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Serine proteases and their role in cancer cell metastasis

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Abstract

Serine proteases are a diverse group of enzymes crucial in regulating various physiological functions. They can suppress inflammatory responses and promote tissue regrowth. These enzymes also involve the complex interplay between the tumor environment and cancer cell growth. This study aims to investigate the multifaceted roles of serine proteases in cancer, shedding light on how they can both promote and inhibit tumor growth. The research explores how these enzymes facilitate processes such as angiogenesis, tumor aggression, and metastasis, which makes them potential targets for cancer treatment. The study also addresses the challenges associated with developing effective therapies, focusing on strategies that involve modulating serine protease activity. Furthermore, the review discusses novel approaches for utilizing serine proteases in cancer diagnosis and treatment, highlighting their potential as valuable therapeutic targets. This comprehensive overview emphasizes the intricate relationship between serine proteases and cancer, demonstrating their capacity to contribute to disease progression while also serving as promising therapeutic targets.

Keywords: cancer, enzyme, metastasis, serine protease

1- Introduction

More than 90 percent of cancer-related deaths arise from metastasis[1]. Metastasis involves the movement of tumor cells and the destruction of surrounding tissue barriers to form secondary organs, which requires proteolytic activity, including serine proteases[1]. This complex process involves five consecutive stages: First, cells invade nearby tissues[1]. Second, they split from tumors and enter the circulatory system[1]. Third, they travel through the circulatory system[1]. They get trapped in the small blood vessels around organs[1]. Fourth, they leave the circulatory system and attack new tissues[1]. Fifth, they form new lesions in new places [1]. Cancer cells' key ability is to undergo epithelial-mesenchymal transition (EMT)[1]. EMT enables them to separate and move between nearby cells[1]. They can also move between the extracellular matrix (ECM)[1]. Serine proteases are activated to break down ECM components[2]. This allows cancer cells to cross the ECM barrier[2]. They then move through the space between cells[2]. They use it to attack blood vessels and lymph ducts[2]. Serine proteases are a family of enzymes[2]. They are involved in digestion, homeostasis, blood pressure regulation, and tissue health[2]. They also contribute to cell and humoral immunity[2]. They also aid embryonic development and fertilization[2]. Serine 195 is part of the SER-His-Asp triad[2]. It performs the catalytic function of serine proteases[2]. Serine 195 is activated by histidine 57 and aspartate 102[2]. In this article, we will examine the types of serine proteases[3]. They are a vital cause of cancer spread[3]. We will also look at the drugs that target serine proteases to halt tumor dissemination[3]. Serine proteases are also important biomarkers. They can help detect specific cancers early[3].

2- Methodology

The catalytic triad is the main factor in how serine proteases work[3]. The triad is also present in quasi-chymotrypsin enzymes (in eukaryotes) and subtilisin (in prokaryotes)[3]. The triad includes the amino acids His57, Ser195, and Asp102[3]. They are three amino acids apart in the initial structure of the enzyme[3]. In the third structure, the protein rearranges so these amino acids are placed next to each other[3]. The mechanism generally involves the peptide binding to the enzyme`s active site first, followed by the OH serine group attacking the carbonyl peptide to form a four-membered intermediate. This releases the N-terminal part of the peptide[3]. It forms an acyl-enzyme mediator[3]. Water then helps in the reaction[3]. It acts as a nucleophile, creating another four-way mediator[3]. Finally, breaking the covalent bond between the histidine N-H and the serine O atom releases the peptide C-terminal[3]. The process results in peptide hydrolysis by adding an atom-H to the N end and an atom-OH to the C end[3]. The mechanism of breaking the covalent bond between the carbonyl-C peptide and the oxygen atom is a major factor in the catalytic mechanism of serine proteases[3].

There are two types of serine proteases[3]. They are based on their location in the extracellular space[3]. The first type is secretory[3]. The second type is membrane-anchored. Secretory serine proteases include chymotrypsin, trypsin, and thrombin, and part

of the serine family of S1 proteases[3]. They are produced from secretory vesicles and play a role in biological events such as tissue repair, immunity, and nutrient absorption. Membrane-anchored serine proteases bind to the membrane in three ways[3]. The first way is through a terminal carboxyl membrane passage domain via GPI binding, as seen in human GPI-anchored serine proteases [3]. The second way is through a carboxy-terminal passage domain, like transmembrane serine protease type 1 (tryptase γ1) [3]. The third way is with an amino trans-membrane domain and cytoplasmic expansion as observed in type II transmembrane serine proteases (TTSPs) such as TMPRSS2, matriptase, hepsin, and TMPRSS4 [3].

2-1- Effect of serine proteases on squamous cell carcinoma of the head and neck

Matriptase-2: Matriptase-2 is expressed as a zymogen on the surface of the cell[4]. Matriptase-2 is found in the human liver. It helps dissolve extracellular matrix proteins, such as laminin and fibronectin[4]. This protease is mainly expressed in conjunction with the liver growth factor activator inhibitor-1 (HAI-1), which imbalances and increases the ratio of matriptase-2 to HAI-1 playing a role in cancer metastasis, causing the decomposition of ECM components and reducing cell-to-cell adhesion[4]. Studies have shown that matriptase-2 activates the protease-activated receptor 2 (PAR-2), which metastases this type of cancer are associated with PAR-2, and this receptor causes malignancy in skin, head, and neck cancers[4].

DESC1: The initial study on DESC1 revealed that this serine protease is expressed in normal head and neck tissues but is significantly reduced in head and neck squamous cell carcinoma samples and In some cases, the level of this protease drops to an undetectable degree [4]. DESC1 protein level also decreases during cancer progression and is positively associated with keratinocyte differentiation[4]. Overexpression of DESC1 in primary tumor-derived cell lines reduced cell viability by increasing apoptosis under stress conditions[4].

Prostatin: Prostatin is a potential tumor suppressor in oesophageal squamous cell carcinoma (ESCC), whose levels have been reduced in poorly differentiated SCC tissues[4]. This is due to the promoter hypermethylation of the PRSS8 gene, which silences the expression of Prostatin and can be reversed by treatment with a demethylating agent[4]. Prostatin suppresses ESCC tumors. It does this by reducing cell cycle and EMT levels[4].

TMPRSS4: TMPRSS4 plays an important role in the progression of cancer and metastasis. TMPRSS4 is a type II transient serine protease[4]. It overexpresses in the pancreas, thyroid, and cancerous tissues[4]. It helps cancer progress. It does this by causing cells to lose E-cadherin adhesion. It also facilitates epithelial-mesenchymal transition (EMT)[4].

2-2- **Lung cancer**

A study examined the expression of HTRA1, a serine protease, in 99 lung cancer samples[5]. The goal was to understand its role in lung cancer's cause and spread[5]. Studies have shown that it targets proteins inside and outside cells[5]. A lack of this

protease reduces the inhibition of the TGF-beta pathway that contributes to the progression of lung cancer[5].

We compared levels of AAT, ACT, and SLPI inhibitors in metastatic lung cancer[6]. We compared them to levels in non-metastatic cases[6]. AAT blocks proMMP-2 activation and tumor cell invasion in the lab[6]. However, in the body, an imbalance between AAT and neutrophil elastase may cause lung cancer spread[6]. ACT is another inhibitor. It inhibits DNA synthesis in human carcinoma cells[6]. Many types of tumors contain ACT. Plasma from gastric and breast cancer patients shows a significant increase in ACT[6]. Lung adenocarcinoma generates ACT, a reliable indicator of tumor size[6]. SLPI is a major inhibitor of elastase. Elastase is an important molecule for protecting the respiratory epithelium[6]. Elastase breaks down elastin[6]. Collagen and elastic fibers determine the mechanical properties of connective tissue[6]. SLPI levels are much higher in lung cancer patients than in the control group[6]. Several laboratory studies have shown this. They found that cancer cells have traits linked to high SLPI expression[6].

Studies show that plasma levels of serine protease inhibitors AAT, ACT, and SLPI increase in cases of lung cancer relative to the witness Group[6]. AAT and ACT levels were significantly higher in cases of metastatic lung cancer compared to cases with a topical tumor[6].

2-3- gastric cancer

Gastric cancer is a common solid tumor worldwide[7]. It causes approximately one million new cases each year[7]. These cases result in over 0.7 million deaths[7]. HtrA1 is a member of the protease serine family[7]. It is widely expressed in normal tissues[7]. HtrA1 plays a key role in signal transmission in the FGF and IGFR pathways[7]. It reduces tumor progression and metastasis[7]. Too much HtrA1 stops cell growth[7]. It also is linked to the invasion and migration of tumor cells in gastric cancer[7]. We used immunohistochemical methods to check HtrA1 expression in tumor tissues[7]. It shows less expression in tumor tissues than in normal tissues[7]. Htra1 overexpression reduces the growth of gastric cancer cells[7]. It also inhibits tumor growth inside cells and in vitro[7]. Also, high HtrA1 expression is linked to causing apoptosis in ovarian cancer cells[7]. These findings suggest that HtrA1 plays a role in tumor development. It also plays a role in progression. It may be a target for cancer treatment[7].

2-4- Breast cancer

First, we will examine the role of Type II transient proteases serine (TTSPs)[8]. They play a crucial role in breast cancer progression[8]. We will focus on TMPRSS13[8]. Tmprss13 expression in cancer patient tissue samples increases compared to normal breast tissue[8]. Human breast cancer cell culture models express TMPRSS13 at lower levels[8]. This leads to less growth, more apoptosis, and weaker metastasis[8]. The researchers also found that Tmprss13 loss raises prostacyclin levels. This disrupts the survival and invasion of human breast cancer cells[8].

Serpins are often overexpressed in human tumors[9]. This includes PN-1, a serpin that blocks protease activity. It surges in aggressive forms of breast cancer[9]. Studies of breast cancer cell lines show that nexin-1 protease boosts ERK signaling[9]. It also boosts MMP-9 expression[9]. Moreover, it spurs the spread of breast tumors[9]. MMPs are a family of proteolytic enzymes[9]. They play an important role in digesting matrix proteins[9]. These proteins hold cells and help the spread of malignant human tumors[9]. Breast cancer patients have high levels of the protease nexin-1[9]. They are more likely to develop metastasis[9]. The findings suggest that nexin-1 protease could become a marker for breast cancer. It could help predict the likely outcome of the disease[9].

3- Conclusions

Serine proteases play a crucial role in the process of cancer metastasis. They facilitate the spread of cancer cells through various mechanisms. These enzymes degrade the extracellular matrix and basal membrane, allowing cancer cells to detach from the primary site and migrate to other parts of the body. Additionally, serine proteases promote metastasis by activating molecules involved in cell migration and angiogenesis. Some serine proteases disrupt cell adhesion by cleaving cell adhesion molecules like cadherins and integrins, which enhance the mobility of tumor cells and facilitate their detachment from the primary tumor mass, leading to distant metastases. Moreover, apart from their extracellular functions, some serine proteases can modulate signaling pathways and gene expression, triggering cascades that promote cell proliferation, survival, and motility, ultimately contributing to cancer progression.

Serine proteases play various roles in metastasis, highlighting their potential as targets and biomarkers. In clinical models, the inhibition of serine-specific proteases using small molecules or antibodies has shown promise, paving the way for new anti-metastatic therapies. Targeting these enzymes as biomarkers can offer valuable information for early detection, risk classification, and personalized treatment. Significant progress has been made in understanding the role of serine proteases in metastasis, but many questions remain unanswered. Further research is necessary to elucidate the complex interactions among different serine proteases and clarify their specific functions in various cancer types.

Develop new inhibitors for specific serine proteases to eliminate unwanted reactions and enhance treatment benefits.

The tumor microenvironment and immune system are crucial as they assist serine proteases in driving metastasis, playing a significant role in this process.

The potential of combining serine protease inhibitors with other targeted therapies for optimal antimetastatic responses

Studying these subjects helps us understand the roles of serine proteases, which are crucial for the spread of cancer due to their complex functions. This knowledge can then be applied to develop treatments for patients suffering from this devastating disease.

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