. Finally, the unified mechanism by which MSLN acts as a protein that conveys tumor aggressiveness remains elusive. What is clear is that there is much yet to be discovered in this realm and doing so may have large implications for treatment of otherwise lethal malignancies.

Keywords: Mesothelin; Targeted therapy; Pancreatic adenocarcinoma; Mesothelioma; Triple negative breast cancer; Gastric adenocarcinoma; Ovarian carcinoma

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Introduction

Mesothelin (MSLN) is a cell surface glycoprotein discovered in 1992 by Kai Chang, Ira Pastan, and Mark Willingham at the National Cancer Institute in Bethesda, MD [1, 2]. It is synthesized as a 69-kDa protein which forms two proteins, membrane-bound MSLN and the soluble megakaryocyte potentiating factor (MPF) [3]. Further investigation revealed a strong differential expression pattern between multiple tumor types and normal tissue. Specifically, it is not expressed in the parenchyma of any vital organs but rather is found on pleura, pericardium, and peritoneum. It is commonly expressed on mesothelioma, epithelial ovarian cancer, pancreatic adenocarcinoma, gastric cancer and triple negative breast cancer (TNBC). Hoping to echo the success of the discovery of human epidermal growth factor receptor 2 (HER2) and its exploitation as a drug target, efforts to leverage the favorable expression profile of MSLN into effective targeted therapies have been ongoing since its discovery. These include monoclonal antibodies, immunotoxins, antibody-drug conjugates, vaccines, and chimeric antigens receptor-T (CAR-T) cells [4-11]. These efforts have been met with mixed results. Treatments with MSLN-targeted immunotoxins have yielded some remarkable responses when combined with various agents [12, 13]. However, administration is limited by toxicity and anti-drug antibodies. Multiple review papers have been published on MSLN-targeted therapies that detail the benefits and challenges of such therapies [11, 14-16]. Because of the desire to target MSLN, understanding its role and function in tumor biology has become an important avenue for research. While some studies have suggested that MSLN expression is associated with invasiveness and prognosis, it is unclear whether this is a causative relationship and, if so, what mechanisms are responsible. Here we set out to review the existing literature on MSLN biology and summarize the seminal work that has been performed to investigate this intriguing tumor marker.

Discovery of MSLN

In the early 1990s, Kai Chang and Ira Pastan, in search for a druggable target for solid tumors, isolated monoclonal antibodies (mAb) from mice that had been immunized with an ovarian cancer cell line OVCAR3 [17]. The antibodies isolated were then checked for cross-reactivity with vital organs via immunohistochemistry and discarded if staining was noted.

Table 1. Summary of Mesothelin Positivity in Selected Tumor Types Across Multiple Reports and Antibodies Used

Tumor type	Reference	# Positive	mAb used	Total portion positive
Epithelioid mesothelioma	Chang [19]	15/15	K1	150/163 (92.0%)
	Ordonez [20]	44/44	5B2	
	Weidemann [24]	16/25	MSVA-235	
	Inaguma [33]	73/79	5B2	
	Inaguma [33]	75/79	MN1	
Epithelial ovarian cancer*	Chang [19]	10/15	K1	617/655 (94.2%)
	Hassan [25]	34/48	K1	
	Ordonez [20]	32/34	5B2	
	Weidemann [24]	497/511	MSVA-235	
	Inaguma [33]	42/47	5B2	
	Inaguma [33]	44/47	MN1	
Pancreatic adenocarcinoma	Ordonez [20]	12/14	5B2	267/298 (89.6%)
	Hassan [21]	18/18	5B2	
	Argani [22]	60/60	5B2	
	Johnston [26]	10/10	5B2	
	Weidemann [24]	48/64	MSVA-235	
	Inaguma [33]	100/132	5B2	
	Inaguma [33]	119/132	MN1	
Gastric adenocarcinoma	Ordonez [20]	2/7	5B2	920/1,878 (49.0%)
	Baba [27]	124/212	HBME-1	
	Einama [28]	49/110	5B2	
	Han [29]	30/117	Not reported	
	Shin [30]	476/958	SP74	
	Weidemann [24]	176/393	MSVA-235	
	Inaguma [33]	60/81	5B2	
	Inaguma [33]	63/81	MN1	
Triple negative breast cancer	Tchou [23]	29/43	5B2	178/449 (39.6%)
	Bayoglu [31]	30/71	SP74	
	Tozbikian [32]	82/226	5B2	
	Parinyanitikul [34]	37/109	5B2	

*Non-mucinous. Totals do not include those stained with 5B2 by Inaguma et al to avoid counting the same patients twice.

The result was isolation of K1 mAb, which reacted strongly to the OVCAR3 cells but not with vital organs. Further experiments revealed that K1 mAb also reacted with squamous tumors of the esophagus and cervical cancer [1]. The only normal adult tissues that demonstrated staining with the K1 mAb on immunohistochemistry (IHC) were the peritoneal, pleural, and pericardial membranes. There was no cross-reactivity with the parenchyma of vital organs. The summary of evidence suggested that the antigen to K1 mAb was a heretofore undescribed molecule similar to that recognized by OC125 (CA125) but clearly distinct in that CA125 was present in supernatant but K1's antigen was only cell-associated. The antigen was dubbed CAK1.

Further characterization of CAK1 demonstrated a 2,138-bp cDNA encoding the antigen with a 69-kDa precursor protein that is further processed to a 40-kDa form that is expressed in the membrane [18]. The protein was named mesothelin due to its presence in mesothelial cells and mesothelial-derived cancers. Cancers that were noted to have strong MSLN with the K1 antibody were of mesothelioma and squamous cell carcinomas of the esophagus and cervix [2, 19]. Improvements in engineering yielded antibodies with higher affinity and enabled staining for MSLN in formalin-fixed paraffin-embedded tissues [20]. Other tumors that were then found to frequently demonstrate MSLN staining were non-mucinous carcinomas of the ovary; adenocarcinomas of the pancreas, endometrium, lung and bile ducts; and TNBC [20-24]. Herein we summarize the MSLN staining patterns of the most clinically relevant tumor types (Table 1) [19-34].

MSLN Expression Patterns in Select Solid Tumors

Mesothelioma

Mesothelioma is a rare disease and thus there is a paucity of available systemic therapies, particularly novel targeted therapeutics. Staining of tumor sections obtained from patients with pleural mesothelioma with K1 mAb revealed that all 15 cases of epithelial mesotheliomas expressed MSLN, but no cases of sarcomatoid mesothelioma stained positive [19]. Similarly, a study by Ordonez reported that staining with the high-affinity mAb 5B2 revealed MSLN staining in 44/44 epithelioid mesotheliomas. On the contrary, 0/8 sarcomatoid mesothelioma tissues, 3/17 squamous carcinomas, and 12/31 adenocarcinomas of the lung stained positive [35]. Given the ubiquitous expression of MSLN in epithelioid mesothelioma, and the knowledge that a portion of MSLN is shed into the serum at detectable levels, some have proposed a role for the soluble portion as a clinical marker for diagnosis and monitoring of the disease [36-38]. This is perhaps the most notable clinical application of MSLN and is currently listed in the National Comprehensive Cancer Network (NCCN) guidelines for pleural and peritoneal mesothelioma [39, 40].

Ovarian carcinoma

The initial discovery of the K1 antibody was accomplished using ovarian cancer cells. The subsequent studies of K1 reactivity noted that 10/15 non-mucinous ovarian cancers reacted with K1 as opposed to 0/4 mucinous ovarian cancers [1]. Further studies by Ordonez using the 5B2 antibody found that the vast majority of that cohort patient tumors were positive for MSLN with the notable exception of the mucinous carcinomas (0/4) [20]. Finally, Hassan and colleagues reported on patients screened for clinical phase 1 trials of a recombinant immunotoxin targeting MSLN, for which eligibility was dependent on MSLN expression. Of the 48 patients with ovarian cancer who were screened, 34 were found to be positive using the K1 antibody [25]. Taken together, these data provide convincing evidence that most non-mucinous epithelial ovarian cancers express MSLN.

Pancreatic ductal adenocarcinoma (PDAC)

Given the high mortality rate and propensity for peritoneal and systemic recurrence, there is much interest in exploiting MSLN as a target in pancreatic cancer. Tumor sections of resected pancreatic adenocarcinoma tumors were stained with the 5B2 antibody and found to have 100% expression by Hassan and colleagues and 12/14 by Ordonez [20, 21]. Normal pancreas tissue has never been reported to express MSLN. Additionally, only one out of 17 cases of chronic pancreatitis was found to have MSLN expression. However, in a study of patients with both PDAC and other pancreatic disease, circulating MSLN was discovered in all five patients with biopsy-proven benign pancreatic disease [26]. MSLN was not found to be expressed in pancreatic intraepithelial neoplasia (PanIN), but rather found to be strongly up-regulated during or after transformation to invasive cancer [41, 42]. Supporting the above findings, MSLN mRNA expression was studied by Argani and colleagues who found that 13 out of 20 pancreatic cancer cell lines demonstrated strong expression and five others demonstrated weak expression. Furthermore, they found that 60/60 resected PDAC samples stained for MSLN on IHC [22]. This led to interest in exploring MSLN as a useful biomarker in the diagnosis of PDAC. In one study, it was reported that 52% of PDACs, 45% of intraductal papillary mucinous neoplasms (IPMNs) and 14% of chronic pancreatitis patients had MSLN mRNA detected in their pancreatic pure pancreatic juice [43]. This yielded a diagnostic sensitivity of 52% and specificity of 86% for invasive PDAC. Supporting this, Einama et al reported that 21 of 37 IPMNs studied demonstrated MSLN expression and the presence of luminal membrane expression was associated with recurrence [44]. Thus, there is strong evidence that MSLN is expressed almost universally in invasive PDAC but almost never in pre-invasive stages or in normal pancreas and may have clinical utility as a diagnostic marker.

Gastric adenocarcinoma

Gastric cancer is a lethal malignancy and peritoneal spread is common at the time of diagnosis. There are few available effective systemic treatments beyond cytotoxic chemotherapy. In his seminal series, Ordonez discovered that 2/7 cases of gastric adenocarcinoma stained positive for MSLN [20]. In a study of 212 consecutive resected gastric patients, Baba et al found that the majority of specimens stained positive [27]. In contrast to that report but congruent with Ordonez's results, studies by Einama and Han found that a minority of examined specimens demonstrated MSLN expression on IHC [28, 29]. Shin and colleagues performed an impressively large study of 958 patients with resected locally advanced gastric cancer wherein they discovered about half of the samples were positive for MSLN [30]. Given the above data, it can be concluded that MSLN is an important tumor marker for gastric cancer and efforts at targeting may benefit a large portion of patients who may not have other options for treatment.

TNBC

MSLN is infrequently expressed in breast cancer [20, 24, 45, 46]. However, in TNBC, where there is particular interest in identifying targetable alterations, MSLN expression is seen with some regularity. Tchou and colleagues found that MSLN was expressed in a majority of resected TNBC specimens [23]. Conversely, studies by Bayoglu and Tozkikian found that 30/71 and 82/226 patients respectively with TNBC had positive MSLN staining on formalin-fixed paraffin-embedded specimens [31, 32]. Taken together, these data demonstrate that MSLN expression is more prevalent in TNBC than hor-

mone receptor and/or HER2 positive disease. However, it is not as prevalent as in other forms of cancer such as PDAC and mesothelioma. This may signify its role in tumor aggressiveness and may present a useful target for therapy.

Structure and Function of MSLN

The variability in reports of MSLN with relation to prognosis raises questions with regards to its function. However, these efforts have been met with equally ambiguous results. In early experiments, Pastan and Bera found that knockout mice had no alterations in development, physiology or reproduction [47]. Since then, there have been many *in vivo* and *in vitro* studies undertaken in an attempt to fully understand the role MSLN plays within the cell and its effects on tumor biology. In this section, we will summarize the existing literature on MSLN genetics, protein structure, cellular function, and role in tumor biology.

Genetics

The MSLN gene contains an 1,884-bp open reading frame. It is encoded by 15 exons and is contained within human chromosome 16. The coding region lacks a TATA box or SP1 sites but does contain mesothelium-specific control elements [48]. There are three variants of MSLN transcripts that have been reported. Variants 1 and 2 encode the MSLN and MPF proteins respectively. The third variant encodes a spliced cDNA that has an alternative C-terminus and disrupted GPI-anchor motif. It is restricted to the nuclear fraction. The significance of the third variant with regards to tumor biology remains to be seen [49]. There have been multiple studies of gene polymorphisms and the effect on tumor biology. Shen and colleagues identified five distinct polymorphisms and investigated their relationship to prognosis in gastric cancer. They found two (rs376427 and rs3764246) that were associated with reduced risk while patients with rs3764247 had poorer survival rates adjusting for other relevant factors [50]. More recently, the same group reported that the polymorphism rs1057147 was associated with higher likelihood of lymph node metastasis in gastric cancer [51]. There are no reports of common targetable alterations or pathogenic variant mutations in the amino acid sequence as it relates to tumor invasiveness, prognosis, or drug targeting.

Structure

The protein is synthesized as a 69-kDa precursor. It is further processed by the endoprotease furin yielding a 40-kDa glycosylphosphatidylinositol-anchored MSLN molecule and the 31-kDa MPF. The final sequence of MSLN contains 303 residues and five alpha-helix regions [52]. BLAST searches demonstrate homology to inner-ear proteins otoancorin and stereocilin. These proteins are also GPI-linked membrane proteins. They are expressed on inner ear sensory and non-sensory epithelial cells and are associated with deafness. Three-dimensional prediction programs predict that MSLN has a superhelical structure made of ARM-type helical repeats. This leads to the hypothesis that MSLN functions as a superhelical lectin that binds extracellular matrix to the surface of the cell to which it is anchored [53].

Function

The question of why MSLN is over-expressed in some tumor types more frequently than others is perhaps most germane to understanding it. Sato and colleagues shed some light on this when studying patterns of hypomethylation in frequently overexpressed genes in pancreatic adenocarcinoma. They reported that MSLN, along with six other commonly overexpressed genes, was frequently hypomethylated in pancreatic cancer cell lines and primary adenocarcinomas [54]. In parallel, Prieve and Moon, when studying Wnt signaling pathways in relation to carcinogenesis found that MSLN was up-regulated by Wnt-1 and Wnt-5a in mouse mammary epithelial cells [55]. Subsequently, Hucl et al set out to specifically determine the mechanism of MSLN overexpression in pancreatic cancer. They reported that an upstream enhancer and its interaction with transcription enhancer factor (TEF)-1 were responsible for the observed expression patterns [56]. Taken together, these data make it difficult to make definitive statements on why MSLN is overexpressed in certain cancers.

A critical breakthrough followed soon after when Rump et al investigated the interaction between MSLN and CA125 in ovarian cancer. In their experiments, they were able to demonstrate that CA125 binds specifically to MSLN and the interaction of membrane-bound MSLN and CA125 mediates cell adhesion, potentially contributing to peritoneal metastasis [57]. Further studies by Gubbels et al, in collaboration with Dr. Pastan's group, confirmed the strong and specific binding of MSLN to CA125 [58]. This was certainly provocative given the propensity MSLN-expression cancers (i.e., pancreatic, ovarian, mesothelioma, and gastric) have for peritoneal dissemination. It was thus hypothesized that MSLN is important in the development of peritoneal metastasis in ovarian and other cancers. Shin and colleagues performed a study of 958 resected gastric cancer patients and found MSLN to be independently associated with worse recurrence-free survival and peritoneal recurrence [30].

The role of MSLN in development of peritoneal metastasis was further investigated by Avula et al. They found that MSLN promotes carcinomatosis by positively regulating angiogenesis, proliferation and invasion during metastatic colonization and that prevention of binding to MUC16 disrupts this activity [59]. Contrary to prior reports of Chen et al - which demonstrated metalloproteinase (MMP)-7 activation as the mechanism of increased invasiveness of MSLN and CA125 binding - Avula did not identify a specific transcriptomic mechanism to account for these observations [60]. These findings may lead one to presume that any mechanism for MSLN action may rely on its binding to CA125. However, in experiments using breast cancer cells, Uehara and colleagues found that ectopic MSLN expression prevented apoptosis and promoted growth in soft

agar, independent of anchorage or cellular binding via activation of ERK1/2 [61].

MSLN does not have an intracellular binding domain. Thus, it is not thought to act as a classical oncogene or tumor driver. It is clear, however, that expression increases tumor aggressiveness, and this is not entirely due to binding with MUC16. There have been multiple studies to identify cellular signaling pathways linked to MSLN expression that would explain the observed phenotype of MSLN positive tumors *in vitro* and *in vivo* as well as the survival data mentioned above. Li et al found that silencing of MSLN suppressed cell proliferation and tumor progression *in vivo* but did not implicate a specific mechanism for their observations [10]. Subsequently they reported that MSLN appeared to be acting through signal transducer and activator of transcription factor protein 3 (Stat3) to upregulate cyclin E resulting in increased cell proliferation and faster cell cycle progression [62]. They went on to further establish an autocrine/paracrine mechanism of MSLN action whereby activation of nuclear factor kappa B (NF-κB) induced interleukin (IL)-6 release which then acts as a growth factor to support cell survival and proliferation [63, 64]. The same group then found that MSLN, through an unclear mechanism, acts on NF-κB and OCT-2 leading to down-regulation of miR-198, which acts as a tumor suppressor [65]. Taking an *in-silico* approach, Lurie et al utilized the cancer genome atlas (TCGA) to perform histoepigenetic analysis of MSLN and its network. They demonstrated that MSLN interacts with retinoic acid receptor gamma (RARG) and tyrosine kinase non receptor 2 (TNK2) to activate AKT [66]. The interaction network they describe may have implications for both MSLN drug targeting and understanding of its function within the tumor.

Taken together, these data provide strong evidence that MSLN participates in tumor cell proliferation and dissemination. Furthermore, it likely plays an integral role in peritoneal dissemination. Despite a large body of literature, mechanisms whereby this is accomplished is yet to be fully understood. There are a handful of cellular pathways that have been implicated but none have been able to be validated. This certainly has implications for the ongoing effort to exploit MSLN for therapeutic benefit as there appears to be little utility to simply blocking it with an antibody and no well-defined target to inhibit its activity [5, 11]. Certainly, further investigation is warranted as there are few more ideal molecules suited for such an approach.

MSLN as a Prognosticator

Given the enthusiasm for MSLN as both a diagnostic and therapeutic target, great effort has been put forth to understand its prognostic significance. Unfortunately, there is no unified answer to the question "Does MSLN expression predict worse survival?" There are multiple factors that prevent a simple yes or no. For starters, there are a variety of tumor types that express the antigen, and they each have distinct biological behavior. Additionally, there is variability in how researchers group patients and samples according to level of MSLN expression. Some studies group patients according to presence/absence of IHC staining while others use degree of staining or group patients according to the transcript level. Furthering the dilemma, IHC methods vary between institution and sensitivity of MSLN detection depends on the mAb used. In this section we attempt to summarize the existing data on the value of MSLN as a prognostic marker to provide clarity in this murky area of cancer research.

In a case-control study of 47 mesothelioma patients, Roe and colleagues found that < 50% MSLN staining on IHC corresponded to significantly worse overall survival in all cases and within the epithelioid subgroup [67]. Supporting those findings are studies by Inaguma and Chu who found that higher MSLN expression was associated with prolonged overall survival [33, 68]. Both studies used IHC staining to group patients according to high and low MSLN expression. Furthermore, in a study integrating MSLN, BRCA1-associated protein 1 (BAP1) and programmed death-ligand 1 (PD-L1) expression in mesothelioma, it was reported that loss of MSLN expression in combination with BAP1 loss and PD-L1 > 1% portended extremely poor prognosis compared to all other combinations [69]. Conversely, when grouping patients according to levels of circulating serum mesothelin-related proteins (SMRPs), those with levels above a cutoff of 1 nM had abbreviated survival compared to those below the cutoff [70]. Grigoriu et al also found that elevated SMRP above a threshold of 3.5 nmol/L was independently associated with worse overall survival. These data suggest that loss of MSLN expression at the tumor level is associated with worse overall survival. One potential explanation is that loss of MSLN signals loss of differentiation and thus a more aggressive tumor. Circulating SMRP likely reflects gross tumor burden, thus it is not necessarily contradictory that higher SMRP portends worse prognosis while presence of MSLN in the tumor does the opposite.

Outside of mesothelioma, the prognostic significance of MSLN becomes much less clear. To investigate this question with regards to ovarian carcinoma, Yen and colleagues performed a study of 105 patients with resected tumor samples available for IHC staining. Focusing on those with high-grade advanced stage serous carcinomas who underwent resection and systemic therapy, they found that patients with diffuse immunoreactivity on IHC has significantly better survival than those without [71]. In contrast, a study of 139 epithelial ovarian carcinoma utilized RT-PCR to detect MSLN mRNA levels and determined that high expression level was a poor prognostic factor and was associated with chemoresistance [72]. The findings held true when controlling for factors such as stage and suboptimal debulking surgery.

In a study of gastric cancer patients divided according to "positive or negative" IHC staining, Baba et al found similarly that MSLN expression was associated with higher 5-year survival when controlling for age, gender, stage and lymphovascular invasion [27]. This was contradicted in studies by Han and Einama [28, 29]. Both divided patients by "positive or negative" MSLN staining and reported that MSLN expression was associated with worse prognosis. Critically, the Einama study found that luminal membrane expression was independently associated with worse overall survival when controlling for stage and lymphovascular invasion. It should be noted that while there may be differences between the three studies in

how they classified tumors, each had similar rates of MSLN positivity, suggesting that there would likely be agreement as to which patients belong in which group.

With regards to pancreatic adenocarcinoma, the existing data are not so ambiguous. Einama and colleagues performed a study of 66 patients who underwent pancreatectomy for curative intent and found that MSLN expression alone and co-expression with CA125 corresponded to worse overall survival [73]. In a similar study, Shimizu et al found that co-expression of MSLN and CA125 (referred to as MUC16) conferred worse progression-free and overall survival that remained when controlling for relevant clinicopathologic factors [74]. Winter and colleagues performed studies on a dichotomized cohort of long-term and short-term survivors. Among 13 candidate biomarkers selected, MSLN and CA1 were found to have significant association with short cancer-specific survival [75]. In fact, as the degree of MSLN staining went up, so did the portion of patients in the short-term survival group, lending a slightly more nuanced look at the actual level of expression as it relates to outcome as opposed to a binary classification. A more recent study, however, found that MSLN expression was not related to aggressive features such as tumor stage, grade, or metastasis [76]. They did not report on overall survival. Thus, despite conflicting evidence in ovarian and gastric cancer, the literature is relatively convincing that MSLN acts as a poor prognosticator in pancreatic adenocarcinoma.

In a study of 109 patients with TNBC, Parinyanitikul et al reported that positive MSLN staining had no association with relapse-free or overall survival [34]. Of note, they classified subjects as according to an H score with a maximal score of 300. Patients with a score less than 10 were considered negative. Subsequently, Tozbikian and colleagues found that TNBC patients who were MSLN positive had abbreviated overall survival compared to those that were MSLN negative independent of lymph node status [32]. When looking at patients with all subtypes of breast cancer, Wang et al reported that patients with MSLN positive tumors had worse overall survival on their multivariate model taking into account tumor size, lymph node and HER2 status [45]. Interestingly, Suzuki and colleagues found MSLN expression to associate with poor prognosis only in luminal type cancer but no other subtypes [77]. Li et al performed a study of breast cancer patients using both a discovery cohort (classified by IHC) and a validation cohort (TCGA, classified by mRNA expression). Without stratifying by receptor status, they found in both cohorts MSLN positivity was correlated with worse overall survival [78]. When considering receptor status, however, the correlation did not hold true. Similarly, Bayoglu and colleagues reported in patients with TNBC, MSLN positive status was not associated with survival in a multivariable model [31]. Thus, it is unclear whether or not MSLN alone acts as an agent of worse disease biology in TNBC.

In summary, the relationship between MSLN expression and prognosis has been studied in a variety of tumor types. The majority of the literature suggests it is associated with worse biology and survival in pancreatic cancer. It has also been associated with worse overall survival in cancers of the bile ducts, lung and colon [79-83]. On the contrary, it appears to have a favorable association in malignant pleural mesothelioma. In epithelial ovarian cancer, TNBC, and gastric cancer, there is conflicting evidence that it is a harbinger of worse outcomes and may not be related to disease biology. As mentioned previously, the variability in literature likely owes to differences in classification of tumor staining and how subjects are categorized in each study. Further research is needed in this arena with standardization of what constitutes MSLN "positive" and more nuanced methods of measuring expression such as mRNA levels.

Conclusion

Here we have reviewed the existing literature on expression patterns, prognostic implications, and function of MSLN. Though there has been a large volume of elegant, quality science performed to understand the molecule, there remains an ambiguity and mystery. What seems to be clear is that MSLN is expressed on the vast majority of mesotheliomas, pancreatic cancers, and ovarian cancers and it is expressed on roughly half of gastric cancer and TNBC. These are all significantly different malignancies but each is characterized by poor outcomes and lack of available effective systemic therapies. The expression of MSLN and its relation of prognosis seems to depend on the type of tumor. Finally, the unified mechanism by which MSLN acts as a protein that conveys tumor aggressiveness remains elusive.

What is clear is that there is much yet to be discovered about MSLN and doing so may have large implications for treatment of multiple lethal malignancies. Closing current gaps in knowledge regarding the function and biological relevance of MSLN may be key to decreasing the burden of these diseases on the affected population and their loved ones. There are several ways by which this may be accomplished. First, more large epidemiologic studies using large databases with genomic and transcriptomic information will be crucial in understanding the relevance of MSLN expression. These are easily performed with the right resources and may go a long way in increasing our understanding of MSLN. Second, ongoing bench research to understand how MSLN interacts within the cell and tumor microenvironment may unlock several clues as to how it is functioning. Specifically, the interaction with MUC16 is intriguing and may well have implications for treatment of peritoneal malignancies. Finally, MSLN expression and function should be studied further using sound, well-reasoned clinical research. This highlights the importance of tissue banking and genomic testing of our patients so we may do our patients justice by learning from them while providing the best possible care. It is imperative that the oncologic community continues to make every effort to advance our understanding of this issue and others in order to end cancer as we know it.

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Author Contributions

BH and KT: literature review, writing - original draft, writing - review and editing.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

MSLN: mesothelin; MPF: megakaryocyte potentiating factor; SMRP: serum mesothelin-related protein; PDAC: pancreatic ductal adenocarcinoma; IPMN: intraductal papillary mucinous neoplasm; TNBC: triple negative breast cancer

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