Review Article

Tryptase: A Novel Prognostic Biomarker in Chronic Myeloid Leukemia

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Abstract

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the presence of the Philadelphia chromosome. It is treated with tyrosine kinase inhibitor agents targeted against the breakpoint cluster region-Abelson murine leukemia 1 fusion transcript. Disease risk stratification at diagnosis of chronic-phase (CP) CML is done using Sokal, Hasford, and EUTOS scores which use basophilia as a major component. However, basophil counts can be both variable and inaccurate. The serum tryptase level is being studied as a novel biomarker which represents the total basophil compartment. Tryptase, deriving its name from trypsin-like activity commonly expressed by mast cells, and also by immature basophils of patients suffering from various myeloid and leukemic disorders, has a role in tumor proliferation. Patients with seemingly low-normal levels of basophils and raised tryptase levels progress further in disease despite treatment. There is a recent interest in the role of serum tryptase as a prognostic marker in CML-CP.

Keywords: Chronic myeloid leukemia, novel biomarker, prognostic marker, tryptase

Introduction

Chronic myeloid leukemia (CML), the most common leukemia of adults, is a myeloproliferative neoplasm mostly characterized by the presence of Philadelphia chromosome,[1] which accounts for 30% of adult leukemia.[2] Currently, breakpoint cluster region-Abelson murine leukemia (BCR-ABL)-positive CML is treated with tyrosine kinase inhibitor (TKI) and prognosticated using clinical scores such as Sokal/EUTOS score.[3,4] Tryptase, a 134 kDa serine protease expressed by mast cells, derives its name from its trypsin-like activity of cleaving peptides or protein substrates on the carboxyl end of lysine or arginine residues.[5] Tryptase, of α- and β-subtypes, is encoded on the short arm of chromosome 16.[6,7]

Tryptase Has a Pivotal Role in Cancer Proliferation

Ilaria Marech *et al*. elucidated that tryptase is released when the stem cell factor binds to tyrosine kinase C-KIT receptor on the mast cell surface, leading to cellular degranulation by activating proteinase-activated receptor-2 (PAR-2). This acts as an agonist of G-protein couple receptor super-family of the epithelial and endothelial cells, resulting in G-protein coupled transduction leading to phosphatidylinositol hydrolysis and elevation of Ca^{2+} in tumor cells leading to tumor cell angiogenesis and proliferation.[5,8] This also causes the phosphorylation of mitogen-activated protein kinase/extracellular signal-related kinase and mitogen-activated protein kinase pathway.[5,8]

Increased calcium levels lead to activation and increased secretion of cyclo-oxygenase-2 and prostaglandin E_2 and activation of sodium hydrogen antiporter-3 regulator-1, which, through Erzin/protein kinase A mediation, regulates many transmembrane receptors, transporters, and other proteins, leading to cancer cell proliferation.[8] Tryptase activation of PAR-2 increases vascular endothelial growth factor expression on the endothelial cell surfaces, inducing angiogenesis [Figure 1].[5,8]

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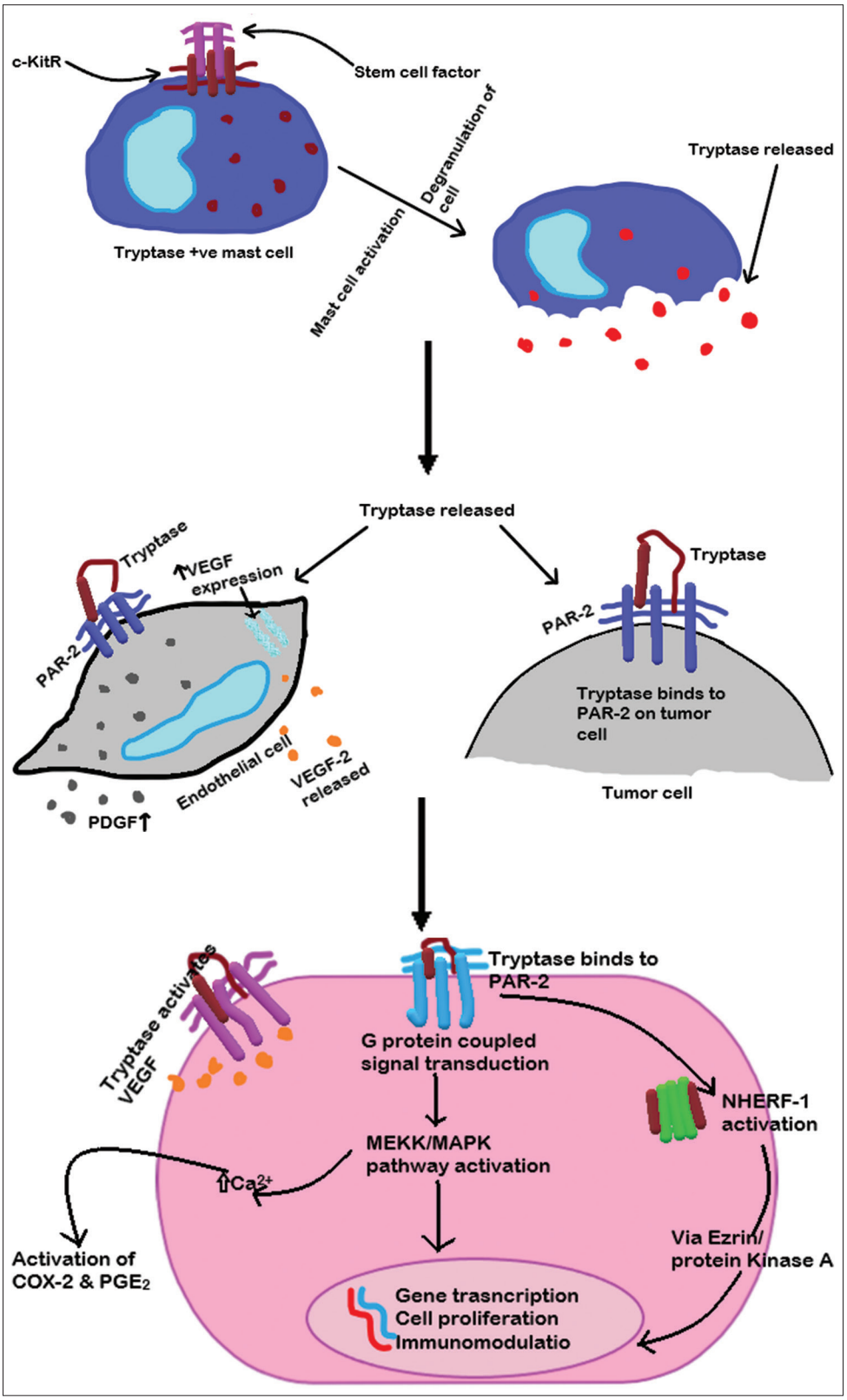

Figure 1: Role of tryptase in tumor proliferation and angiogenesis[5,8]

Tryptase in Chronic Myeloid Leukemia

Leukemia, characterized by abnormal leukocytosis, is subclassified into acute and chronic based on the percentage of peripheral blood/bone marrow blast cells.[1,2] CML has immature cells of myeloid lineage rising levels of erythrocytes, megakaryocytes, and leukocytes. Identifying Philadelphia

Table 1: Studies were done to identify the role of tryptase in Chronic Myeloid Leukemia

Author, reference, year	Study	Study Size	Methodology	Result
Samorapoomichit *et al*., 2001[8]	Brief report	12 healthy volunteers, 6 patients with CML (chronic phase), 3 patients with MDS	Isolation and culture of mast cells and basophils Electron microscopy and immunomicroscopy Real-time PCR	Tryptase expressed in both mast cell and immature basophils but not mature basophils Abnormal expression in patients of CML and MDS
Valent *et al*., 2014[11]	Review	Review of multiple studies	Review of multiple studies	Primarily expressed by immature basophils Correlated with CML total basophil burden Prognostic marker
Sperr *et al*., 2015[10]	longitudinal study	Seventy-nine patients with Ph+ CML	Fluoroenzyme immunoassay of tryptase at baseline qPCR of BCR-ABL and tryptase mRNA level in peripheral blood cells	Potential basophilia marker Enzyme levels significantly higher in high-risk patients with low Sokal, Hasford, and EUTOS score EUTOS T (tryptase levels included) distinguishes between low and high-risk patient regarding event-free survival
Ghalaut *et al*., 2015[12]	Observational	20 AML patients and 20 CML patients	ELISA to assess the level of human MCT qPCR for BCR-ABL	Levels elevated in both CML and AML patients Useful for diagnosis, assessment of severity and prognosis in AML and CML
Kelta *et al*., 2018[5]	Observational	60 confirmed CML patients and 24 confirmed AML patients	Fluoroimmuno assay for tryptase used and correlated with the stage of CML	Elevated in both CML and AML patients Raised in CML-CP Useful as a biomarker in both CML and AML

CML: Chronic myeloid leukemia, AMI: Acute myeloid leukemia, CP: Chronic phase, MCT: Mast cell tryptase, EUTOS: European Treatment and Outcome Study, BCR-ABL: Breakpoint cluster region-Abelson murine leukemia, qPCR: Quantitative polymerase chain reaction, MDS: Myelodysplastic syndrome

chromosome (reciprocal translocation of chromosome 9 [ABL-gene] to chromosome 21 [BCR-gene]) confirms diagnosis.[1] This translocation makes CML patients responsive to TKIs.[2,3]

Role of Tryptase in Chronic Myeloid Leukemia

CML disease risk stratification and prognostication are done at diagnosis using scores such as Sokal, Hasford, and EUTOS scores recommended by the European Leukemia Net. These risk scores rely on various factors, most importantly spleen size and percentage of the peripheral blood basophils as prognostic parameters.[4] However, scores can be misleading due to variations in basophil percentage and inaccuracies in the identification of mature basophils and basophil precursors on the peripheral blood film. As shown by Samorapoomphichit et al. tryptase expression was more in neoplastic immature basophils in comparison to normal mature basophils which showed <1% tryptase secretion. Thus, tryptase is a promising marker of basophil compartment in CML as only immature basophils (which increase in CML) secrete tryptase.[9,10] Raised tryptase levels in patients with hematological malignancies have been documented with a proven escalation of mRNA tryptase.[9,11]

Tryptase in Different Phases of Chronic Myeloid Leukemia

Tryptase levels are notably higher in advanced CML compared to CML-CP. With a study reporting that raised levels of serum tryptase (>15 ng/ml), 70% were of patients in an advanced phase and 26% of CML-CP.[10] Conflictingly, Kelta *et al.* reported that higher mean ± standard deviation (SD) was found in CML-CP.[5]

Tryptase as a Prognostic Marker in Chronic Myeloid Leukemia

Patients with higher tryptase levels had a higher risk of progression and development of events during their course of treatment, while a decrease in BCR-ABL transcripts was faster and deeper in patients with normal serum tryptase levels.[9-11] Ghalaut noticed that blast cell persistence was associated with elevated serum tryptase levels [Table 1].[12]

Sperr *et al.* used serum tryptase replacing basophil count in the EUTOS score (spleen size × 4+ basophils × 7), renamed as EUTOS-T score (serum tryptase [ng/ml + 5 × spleen size). New score significantly differentiated patients of CML-CP as high risk (11.6%) and low risk (88.4%).[10] EUTOS-T scores were found to identify high-risk patients better than the EUTOS score.

Five-year survival rate was 84% and 0% in patients classified as low risk and high risk, respectively, according to the EUTOS-T score ($P < 0.05$). 11.5% of the patients from the low-risk group and 62.5% of patients from high-risk group had disease progression. 75% of high-risk patients and 21.3% of low-risk patients developed an event (death or progression) during the study. However, no significant differences were found in overall survival of the patients.[10,11]

Conclusion

Studies support the role of tryptase as a potential novel prognostic biomarker in CML. It has potential use as a more

accurate estimation of the total basophil compartment, itself a prognostic marker in CML.

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Conflicts of interest

There are no conflicts of interest.

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