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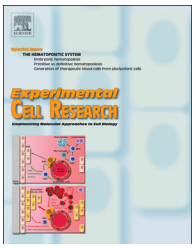

Review Article

Q2 Tryptase, a novel angiogenic factor stored in mast cell granules

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ABSTRACT

Human mast cells (MCs) are a rich reservoir of neutral proteases, packed in large amounts in their granules and comprising a high fraction of all cellular proteins. Among these proteases, tryptase is involved in angiogenesis after their release from activated MC granules, as it has been demonstrated in different *in vitro* and *in vivo* assays. Moreover, tryptase-positive MCs increase in number and vascularization increases in a linear fashion in different solid and hematological tumors. This complex interplay between MCs and tumor angiogenesis have led to consider the therapeutic use of angiogenesis inhibitors, which specifically target the angiogenic activity of tryptase, such as gabexate mesilate and nafamostat mesilate, two inhibitors of trypsin-like serine proteases.

Contents

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Introduction

The most characteristic cytoplasmic organelles in human mast cells (MCs) are the membrane-bound, moderately electron-dense secretory granules. They are very abundant and correspond to the metachromatic granules seen at the light microscopic level. Significant granule heterogeneity can be found in any particular tissue and even between granules of a single MC.

Human MCs are a rich reservoir of neutral proteases, packed in large amounts in their granules and comprising a high fraction of all cellular proteins. MCs contain in their secretory granules almost five neutral proteases, including trypatse, chymase, cathepsin G, carboxypeptidase A3, ans dipeptidylpeptidase (also known as cathepsin C) [1].

Tryptase is a neutral serine protease with trypsin-like specificity, hydrolyzing peptide bonds on the carboxyl terminus of basic residues, such as arginine or lysine, a molecular weight of 134 kDa and a tetrameric structure consisting of non-covalently linked subunits. Tryptase is stored in a fully active form in MC granules [2]. In human MCs, four different forms of tryptase have been described: α- (released from MCs in the bloodstream); β-(concentrated in the secretory granules of MCs and released only after degranulation); γ- and δ-tryptase [3]. The major protease present in human MCs is β-tryptase [4].

MCs are conventionally divided in two types depending on the expression of different proteases in their granules [5]. MCs that contain tryptase only, are designed as MC_T of "immune associated" MCs. They are predominantly located in the respiratory and intestinal mucosa, where they co-localize around T lymphocytes. MCs that contain both tryptase and chymase, along with other proteases such as carboxypeptidase A and cathepsin G, are referred as MC_{TC}. They are predominantly found in the connective tissue areas, such as skin, hypodermis and intestine, breast parenchyma, myocardium, lymph node, conjunctiva, and synovium. A third type of MC, called MCc has been identified, which express chymase without tryptase and resides mainly in the submucosa and mucosa of the stomach, small intestinal submucosa, and colonic mucosa [6].

Tryptases are released with histamine from human skin MCs in acute and chronic *in vivo* responses to allergens and are clinically used a markers of mastocytosis and systemic anaphylaxis [7]. Moreover, tryptases are potent activators of fibroblast migration and proliferationhepa, and collagen synthesis, stimulating tissue repair in wound healing and fibrosis [8], induce the proliferation of airway smooth muscle, contributing to the smooth-muscle cell hyperplasia occurring in bronchial asthma [9]. Immunohistochemical analysis of biopsy specimens revealed a striking increase in MCs in the bundle of smooth muscle from patients with asthma [10].

Tryptases play an important role in host defense, linking adaptive and innate immunity. MC tryptase mMCP-6, for instance plays a protective function in bacterial and parasite infection. MC deficient mice pretreated with human tryptase defend themselves more effectively against intratracheally delivered *Klebsiella pneumoniae* [11]. mMCP-6-deficient-mice are less able to clear *Klebsiella pneumonia* injected in the peritoneal cavity due to less of recruitment of neutrophils [12].

Angiogenesis and inflammation

There is increasing evidence to support the view that angiogenesis and inflammation are mutually dependent [13]. During inflammatory reactions, immune cells, including macrophages, neutrophils, lymphocytes and mast cells, synthesize and secrete pro-angiogenic factors that promote neovascularization. On the other hand, the newly formed vascular supply contributes to the perpetuation of inflammation by promoting the migration of inflammatory cells to the site of inflammation.

Tumor cells are surrounded by an infiltrate of inflammatory cells, which communicate via a complex network of intercellular signaling pathways, mediated by surface adhesion molecules, cytokines and their receptors. Accordingly, immune cells cooperate and synergize with stromal cells as well as malignant cells in stimulating endothelial cell proliferation and blood vessel formation [14].

Tumor microenvironment plays an important role in the initiation and progression of tumors [15]. Studies on neoplastic transformation have focused on events that occur within transformed cells, and have addressed the microenvironment of tumor cells documenting its importance in supporting tumor progression. The pathogenesis of most cancers includes complex and mutual interactions that affect the number and phenotype of the tumor cells and various normal stromal cells, and these intricate tumor-microenvironmental interactions are increasingly recognized as critical features of several neoplasias.

MCs may release in the tumor stroma cytokines and growth factors, such as fibroblast growth factor-2 (FGF-2), vascular endothelial growth factor (VEGF), nerve growth factor (NGF), platelet derived growth factor (PDGF), interleukin-8 and -10 (IL-8 and IL-10), which have detrimental effects to the host by stimulating tumor cell expansion. Mast cells are a major source of histamine, which can induce tumor cell proliferation through H1 receptors, while suppressing the immune system through H2 receptors. In addition, mast cells synthesize and store angiogenic factors as well as matrix metalloproteinases (MMPs), which promote tumor vascularization and tumor invasiveness, respectively. Mast cells may also generate immunosuppression by releasing IL-10, histamine and tumor necrosis factor alpha (TNF-α). By contrast, mast cells may promote inhibition of tumor cell growth, tumor cell apoptosis and inflammation by releasing cytokines such as IL-1, IL-4, IL-6, and TNF-α [14].

Isolated rat MCs and their secretory granules, but not degranulated MCs, induce an angiogenic response in the *in vivo* chick embryo chorioallantoic membrane (CAM) assay [16]. Addition of anti-FGF-2 or anti-VEGF antibodies reduced the angiogenic response of both MCs and their secretory granules by 50% and 30% respectively. These data support the evidence that the angiogenic properties of MCs depend on the angiogenic molecules contained in their secretory granules, and indicate that FGF-2 and VEGF are the angiogenic cytokines primarily and perhaps synergistically responsible for this vasoproliferative activity [16]. Detoraki et al. [17] demonstrated that primary human lung MCs are angiogenic in the CAM assay and this effect is inhibited by an antibody anti-VEGF-A. MCs are angiogenic *in vivo* in other assays, such as the rat mesentery assay [18] and the limb ischemic reperfusion assay [19].

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