Mast cells and the power of local RAS activation*

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More than 100 years ago, mast cells were discovered and named by Paul Ehrlich, who was the first to recognize this well-fed appearing cell loaded with huge cytoplasmic granules in various tissues [1]. Mast cells derive from CD34⁺ multipotent bone marrow progenitor cells which circulate in small numbers in the blood as basophilic leucocytes, and enter the mucosal surfaces and connective tissue compartments of multiple organs [2]. This distinct cell type is today best known for its key role in immunoglobulin-E-mediated allergic reactions such as bronchial asthma and anaphylactic reactions. More recently, however, mast cells have been found to be important modulators and mediators of innate immunity, chronic inflammation, tissue remodelling and organ fibrosis [3–5].

Mast cell renin expression

Following up on novel non-immune functions of mast cells, a recent pioneering study by the group of Roberto Levi [6] from the Weill Medical College, Cornwall University, New York, provided compelling evidence that mast cells critically contribute to ventricular arrhythmias in myocardial ischaemia/reperfusion [6]. This group had previously documented that in normal hearts, mast cells are a rich extrarenal source of renin expression and release [7]. Renin, an aspartyl protease, is classically produced by the renal afferent arterioles. Its secretion into the circulation is tightly controlled via the juxtaglomerular apparatus by renal baroreceptors and the sodium chloride delivery to the macula densa in order to maintain body fluid volume and blood pressure homeostasis. Since angiotensinogen is present in excess in the blood stream and angiotensin-converting enzyme (ACE) is ubiquitously expressed in the vascular endothelium, renal release of renin is rate-limiting for activation of the systemic renin-angiotensin system (RAS). In addition to renin, it has lain been known for a long time that mast cells produce large amounts of chymase, an alternative enzymatic pathway to generate angiotensin II from angiotensin I [1]. Thus, mast cells by themselves bear the capacity to generate angiotensin II in local compartments from present angiotensinogen.

Mast cell renin function

Having identified local renin expression in cardiac mast cells, Levi’s group [6] then assessed the functional consequences of mast cell renin release in experimental cardiac ischaemia/reperfusion using ex vivo Langendorff mouse and guinea pig hearts. The group found that: (i) Stimulation of mast cell degranulation resulted in significant renin-mediated formation of angiotensin I in normal animal hearts. Subsequent local production of angiotensin II elicited norepinephrine release from cardiac sympathetic nerve terminals via the AT1 receptor (Figure 1); (ii) Experimental ischaemia/reperfusion showed a significant spill over of renin and norepinephrine in parallel to ventricular arrhythmias in guinea pig and mouse hearts; (iii) Both pharmacological mast cell stabilization and use of mast-cell-deficient mice markedly attenuated the chain of renin overflow, angiotensin II formation, nerve terminal norepinephrine release and ventricular arrhythmias. Comparable protection was achieved with specific renin and AT1 antagonism.

The study by Levi et al. [6] is pioneering on two major issues: (i) Although the components of the renin–angiotensin system are locally expressed in various tissues, it has as yet been difficult to prove whether local RAS indeed may act autonomously.

*Basic science article this editorial is based on: Cardiac mast cell-derived renin promotes local angiotensin II formation, norepinephrine release and arrhythmias in ischaemia/reperfusion. Mackins CJ, Kano S, Seyedi N et al. J Clin Invest 2006; 116: 1063–1070

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A proof of concept for the functional relevance of renin release outside the kidney has now been provided by Levi et al. [6]; (ii) Ventricular dysrhythmias following cardiac ischaemia/reperfusion have been thought to be of only cardiac cell origin. Levi’s group now documents that mast cells, i.e. cells of the immune system, can be critical mediators of cardiac dysfunction as well. Accordingly, the study suggests that cardiac dysrhythmias following myocardial infarction may become preventable by mast cell pharmacological stabilization with drugs generally used to treat allergies and asthma.

The power of mast cells

Mast cells contain a multitude of various secretory granules, indicating that their impact on physiology and pathophysiology is likely to go beyond just the local activation of RAS [1,4,5]. Upon stimulation, mast cells release a plethora of preformed and newly synthesized substances that are known to influence inflammation, organ function and remodelling, haemodynamics and tissue fibrosis. These substances include an array of proteases, vasoactive mediator, cytokines, chemokines and growth factors (overview in Table 1). How powerful and far-reaching mast cells can be is illustrated in cutaneous urticaria. In this clinical paradigm, a few dermal mast cells can trigger a dramatic change of large dermal surface areas.

Mast cells in kidney disease

Reports on mast cells in renal disease are scattered [1,4,5]. Mast cell accumulation has been described in several immune kidney disorders such as IgA nephropathy, membranous nephropathy, crescentic glomerulonephritis and allograft rejection. In non-immune renal diseases, an increase in mast cell number

Table 1. Modulators and mediators known to be released from activated mature mast cells [1–5]

<table>
<thead>
<tr>
<th>Category</th>
<th>Substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzymes, proteases and vasoactives</td>
<td>Renin, chymase, tryptase, histamine, heparin, acid hydrolases, cathepsin G, carboxypeptidase, prostaglandin D2, leucotriene C4, thromboxane A2, polyclonal antibody, endothelin, nitric oxide, matrix metalloproteinases</td>
</tr>
<tr>
<td>Interleukins</td>
<td>Tumour necrosis factor-α, interleukin (IL)-1, IL-3–6, IL-13, interferon-γ</td>
</tr>
<tr>
<td>Chemokines</td>
<td>Macrophage inflammatory protein-1, trichloroacetic acid-3, monocyte chemoattractantprotein-1</td>
</tr>
<tr>
<td>Growth factors</td>
<td>Platelet-derived growth factor, fibroblast growth factor, transforming growth factor-β1</td>
</tr>
</tbody>
</table>

Fig. 1. Local activation of the RAS by mast cells in experimental cardiac ischaemia/reperfusion (NE, norepinephrine, NHE, Na⁺/H⁺ exchanger).
has been reported in diabetic and hypertensive nephropathy [4,8].

**Renal mast cells may act profibrotic**

Only a little is known about the function of mast cells in renal disease, but most information so far available points to a profibrotic role. A recent experimental study on non-immune hypertensive nephropathy provided strong indirect evidence for this [9]. In rats following 5/6-nephrectomy, mast cells were predominantly localized to regions of peritubular fibrosis and expressed the key fibrosis mediator transforming growth factor-β1. In addition, interstitial mast cell accumulation was found to be reduced when the rats received renoprotective angiotensin II blockade. In line with these experimental findings is that in human IgA nephropathy and chronic allograft rejection, mast cells were predominately located in the renal interstitium and their number correlated positively with interstitial fibrosis and negatively with renal function [5]. On the other hand, interstitial fibrosis was not found to be attenuated in a strain of mast-cell-deficient rats with puromycin aminonucleoside nephrosis [10].

In conclusion, mast cells have been identified as a powerful source of local RAS activation in the heart. The occurrence of mast cells in primarily non-immune organ disorders, including the kidney, is intriguing and deserves clearly our future scientific attention.

**Conflict of interest statement.** None declared.

**References**


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