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Mast cell proteases as pharmacological targets

George H. Caughey [a,b,c,*]

[a] Cardiovascular Research Institute, School of Medicine, University of California at San Francisco, CA, United States
[b] Department of Medicine, School of Medicine, University of California at San Francisco, CA, United States
[c] Veterans Affairs Medical Center, San Francisco, CA, United States

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ABSTRACT

Mast cells are rich in proteases, which are the major proteins of intracellular granules and are released with histamine and heparin by activated cells. Most of these proteases are active in the granule as well as outside of the mast cell when secreted, and can cleave targets near degranulating mast cells and in adjoining tissue compartments. Some proteases released from mast cells reach the bloodstream and may have far-reaching actions. In terms of relative amounts, the major mast cell proteases include the tryptases, chymases, cathepsin G, carboxypeptidase A3, dipeptidylpeptidase I/cathepsin C, and cathepsins L and S. Some mast cells also produce granzyme B, plasminogen activators, and matrix metalloproteinases. Tryptases and chymases are almost entirely mast cell-specific, whereas other proteases, such as cathepsins G, C, and L are expressed by a variety of inflammatory cells. Carboxypeptidase A3 expression is a property shared by basophils and mast cells. Other proteases, such as mastins, are largely basophil-specific, although human basophils are protease-deficient compared with their murine counterparts. The major classes of mast cell proteases have been targeted for development of therapeutic inhibitors. Also, a human β-tryptase has been proposed as a potential drug itself, to inactivate of snake venins. Diseases linked to mast cell proteases include allergic diseases, such as asthma, eczema, and anaphylaxis, but also include non-allergic diseases such as inflammatory bowel disease, autoimmune arthritis, atherosclerosis, aortic aneurysms, hypertension, myocardial infarction, heart failure, pulmonary hypertension and scarring diseases of lungs and other organs. In some cases, studies performed in mouse models suggest protective or homeostatic roles for specific proteases (or groups of proteases) in infections by bacteria, worms and other parasites, and even in allergic inflammation. At the same time, a clearer picture has emerged of differences in the properties and patterns of expression of proteases expressed in human mast cell subsets, and in humans versus other mammals. These considerations are influencing prioritization of specific protease targets for therapeutic inhibition, as well as options of pre-clinical models, disease indications, and choice of topical versus systemic routes of inhibitor administration.

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1. Introduction

A number of reviews published over the past decade have focused on mammalian mast cell and basophil proteases (Cairns, 2005; Caughey, 2007, 2011; Douaiher et al., 2014; Hallgren and Pejler, 2006; Harvima et al., 2014; Hellman and Thorpe, 2014; Pejler et al., 2010; Schwartz, 2006; Stevens and Adachi, 2007; Tojo and Urata, 2013; Trivedi and Caughey, 2010; Valent et al., 2012). These reviews emphasized major thrusts of research, including the use of these proteases in histochemical visualization and mast cell subsetting, their uses in clinical practice and research as biomarkers of mast cell activation, mastocytosis, and allergic disease phenotypes, their links to diseases not known to be associated with allergy and atopy, their sometimes unique properties as enzymes, their modes of activation, packing into granules, pathways of regulation and inactivation following release, and druggability, their genetic evolution in mammals, natural variation in mouse strains and human populations, their deficiency phenotypes, and, more recently, their suspected roles in homeostasis and host defense. The present review emphasizes recent developments and challenges in targeting mast cell granule-associated proteases for therapeutic inhibition. The primary focus is on human enzymes because these are presently the main targets of pharmaceutical development. The secondary focus is on mouse proteases because numerous genetically modified strains have been developed, including strains

* Correspondence to: VAMC 111-D, 4150 Clement Street, San Francisco, CA 94121, USA. Tel.: +1 415 221 4810x6385.
E-mail address: George.Caughey@ucsf.edu

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deficient in or over-expressing one or more mast cell proteases. Some of these strains have been offered as models of human disease. The differences between mouse and human mast cell and basophil proteases, in addition to their similarities, need to be appreciated to translate mouse genetic and pharmacological studies to human diseases and therapeutic responses (Table 1).

This review concentrates on granule-associated proteases, especially those that are released outside of the cell in an active form with histamine following mast cell activation by allergen-bound IgE or other stimuli. However, it should be borne in mind that some secreted proteases, notably the soluble tryptases and the matrix metalloproteinase (MMP)9, are also shed in a non-regulated (i.e., constitutive) manner by unstimulated mast cells as pro-enzymes that may be activatable outside of the cell. The fate and roles, if any, of constitutively shed pro-tryptases are not yet clear. The granule-associated enzymes released in a regulated manner include serine-class proteases, such as soluble and transmembrane tryptases, chymases, cathepsin G, thiol (cysteine)-class proteases, such as dipeptidylpeptidase I (otherwise known as the exopeptidase cathepsin C), and the zinc metallo-exopeptidase carboxypeptidase A3. Expression of the zinc metallo-endopeptidase MMP9 in mast cells may be regulated separately from the classic secretory granule serine proteases and may be released from separate structures, although this remains to be determined (Di Girolamo et al., 2006; Fang et al., 1997; Fang et al., 1996; Fang et al., 1999) (Table 2).

Mast cell proteases receive more attention than basophil proteases not only because we know more about the mast cell enzymes but because human basophils appear to have fewer and much smaller amounts of proteases compared with, for example, mouse basophils (Jogie-Brahim et al., 2004; Liu et al., 2012; Poorafshar et al., 2000; Raymond et al., 2005; Ugajin et al., 2009; Xia et al., 1995), and so have not been specifically targeted for therapeutic purposes. It is also worth stressing the general point that although mast cell proteases were at one time assumed to be destructive, inflammatory, and "bad" in the context of allergic disease, more recent evidence suggests that some of these proteases play homeostatic, protective, and even anti-inflammatory roles, with the present evidence being more definitive in mice than in humans (Balzar et al., 2005; Caughey et al., 1988; Dougherty et al., 2010; Mallen-St Clair et al., 2004; Maurer et al., 2004; Metz et al., 2006; Piliponsky et al., 2008; Piliponsky et al., 2012; Roy et al., 2014; Sugimoto et al., 2012; Thakurdas et al., 2007; Waern et al., 2013). In gauging the value of individual mast cell proteases as targets for therapeutic inhibition, one of course needs to consider what functions of general value may be lost to the host as a consequence of inhibition or depletion, in addition to impacts on a particular disease for which targeting of one or more mast cell proteases may be advantageous. This calculus is easier for some targets than others. And it should be noted that mast

Table 2
Cell-specific expression of mast cell-associated proteases.[a]

Mast Cell					
Mucosal	Connective	tissue	Basophil	Neutrophil	Eosinophil
Tryptases					
Human	+++	++++	+	−	−
Mouse	+++	+++	MCP-11/mastin -?	−	?
Chymase					
Human	−	+++	−	−	−
Mouse	+++	+++	−	−	?
Cathepsin G					
Human	+	+++	−	+++	−
Mouse	+	++	?	+++	?
Carboxypeptidase A3					
Human	++	+++	+++	−	−
Mouse	+/−	+++	+++	?	−
Cathepsin C/dipeptidylpeptidase I					
Human	+++	+++	?	++	?
Mouse	++	++	?	++	?

[a] Data derived from some of the following references: Feyerabend et al. (2011), Irani et al. (1989), Irani et al. (1991), Lilla et al. (2011), Saito et al. (2006), Schechter et al. (1990), Takabayashi et al. (2012), Voehringer et al. (2004), Waern et al. (2009), and Xing et al. (2011).

Table 1
Disease associations.

Tryptases

Anaphylaxis (Caughey, 2006; Schwartz, 2006)
Asthma (Cairns, 2005; Chen et al., 2006; Costanzo et al., 2008; Krishna et al., 2001)
Allergic rhinitis (Erin et al., 2006; Takabayashi et al., 2012)
Eosinophilic esophagitis (Abonia et al., 2010)
Inflammatory bowel disease (Hamilton et al., 2010; Hansbro et al., 2014; Isozaki et al., 2006; Tremaine et al., 2002)
Arthritis (Shin et al., 2009)
Cigarette-associated lung and airway disease (Beckett et al., 2013; Hansbro et al., 2014)
Allergic skin disease (Järvikallio et al., 1997)
Bacterial infection (protective) (Thakurdas et al., 2007)
Aortic aneurysm (Zhang et al., 2011)

Chymases
Systemic arterial hypertension (Ju et al., 2001; Koga et al., 2003; Wei et al., 2010)
Ischemia-reperfusion injury (Abonia et al., 2005; Jin et al., 2001; Morikawa et al., 2005; Pat et al., 2010)
Fibrosis: skin, lung, kidney, heart, liver (Cha et al., 2012; Shiota et al., 1997; Tchougounova et al., 2005)
Pulmonary artery hypertension (Kosanovic et al., 2014; Wang et al., 2010)
Asthma (protective) (Balzar et al., 2005; Sugimoto et al., 2012; Waern et al., 2009)
Envenomation (protective) (Akahoshi et al., 2011)
Intestinal parasitosis (protective) (Knight et al., 2000)
Skin malignancy (Coussens et al., 1999)
Aortic aneurysm (Furubayashi et al., 2008; Inoue et al., 2009; Sun et al., 2009)

Carboxypeptidase A3
Envenomation (protective) (Metz et al., 2006)

Cathepsin C/Dipeptidylpeptidase I
Septic peritonitis (Mallen-St Clair et al., 2004)
Gram-negative pneumonia (Sutherland et al., 2014)
Periodontitis/Papillon–Lefevre syndrome (Pham et al., 2004)