

Review Article

Tryptase plays a role in solid tumor angiogenesis and cell proliferation

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ABSTRACT

Tryptase, a serine protease released during mast cell degranulation has been associated with anaphylactic reactions and inflammations. In recent studies on solid tumor proliferation, it has been seen that tryptase has a role in tumor angiogenesis and tumor cell proliferation. This also makes tryptase a potential therapeutic target. Many anti-tryptase agents have shown to decrease tumor angiogenesis and proliferation. Authors have thus reviewed various articles which have done extensive studies on the role of tryptase as an important factor in tumor proliferation and angiogenesis.

Keywords: Solid tumor, Tryptase, Tumor angiogenesis

INTRODUCTION

Tryptase is a 134 kDa serine protease enzyme, deriving its name from its trypsin-like activity of cleaving peptides or protein substrates. In theory, tryptase cleaves a fragile or amide bond at the carboxyl end of lysine or arginine residues. Tryptase has been commonly expressed by mast cells and seen minorly in immature basophils and leukemic cells of patients suffering from various myeloid and leukemic disorders. The normal levels of tryptase have been recorded as 5-11 ng/dl.¹⁻⁴

Tryptase is encoded on the short arm of chromosome 16, specifically expressed by mast cells (MC's) which are of subtypes, α , β , γ and δ . Each type encodes a leader chain of 30 AA and catalytic proteins of 245 AA. Tryptase was originally identified to be a marker of anaphylaxis and inflammation, as its serum levels rise alongside histamine during an attack of anaphylaxis. This is because of increased mast cell production during anaphylactic shock. Tryptase is also seen increased in people with a history of asthma, allergic rhinitis, etc., due to the massive

involvement of mast cell in these conditions.^{1,5-7} Further studies also revealed that mast cell tryptase plays a role in the proliferation and angiogenesis of solid tumors.

TRYPTASE INCREASES TUMOR PROLIFERATION AND ANGIOGENESIS

Tumor microenvironment includes not only the malignant cells but also a milieu of the immune cells and increased vasculature and lymphatic systems. These include T and B lymphocytes, tumor-associated macrophages, MC's, endothelial cells, etc. These factors increase signal transduction pathways such as mitogen-activated protein kinase kinase kinase (MEKK) pathway and also induce increased expression of angiogenic factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), etc. All these increase tumor cell proliferations and angiogenesis (Table 1).⁸

Tryptase is released from MC's when the stem factor binds to tyrosine kinase c-kit R on MC surface, leading to

degranulation of cells and release of tryptase. Tryptase acts as an agonist of G-protein coupled receptor super family, proteinase-activated receptor-2 (PAR-2) of epithelial and endothelial cells. Tryptase activates PAR-2. This in turn results in G-protein coupled transduction resulting in phosphatidylinositol hydrolysis and elevation of Ca²⁺ in tumor cells. Increased calcium levels activate G-protein coupled signal transduction and phosphorylated extracellular signal-related kinase (ERK) and mitogen-activated protein kinase (MEKK/MAPK). Increased calcium levels also activate increased secretion of prostaglandin E2 (PGE2) and cyclo-oxygenase-2 (COX-2). Sodium hydrogen antiporter-3 regulator-1 (NHERF-1), present in various normal and tumor cells, is activated through Erzin/protein kinase A mediation, and regulates many transmembrane receptors, transporters

and other proteins which play a role in cancer cell proliferation (Table 1).^{1,7,9}

VEGF expression on endothelial and intestinal cell surfaces is also increased by tryptase activated PAR-2, thus playing a role in tumor proliferation, growth, and angiogenesis. This theory was tested out in human colon carcinoma cell lines which were reported by Ilaria Marech et al. Tryptase can be translated as therapeutic targets in cancer due to its role as a tumor angiogenesis factor. Release of tryptase from mast cells can be inhibited with help of tryptase inhibitors such as gabexate mesylate and nafamostat mesylate in combination with tyrosine kinase inhibitors imatinib/ masitinib which hinder mast cell activation and c-KIT2 induced degranulation (Table 1).^{1,7,9-10}

Table 1: Studies on the role of tryptase in tumor angiogenesis in cancer.

Study	Methodology	Result	Conclusion
Kankkunen et al¹⁵	Immunohistochemistry and Microscopy of Mast cells -Polyclonal anti-tryptase antibody (Rabbit) -MAbs- anti-chymase antibody B7 (Mouse)	-In benign lesion, tryptase activity was equal to that of chymase -In malignant breast cancer tryptase activity was higher than chymase	Mast cells showed higher tryptase activity than Chymase activity, especially in malignant breast tissues than in benign breast tissues.
Ribatti et al¹⁶	Immunohistochemistry Antibodies used -MAbs against endothelial cell marker (CD31) (MAb 1A10) and tryptase	-Tryptase +ve MCs increased with microvascular count especially in lymph nodes -Angiogenesis in SLN was contributed by tryptase mast cell	Tryptase is associated with increased microvascular count signifying its role with angiogenesis in tumor cell
Ranieri¹⁷	Immunohistochemistry -Anti-CD34 and anti-tryptase Human-specific monoclonal antibodies	-Tryptase +ve mast cells were increased around vascularized regions and was involved in tissue remodelling. -Tryptase indirectly induced tissue neovascularization by releasing angiogenic factors	Raised levels of tryptase +ve mast cell is associated with tumor cell neovascularization and tissue re-modelling
Xiang et al¹⁴	Immunohistochemistry assay -IgG1κ monoclonal antibody B12; acts on epitope of Tryptase Cell culture: -MDA-MB231 -Migration assays and in vitro cell invasion Gelatin zymography to evaluate MMP-2 expression	-Grade 3 breast cancer specimens had higher tryptase expression when compared with grade 1 and 2 -no significant in cell proliferation despite tryptase treatment -Tryptase increased invasion of breast cancer cells -Groups having increased Tryptase levels also had increased cell invasion	Grade 3 breast cancer has higher tryptase expression and this was associated with cellular invasions, however there was no significant role of tryptase in cell proliferation
Marech et al¹²	Immunohistochemistry -Specific monoclonal antibodies anti-tryptase and anti-CD34 staining in adjacent sections Morphometrical assay -(Quantimet500 Leica, Wetzlar, Germany) image analysis system was utilized	-Tryptase burden was from mast cell degranulation -Tryptase stimulates formation of vascular tubes in vitro and in vivo experimental models. -Tryptase acting as an agonist of PAR-2, stimulates release of latent angiogenic factors	Tryptase as a PAR-2 agonist promotes tumor angiogenesis via stimulation and release of other angiogenic factors
Marech et al¹³	Immunohistochemistry assay -Human specific MAbs (anti-CD34) -Rabbit polyclonal antibodies to c-KitR (ANTI-CD 117))	-In vitro, tryptase inhibitors suppressed ECs proliferation, suggesting proliferation is activated by tryptase -MCs-c-KitR and tryptase promotes angiogenesis in breast cancer	With the use of tryptase inhibitors, it established that mast cell tryptase and Mast Cell-c-KitR stimulates angiogenesis

Continued.

Study	Methodology	Result	Conclusion
Qian et al¹¹	<p>Method: Cell culture EGM In vitro wound-healing assay western blot electrophoresis culture and identification of EPCs -Proliferation, migration, and assay of EPCs (lumen formation). RT-qPCR and semi-quantitative -Primers used: PAR-2 forward and reverse, VEGFR-2 forward and reverse, GAPDH as control</p>	<p>-Tryptase inhibited EPC migration and tube formation which was reversed by both tryptase inhibitor (APC366) and PAR-2 inhibitor (SAM 11) -Significantly increase in VEGFR-2 mRNA level in EPCs when treated with tryptase or a PAR-2 agonist -Tryptase may have direct role in EPC activation and migration through PAR-2/ERK signalling pathways</p>	<p>Tryptase activated PAR-2 receptors increased VEGFR-2 expression, playing a direct role in EPC activation and migration</p>
Pancreatic cancer			
Strouch et al¹⁸	<p>Adenocarcinoma cell lines PANC-1 and AsPC1 Mast cell migration assay Proliferation and invasion assay Immunohistochemistry -Mouse based anti-human tryptase antibody (primary) -Dako anti-mouse IgG antibody (secondary) Serum tryptase activity (mast cell degranulation assay) by quantitative spectrophotometric Cell culture line: -Human pancreatic ductal cell line</p>	<p>-Increased mast cell infiltration was statistically significant in the stroma of pancreatic cancer tissue especially when compared to adjacent normal pancreatic tissue and benign pancreatic tissue -In 36 serum samples of adenocarcinoma patients there was elevated serum tryptase activity -Mast cell migration orchestrated by tryptase activity</p>	<p>Significant mast cell infiltration in tumor pancreatic cells which was associated with elevated tryptase and increased mast cell migration</p>
Guo et al¹⁹	<p>IHC assay, ELISA assay -Serum Mast Cell Tryptase (MCT) level qPCR -ANGPT1, TIE2, VEGF and PDGF mRNA expression Cell culture- proliferation and tube formation HUVEC cells and PANC-1 cell line Western blotting nude mouse model -tumor formation assay</p>	<p>-In pancreatic cancer patients, serum tryptase was significantly correlated with higher microvascular density -Nafamostat, an MCT inhibitor could partly reverse the proliferative effect of tryptase -Promotion of endothelial cell growth and activate vascularization of tumor cells by Mast cell tryptase</p>	<p>In pancreatic cancer cell lines, tryptase promotes endothelial cell growth and activate tumor vascularisation</p>
Ammendola et al²⁰	<p>Immunohistochemistry -Incubated with MAbs anti-CD31 -Using biotinylated secondary antibody, bound antibody was visualized, avidin-biotin Morphometrical assay</p>	<p>-In areas recognized as hot angiogenic beds, mast cells were identified in huge number -Increased angiogenesis associated with increased count of c-Kit+ MCs and MCD-T -c-Kit-R activation released Tryptase following degranulated MCs -Novel surrogate angiogenic markers in pancreatic cancer: c-Kit+ MCs and MCD-T</p>	<p>Tryptase release mediated by c-Kit+ activated degranulation of Mast Cells is a factor of increased tumor angiogenesis and can be used as a novel surrogate marker of pancreatic cancer</p>
Gastric and colorectal cancer			
Ammendola et al²¹	<p>Immunohistochemistry -Human-specific monoclonal antibodies against tryptase Morphometric Assay image For tryptase positive cells counted at a magnification of ×40</p>	<p>-MCT levels and number of metastatic lymph nodes showed positive correlation -Significant correlation among increased metastasis and tryptase positive mast cell density</p>	<p>MCT in primary tumor tissue considered as a marker of prognosis in gastrointestinal cancer patients before radical surgical treatment</p>

Continued.

Study	Methodology	Result	Conclusion
Malfettone et al²²	Immunohistochemical analysis for MCs -In the tissue stroma, appearance of tryptase (+) MCs -Sections incubated with polyclonal EBP50 antibody for NHERF1 (rabbit) -Antibodies against human MC-tryptase Immuno histo-fluorescence	-Low expression of PAR-2 in normal mucosa but highly expressed along tumor borders adjacent to vascular structures -Higher density of tryptase (+) MCs in tumors with distant metastases and poor differentiation grade -During wound healing and cancer, Tryptase involved in tissue remodelling by degrading selectively matrix proteins, synthesizing collagen	High density tryptase mast cells can be a marker of tissue remodelling and distant metastasis ^{Continued.}
Ammendola et al²³	Fluoro-enzyme immunoassay -Serum tryptase levels Immunohistochemistry -4 mm-thick serial sections of formalin-fixed and paraffin-embedded tumour sample and -Tumour sections were incubated with an anti-tryptase antibody -Anti-CD34 antibody -Anti-VEGF antibody Morphometrical assay	-Tumour tissue MCT mean and adjacent normal mucosa MT mean showed significant difference (p=0.000). -Increased VEGF expression indicated by a strong cytoplasmic immunostaining in cancer tissue -Mast cells represent main source of serum tryptase in primary CRC tumour tissue	Raised tryptase levels in tumor tissues are important indicators of increased VEGF expression
Suzuki et al²⁴	Immunohistochemistry Tissue sections -Deparaffinized in xylene -Monoclonal antibodies (mouse) to recognize tryptase	-Significant independent predictor of unfavourable overall survival was high peritumoral mast cell infiltration -Tumor cell proliferation and angiogenesis promoted by tryptase which releases interleukin 6 and granulocyte macrophage colony-stimulating factor	Tryptase can be considered as an independent predictor of poor overall survival and tumor cell proliferation
Sammarco et al²⁵	Immunohistochemistry -Anti-tryptase -Anti-CD31 antibody -Secondary antibody (Biotinylated) Morphometrical assay Light microscopy integrated with an image analysis system	-Presence of tumors associated Macrophages (TAMs) and increased mast cell density positive for tryptase (MCDPT) together indicated as significant marker of gastric cancer angiogenesis	Coupled MCDPT and TAMs may be used as a surrogate biomarker of degree of gastric cancer angiogenesis
Endometrial cancer			
Ribatti et al²⁶	Immunohistochemistry -Micro vessel counts -Mast cell counts -Two murine monoclonal antibodies against endothelial cell marker (CD31) and tryptase	-Mast cells scattered in neoplastic tissue were found to be near or around blood capillaries -Tryptase positivity, increased Mast cells and presence of micro vessels makes tumor more invasive	Tryptase +ve mast cells are associated significantly with tumor invasion of greater than half of myometrium

Mab: Monoclonal antibodies, MCs: Mast cells, SLN: Sentinal lymph nodes, MMP-2: Matrix metalloproteinase-2, CD: Cells of differentiation, ECs: Endothelial cells, EGM: Endothelial cell growth medium, EPCs: Endothelial progenitor cells, VEGFR: Vascular endothelial growth factor receptor, RT-qPCR: Reverse transcription quantitative polymerase chain reaction, PAR-2: Proteinase-activated receptor-2.

TRYPTASE AS A MARKER OF ANGIOGENESIS IN SOLID TUMORS

Tryptase which is stored in MC granules as a tetramer complexed with heparin, has various roles such as activation of MCs, increasing blood vessel permeability, inflammatory cells infiltration, epithelial cell proliferation, and stimulation of IL-8 secretion. In

preceding studies related to breast cancer, there was a significant association between increased tryptase and increased expression of VEGF-receptors and c-Kit receptors.¹¹

Marech et al, demonstrated that serum tryptase levels in breast cancer correlated with MC's and microvascular density. In their study, tryptase was found to induce in

in vitro endothelial cell proliferation in matrigel assay.¹² This was supported by other studies in which it was observed that tryptase promoted endothelial progenitor cell (EPC) migration which was inhibited when tryptase inhibitors were used. Tryptase was found to promote endothelial tube formation and this significantly increased VEGFR-2 RNA levels in EPC which was reversed when treated with tryptase and PAR-2 inhibitors. Mangia et al suggested that tryptase may be an initiator of carcinoma-associated fibroblasts.¹²⁻¹⁷

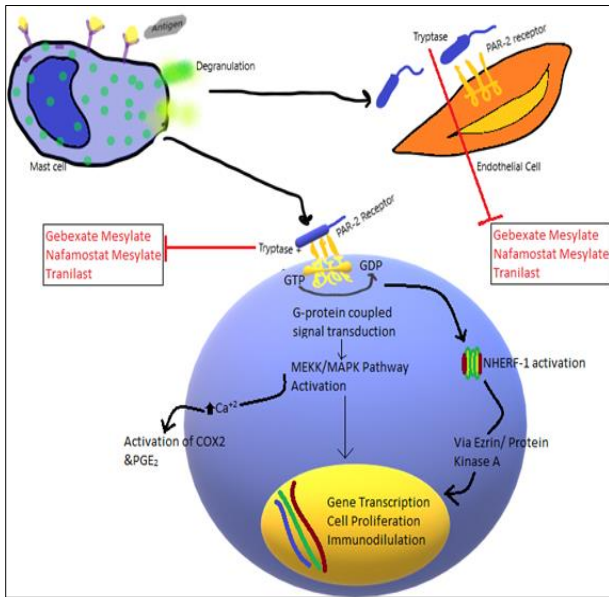


Figure 1: Tryptase inhibitors.

A similar finding was seen in studies involving pancreatic cancer. It was found that MC tryptase levels were higher in pancreatic cancer tissue. These levels also increased with increasing stage of the disease. Tryptase positive MC's also had a correlation with expression of cKit-2 receptor which also significantly correlated with cell migration and angiogenesis. These receptors play an important role in activating VEGFR-2 receptors which also would increase the tumor angiogenesis.¹⁸⁻²⁰

When mast cell density positive tryptase (MCDPT) levels were correlated with microvascular density in gastric, colo-rectal, and endometrial cancers, it was found that MCDPT was heavily populated near vessels in tumor tissue and were significantly in higher number in the tumor tissues than with normal adjacent tissue.²¹⁻²⁶ Most of the tumors were of early-stage unlike study conducted by Xiang et al. It was demonstrated that with an increase in tryptase levels, there is activation of matrix metalloproteinases (MMPs) which also increase angiogenesis in tumors.^{14,22-26}

As shown in Table 1, tryptase has a major role in promoting angiogenesis and tumor invasion in solid cancer which seems to increase with increasing stage of the disease. Further studies may be required to establish

tryptase's role as a marker for disease progression or severity. Treating the cell lines with tryptase inhibitors has shown to decrease the tumor neovascularization and migration of epithelial cells. Tryptase, thus, can serve as a possible new cancer therapy target.¹¹⁻²⁶

TRYPTASE AS A THERAPEUTIC TARGET IN SOLID TUMORS

As mentioned earlier, tryptase activates PAR-2 receptors on both endothelial cells and the tumor cells increasing gene transcription, cell proliferation, and angiogenesis. This increases tumor proliferation and increasing tumor growth.^{9,11-12} Many drugs have been studied as inhibitors of tryptase, some of which are Gabexate mesylate, Nafamostat mesylate, and Tranilast (Figure 1).²⁷

Gabexate mesylate, is a synthetic inhibitor of trypsin-like serine proteases. As tryptase has trypsin-like action, gabexate mesylate has shown selective inhibition of human tryptase producing inhibition of tumor invasion, metastasis, and angiogenesis. The activity of gabexate mesylate has been investigated in cases of colonic and pancreatic cancer cell lines. When used in combination with anti-epidermal growth factor receptor (EGFR) monoclonal antibody like cetuximab, gabexate mesylate has been found to downregulate the trypsin-like action of plasma proteases including tryptase and decreased proliferation of tumor cells.²⁸

Similar to gabexate mesylate, nafamostat mesylate inhibits a variety of serine proteases with trypsin-like activity including those involved in the coagulation process. Nafamostat mesylate has been suggested to be used as a therapeutic agent in conditions of increased tryptase levels like anaphylactic inflammations. nafamostat mesylate action of tryptase inhibition mediates the role of nafamostat mesylate as an anticancer agent. With a mechanism of action similar to that of gabexate mesylate, previous studies showed that nafamostat mesylate antagonizes tryptase induced PAR-2 activity inhibiting invasion and proliferation of pancreatic cancer cells. Nafamostat mesylate anti-tumor activity has also been demonstrated by blockade of activation of nuclear factor kappa-B (NF- κ B), thought to be induced by tryptase activity.^{27,29-32}

Tranilast which inhibits the action of tryptase in MC-mediated inflammations, has been approved as a treatment for various diseases like bronchial asthma, atopic dermatitis, and allergic conjunctivitis, in a few countries namely Japan and Korea.²⁷ There were also reports of, both in vitro and in vivo, the role of tranilast as an inhibitor of VEGF-induced angiogenesis which is concomitant to its inhibitory role on mast cell degranulation. The most common mechanism of action of Tranilast is pathway reduction of MMP 9 and VEGF expression by downregulating TGF- β .^{27,33-34}

CONCLUSION

As tryptase has a proven role in tumor angiogenesis, it can be further studied as a marker of tumor progression and also as an anti-cancer therapy.

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Ethical approval: Not required

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