European Journal of Pharmacology 778 (2016) 103–115

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

The impact of mast cells on cardiovascular diseases

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ARTICLE INFO

Article history:
Received 10 December 2014
Received in revised form
10 April 2015
Accepted 21 April 2015
Available online 8 May 2015

Keywords:
Mast cells
Obesity
Diabetes
Atherosclerosis
Restenosis
Myocardial infarction
Arrhythmia
Aneurysm

ABSTRACT

Mast cells comprise an innate immune cell population, which accumulates in tissues proximal to the outside environment and, upon activation, augments the progression of immunological reactions through the release and diffusion of either pre-formed or newly generated mediators. The released products of mast cells include histamine, proteases, as well as a variety of cytokines, chemokines and growth factors, which act on the surrounding microenvironment thereby shaping the immune responses triggered in various diseased states. Mast cells have also been detected in the arterial wall and are implicated in the onset and progression of numerous cardiovascular diseases. Notably, modulation of distinct mast cell actions using genetic and pharmacological approaches highlights the crucial role of this cell type in cardiovascular syndromes. The acquired evidence renders mast cells and their mediators as potential prognostic markers and therapeutic targets in a broad spectrum of pathophysiological conditions related to cardiovascular diseases.

1. Introduction

Mast cells are innate immune cells, characterized by a monolobular nucleus and numerous cytoplasmic granules (Beaven, 2009), morphological features which distinguish them from a variety of cell types that comprise the immune system. Originating from hematopoietic stem cells within the bone marrow (Kitamura, 1989), mast cell progenitors are released into the circulation and, upon the influence of cytokine and chemokine signals, home in tissues and further differentiate into mature mast cells (Dahlin and Hallgren, 2015; Maaninka et al., 2013). The place of maturation for mast cells is either mucosal surfaces or connective tissue therefore granting them a wide distribution throughout the body. Tissue resident mature mast cells exert their effector functions after activation triggered by cytokines, antibodies and proteins specific for receptors present on their surface. The most widely studied mast cell activation pathway is the antigen-specific activation by Immunoglobulin-E (IgE) antibodies, which bind to the high affinity membrane receptor Fcepsilon Receptor-1 (FcεR1) (Kraft and Kinet, 2007). However, during the last decades, additional agents triggering mast cell activation have been discovered, such as the Immunoglobulin-G (IgG) antibodies (Woolhiser et al., 2001), complement system components (Erdei et al., 2004), but also pathogenic Toll-like receptor peptides (Varadaradjalou et al., 2003), as well as endogenous ligands like substance P (SP) (Li et al., 2012) and endothelin-1 (ET-1) (Szalay et al., 2000).

The mast cell secretory granules contain a variety of molecules such as proteoglycans (*e.g.* heparin and chondroitin sulfate), histamine, cysteinyl cathepsins, proteases (*e.g.* chymase and tryptase) and a broad spectrum of pro-inflammatory as well as anti-inflammatory cytokines (Wernersson and Pejler, 2014). Through their mediator release, mast cells are able to act on the adjacent cells and shape the local microenvironment.

Human mast cells residing in different tissues exhibit a diverse protease content, and can consequently be separated into various subpopulations. Thus, they are classified into two subtypes based on their differential neutral protease contents, the: MC_T (mast cells containing exclusively tryptase) and the MC_{TC} (mast cells containing both tryptase and chymase, as well as carboxypeptidase A3 and cathepsin G) (Irani and Schwartz, 1994). It is important to note that all human mast cells contain tryptase, and a variable fraction of them contains also chymase, carboxypeptidase A3 and cathepsin G. However, despite the differences in the granule protease composition of each mature mast cell subtype, their content can be actively shaped depending on signals received from the surrounding microenvironment (Friend et al., 1996; Hsieh et al., 2005). Finally, the ultimate protease phenotype in a tissue may switch from one to another in a reversible way (Maaninka et al., 2013). Ultimately, *de novo* formation of mast cell mediators, which extends itself beyond the granule proteases, depends not only on the intrinsic characteristics of each tissue but also on local pathologic conditions at any given point, granting remarkable

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http://dx.doi.org/10.1016/j.ejphar.2015.04.050
0014-2999/

plasticity to mast cells regarding their effector functions (Gordon and Galli, 1991; Galli et al., 2005).

Within the cardiovascular system, mast cells reside in close proximity to blood vessels, as well as in the heart of both humans and rodents (Rakusan et al., 1990), where they participate in physiological functions such as angiogenesis and local generation of the vasoconstrictive hormone Angiotensin II (Ang II) (Silver et al., 2004). The majority of mast cells populating the human heart and vessels contain, in addition to tryptase, also chymase (Balakumar et al., 2008). Also in mice cardiac mast cells are recognized as connective tissue mast cells, which contain granules filled with heparin, chymase and tryptase (Kennedy et al., 2013; Kitamura et al., 2007). However, particularly in humans, the proportion of chymase-containing mast cells in the arterial wall shows remarkable variation among subjects (Kaartinen et al., 1994a), attributing each protease a differential role in the pathophysiology of cardiovascular diseases. Yet, aside from proteases, there is a plethora of additional mast cell mediators which participate in the pathological events observed in cardiovascular syndromes (Fig. 1).

Mast cells in the vasculature are mainly distinguished for their adverse effects in syndromes such as abdominal aortic aneurysm (Swedenborg et al., 2011), myocardial infarction (Levick et al., 2011), and atherosclerosis (Bot and Biessen, 2011), displaying thus a crucial role in the leading cause of death worldwide (Fuster et al., 2011). It is therefore intriguing to pinpoint the overall importance of mast cells in a wide variety of such conditions.

2. Diet-induced obesity

The incidence of obesity, due to high fat diet, has become a Western society epidemic and is closely linked to type 2 diabetes as well as other metabolic and cardiac disorders (Bray and Bellanger, 2006). Increased chronic inflammation at a low degree is observed in white adipose tissue (WAT) of obese humans and mice, with local infiltration of macrophages (Weisberg et al., 2003) and T cells (Boulet et al., 2013). Mast cells have also been detected in obese adipose tissue, located next to microvessels and are directly associated with the pathology of this disorder. More specifically, Liu et al. reported in 2009 an increased number of mast cells in WAT of obese humans and mice, accompanied by elevated serum tryptase levels as well as local and systemic levels of inflammatory cytokines, chemokines and proteases, compared to lean subjects. Here, mast cells contribute to WAT apoptosis and angiogenesis. This effect is exerted *via* Interleukin-6 (IL-6) and Interferon-gamma (IFN-γ) cytokines, which in turn increase cysteinyl cathepsin expression, thus promoting diet-induced obesity. Importantly, in the cited study mast cells are observed to infiltrate obese WAT prior to macrophages. Likewise, mast cells are shown to co-localize with $CD8^+$ T cells in mouse WAT (Xu and Shi, 2012) suggesting a role in adipose tissue inflammation. An additional study reported that mast cell deficient $Kit^{W\text{-}sh/W\text{-}sh}$ mice transplanted with hematopoietic-prostaglandin synthase deficient mast cells are not able to gain weight similarly as mice transplanted with wild-type mast cells, pinpointing the importance of mast cell derived prostaglandins in adipose tissue function (Tanaka et al., 2011). As adipocytes themselves are also an important source of cytokines (Cao, 2014), this adds up to the local inflammatory burden. Interestingly, adipocytokines have been linked to mast cells in the context of allergic inflammation and asthma (Sismanopoulos et al., 2013), introducing a possible crosstalk between the resident cells of adipose tissue and the infiltrating mast cells.

2.1. Type II-diabetes mellitus

Notably, obesity comprises an essential risk factor for the development of type 2 diabetes mellitus (Ervin, 2009). Non-insulin dependent diabetes is a metabolic disease defined by hyperglycemia and insulin-resistance, which is greatly influenced by obesity. Aside from their role in obesity, mast cells have been directly linked to type 2 diabetes. Mice fed a high-fat diet and lacking mast cells show improved glucose homeostasis compared to the wild type strain (Liu et al., 2009). Since tumor necrosis factor-alpha (TNF-α) was found to be overexpressed in obese mice (Hotamisligil et al., 1993), this cytokine has been considered as a key mediator in the induction of insulin resistance (Feinstein et al., 1993). However in experiments using TNF-α deficient mast cells (Liu et al., 2009), TNF-α did not contribute to the effect of mast cells in obesity, indicating that the metabolic changes induced by this cytokine may have been due to TNF-α derived from other inflammatory cells than mast cells.

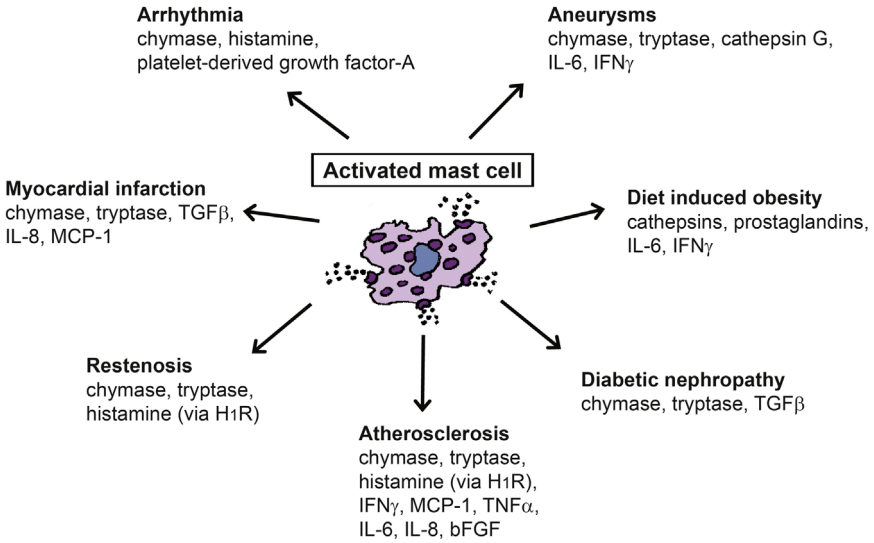

Fig. 1. Mast cells in cardiovascular diseases. This figure depicts major cardiovascular diseases in which mast cells have been implicated. Specific mast cell mediators, summarized here, have been reported in each of these syndromes. Abbreviations: IL-6: Interleukin-6, IL-8: Interleukin-8, TNF-α: tumor necrosis factor-alpha, IFNγ: Interferon-gamma, TGF-β: transforming growth factor-beta, MCP-1: monocyte chemoattractant protein-1, bFGF: basic fibroblast growth factor.