From tadpole tails to transgenic mice: Metalloproteinases have brought about a metamorphosis in our understanding of cardiovascular disease

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Thirty years ago, most biochemical and molecular science concerned what went on inside cells. Hence, release of enzymes into the extracellular space was seen as important only for specialised functions, such as digestion of nutrients or in blood clotting, events that took place outside solid tissues. Moreover, the discovery of ectoenzymes—enzymes with their active sites pointing to the extracellular space—was viewed first with scepticism and then largely as a curiosity. Appreciating the full importance of pericellular metabolism for embryogenesis, morphogenesis and cellular regulation needed a revolution in thinking catalysed in significant part by the seminal discovery that resorption of the tadpole tail during metamorphosis depended on the production of a collagenase [1]. This enzyme we now designate matrix metalloproteinase 1 (MMP-1) in recognition that it was the first secreted member of a family of enzymes that requires a Zn$^{2+}$ ion at the active site. Later on, the first ecto-MMP (membrane type-1 MMP, MMP-14) was discovered [2]. Nagase et al. [3] overview the more than 20 secreted and at least 6 membrane-type MMPs, many of which are present in the cardiovascular system. Their substrates include the major structural matrix components, collagens, elastin, proteoglycan core proteins and glycoproteins, as well as many non-matrix proteins. Disintegrin metalloproteinases (ADAMs) also share the MMP catalytic domain; Manso et al. review their emerging functions in the cardiovascular system [4]. Other groups of extracellular neutral proteases with thiol or serine groups at their active sites synergise with the MMPs, in part by activating MMP proforms [3]. This raises the questions why there is such a rich landscape of extracellular proteases and whether any individual enzymes play an indispensable role in cardiovascular function or disease. Janssens and Lijnen [5] summarise how the power of genetic modification in mice has begun to provide answers, the original study by Wang et al. [6] being a specific example.

In blood vessels and in the heart, as in the tadpole tail, proper regulation of MMP activity is integral to physiological adaptation; examples reviewed here include the vascular and cardiac responses to biomechanical stress [7] and injury [8]. Simple debulking of unwanted matrix is clearly only a beginning. MMPs break existing cell–matrix and cell–cell contacts and promote interactions with fragmented [9] or newly synthesised matrix components. Remodelling of matrix and non-matrix substrates frees cells such as vascular smooth muscle cells to migrate (reviewed by Newby [10]). These changes also regulate migration, proliferation, and death of cells through increasingly well-defined signalling pathways in which cell-surface integrins and cadherins play key roles [4,9,10].

On the other hand, there is clear evidence that dysregulation of MMP activity contributes to cardiovascular disease. For example, Dollery and Libby [11] present a convincing case that MMPs participate in all stages of coronary and carotid atherosclerosis, particularly in its transition to unstable coronary syndromes and stroke. Genetic epidemiological studies reviewed by Ye [12] strongly support this concept in man. Altered MMP expression and activation occur concomitantly with the transition to and progression of heart failure, whether it is caused by myocarditis [13], myocardial infarction [8], or
haemodynamic overload [14]. Moreover, the development and progression of heart failure is accompanied by a specific temporal profile of changes in MMPs and their tissue inhibitors (TIMPs) that is not only of mechanistic consequence, but could have diagnostic and prognostic value.

What, therefore, determines whether the consequence of MMPs’ actions in the cardiovascular system are physiological or pathological? One clue is the clear relationship between inflammation and overproduction of MMPs. This is evident in atherosclerosis [11], heart failure [15], and myocardial diseases such as myocarditis and inflammatory cardiomyopathy [13]. While inflammatory cytokines and ligands such as CD40 play prominent roles in MMP induction in certain cardiovascular disease states, it is likely that multiple regulatory cascades are operative. Original articles by Kodali et al. [16] and Madani et al. [17] underscore this point by identifying specific chemokines and leptin as potential MMP secretagogues. Deschamps and Spinale [15] review a number of the biological signalling pathways that potentially induce MMPs and highlight how multiple intracellular cascades can change MMP expression. The resulting dysfunction may be complex because MMPs are not expressed by a single cell type, such as inflammatory cells or fibroblasts, but rather by all cells that reside in cardiovascular tissue. For example, Janicki et al. [14] emphasise the role of mast cells in MMP release and myocardial remodelling. The factors that induce MMP expression and release are likely to be multiple and disease specific. Elucidating the importance and interaction of these upstream pathways with respect to MMP dysregulation holds much promise for the development of new therapeutic targets for cardiovascular disease.

Translating our extensive knowledge regarding the pathological role of MMPs into new treatments will be a significant challenge. Some well-established drugs probably rely on MMP inhibition for part of their efficacy; original articles illustrating this point for statins and doxorubicin appear in this focussed issue [18,19]. Sluijter et al. [7] review translational research in the context of adverse vascular remodelling, while Peterson’s article [20] summarises more generally the current experience using synthetic MMP inhibitors in clinical practice. Peterson’s article [20] points to the difficulty in targeting pathological as opposed to physiological MMP action using broad-spectrum MMP inhibition because this approach has a narrow therapeutic window. Future basic and translational research should aim to increase understanding of the role of individual MMPs in cardiovascular disease progression and couple this to the development of more selective MMP inhibitors.

This focussed issue testifies to the many significant advances in understanding of cardiovascular adaptation and pathology that have resulted from the relatively short 15 years of research into the cardiovascular functions of MMPs. This body of research, some of which is captured in this focused Spotlight Issue, has correctly re-focussed attention on pericellular metabolism. It powerfully demonstrates the regulatory importance of cell–matrix and cell–cell interactions and how their remodelling drives all aspects of cardiovascular form and function. Past successes motivate our continued research effort to understand this extracellular proteolytic system and devise therapeutic manipulations of dysregulated MMP activity to ameliorate cardiovascular disease.

References


