

## **Metalloproteinases: key and common mediators of multiple GPCRs and candidate therapeutic targets in models of hypertensive cardiac disease**

Xiang Wang<sup>1</sup>, Ana-Maria Bosonea<sup>1</sup>, and Carlos Fernandez-Patron<sup>1,2,\*</sup>

<sup>1</sup>Department of Biochemistry, School of Translational Medicine and the Cardiovascular Research Group, University of Alberta, Edmonton, AB, Canada

<sup>2</sup>Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, AB, Canada

### **Abstract**

Hypertensive cardiac disease remains a major cause of death worldwide because its typically complex etiology renders current treatments ineffective. Primary causative factors include environmental stressors, genetic predisposition and metabolic morbidities such as obesity and diabetes. These factors all trigger a systemic pathological production of agonists of G-protein-coupled receptors (GPCRs). When produced in excess, GPCR agonists transactivate many metalloproteinases, which relay agonist signaling. Here we review evidence supporting a global therapeutic concept for treatment of hypertensive cardiac disease with complex or unknown etiology by targeting common mediators of multiple GPCRs such as metalloproteinases and their downstream effectors.

### **Introduction**

Hypertensive cardiac disease remains a major cause of death worldwide and is characterized by the co-occurrence of sustained hypertension, cardiac hypertrophy and cardiac fibrosis [1]. Despite advances in the identification of triggers of disease, the treatment of cardiovascular disorders remains empirical and ineffective due to the complex and often unknown etiology of hypertensive cardiac disease in the general population [2,3].

Among the primary causative factors of hypertensive cardiac disease are life style, stress, environmental factors and genetic predisposition as well as metabolic morbidities such as diabetes and obesity [1–3].

Here we propose that these factors contribute to the development of hypertensive cardiac disease by activating common effector mechanisms, which involve agonists of G-protein-coupled receptors (GPCRs). GPCRs signal, at least in part, through extracellular matrix metalloproteinases (MMPs) and ‘a disintegrin and metalloproteinases’ (ADAMs).

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\*Corresponding author: C. Fernandez-Patron (cf2@ualberta.ca).

MMPs and ADAMs, which modulate vascular tone and transcription and translation of prohypertrophy and profibrosis genes downstream of multiple GPCRs, are candidate therapeutic targets to treat hypertensive cardiac disease with complex or unknown etiology (Fig. 1).

We review how MMPs and ADAMs are activated, what substrates they cleave and what functions they might serve in models of agonist-induced hypertensive cardiac disease.

## Comorbidities of hypertensive cardiac disease

The prevalence of chronic, noncommunicable diseases is increasing dramatically worldwide with close to 20 million people dying every year from cardiovascular disease associated with hypertension, diabetes, or obesity [1–3]. The association of metabolic disorders such as diabetes type I, insulin resistance (diabetes type II) and obesity with hypertension and cardiac problems is higher than would be the case by chance. The presence of multiple comorbidities makes the treatment of any single morbidity very difficult [1,4].

Over 60% of hypertensive individuals are obese, which has been explained through the chronic activation of the sympathetic nervous system by adipocyte-derived hormones such as leptin, which promotes energy expenditure but also systemic vasoconstriction and pathological cardiovascular remodeling [3].

Obesity predisposes patients to insulin resistance and diabetes type II with about 90% of diabetes type II being attributable to excess weight. In the USA, up to 75% of the adult patients with diabetes have hypertension and renovascular disease [5,6]. The chronic activation of the renin–angiotensin system results in sympathetic activation further impairing cardiovascular and renal functions. The co-occurrence of obesity and diabetic complications makes treatment of hypertension and the associated damage to target organs such as the kidneys and heart very challenging and often ineffective.

Although it remains unclear how diabetes predisposes to hypertension, it is clear that diabetes triggers a systemic hormonal response involving multiple agonists. Indeed, anti-hypertensive drugs targeting signaling by one or more GPCRs such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers and  $\beta$ -blockers are prescribed to treat and prevent cardiovascular complications including microvascular complications of retinopathy and progression of nephropathy in diabetic patients.

Similar to diabetes [5] and obesity [7], chronic stress (e.g. due to job strain, social environment or emotional distress) [6,8–12] and genetic predisposition [2,13] can cause various degrees of hypertension and cardiac disease. The major mechanism of disease by chronic stress is sympathetic nervous system activation, which results in high systemic or local (on target organs) production of stress hormones (e.g. catecholamines). The detrimental cardiovascular effects of high catecholamine levels are well established in humans as well as many disease models including rodents. Genetic predisposition plays a major role in disease development and, therefore, in the responses to antihypertensive treatments [2,5,13,14]. This has been well studied in North America where multiple ethnic groups coexist and are at risk of cardiovascular disease associated with metabolic syndrome.

For instance, the incidence of hypertension, mortality from hypertensive heart disease, stroke and hypertensive renal disease are higher in African Americans. By contrast, Hispanic Americans have a lower overall risk for hypertension but are at a greater risk for hypertension due to diabetes and dyslipidemia. Although poorly understood, when compared to European Americans and other ethnic minorities, African Americans respond less favorably to  $\beta$ -blockers and ACE inhibitors whereas Asian American respond to calcium antagonists better than to ACE inhibitors and equally well to diuretics and  $\beta$ -blockers [14]. These facts indicate that identifying and pharmacologically manipulating common mediators of disease are very important for effective treatment of disease when the exact etiology is complex or unknown, as can be the case for individuals with various genetic predispositions.

## **Metalloproteinases: key and common mediators of multiple GPCRs in models of hypertensive cardiac disease**

As discussed earlier, hypertensive cardiac disease can have a very complex etiology which poses a significant challenge for physicians. Current pharmacologic interventions are designed to interfere with specific causative factors (e.g. when pathological levels of angiotensin II are suspected, inhibitors of angiotensin II-converting enzyme or angiotensin II receptor blockers are prescribed to limit either angiotensin II generation or angiotensin II binding to its cellular receptors). However, when the causative agonists are unknown, current pharmacological interventions may not be effective if the causative factors are not targeted by the drug.

As a result, current treatment of patients with hypertensive cardiac disease remains highly empirical and requires the use of multiple drugs. Each drug is prescribed to afford complete or at least partial blood pressure reduction; however, often the blood pressure reduction target is not met [2,15]. The use of multiple drugs can result in undesired side-effects and elevated treatment costs to patients. Therefore, we believe that the identification of common effector mechanisms of multiple GPCR agonists could suggest more robust and general therapeutic approaches applicable to treat diseases with complex or unknown etiology [16].

Zinc-dependent endopeptidases (i.e. metalloproteinases) from the MMP and ADAM families are emerging as common mediators downstream of multiple GPCRs. The following section will cover how MMPs and ADAMs are activated, what substrates they cleave and what roles they play in models of agonist-induced hypertensive cardiac disease.

### **GPCR agonist-induced transactivation of growth depends on metalloproteinases**

We and others have observed that multiple GPCR agonists transactivate growth factor receptors such as the epidermal growth factor receptor (EGFR) to enhance vascular tone and promote prohypertrophic and profibrotic processes in the cardiovascular system [16].

Transactivation of the EGFR can explain how and why agonists of vasoactive G-protein-coupled receptors (GPCRs) promote cancer cell growth and proliferation of cancer cells [17]. In arteries, EGFR transactivation is also mediated, at least in part, by metalloproteinases, such as MMP-2 and MMP-7, which are overexpressed or activated

downstream of GPCRs including adrenoceptors, endothelin-1 and angiotensin II receptors. Angiotensin II and catecholamines rapidly activate MMP-7 which next sheds EGFR ligands (such as HB-EGF) to trigger intracellular signaling through the EGFR → mitogen-activated protein kinase (MAPK) cascade as well as the PI3K → AKT axis. This metalloproteinase-mediated transactivation mechanism appears to be a common response to multiple agonists irrespective of their chemical structure, enzymatic generators or site of production.

## Activation of metalloproteinases by GPCR agonists

In response to high levels of GPCR agonists, some metalloproteinases are rapidly activated through post-translational mechanisms, which in turn trigger transcription of genes whose overexpression promotes cell proliferation, hypertrophy and profibrotic processes. Agonist-induced metalloproteinase activation can result from either proteolytic or nonproteolytic mechanisms.

### Proteolytic activation of metalloproteinases

In the classical sense, the activation of metalloproteinases requires separation of the catalytic zinc ion from a cysteine residue (PKVCGY) in the metalloproteinase N-terminal prodomain [18]. Some metalloproteinases activate other metalloproteinases by cleaving their prodomain. This is the case for membrane-type MMPs which act in combination with tissue inhibitor of metalloproteinases (TIMP)-2 to activate pro-MMP-2. In addition, MMP-3 can directly cleave and activate pro-MMP-1, pro-MMP-7, pro-MMP-8 pro-MMP-9 and pro-MMP-13. Similarly, MMP-7 activates pro-MMP-1, pro-MMP-2, pro-MMP-8 and pro-MMP-9, whereas MMP-10 activates pro-MMP-7, pro-MMP-8 and pro-MMP-9.

### Nonproteolytic mechanisms

Metalloproteinase activation can result from oxidative stress [19,20], post-translational modifications such as phosphorylation [21] and protein–protein interactions [22,23].

**Oxidative stress**—Agonist-induced  $\text{Ca}^{2+}$  signaling is intimately linked to MMP and ADAM activation, at least in part, by enabling the assembly of NADPH oxidase complex at the plasma membrane where it becomes active. Fully assembled, active NADPH oxidase generates superoxide anion which directly activates the catalytic cysteine switch in metalloproteinases. This may be a major mechanism of metalloproteinase activation in agonist-induced oxidative stress models [24]. For instance, when angiotensin II binds to its GPCR (AT1R), it sparks a  $\text{Ca}^{2+}$  signal that is followed by a burst in reactive oxygen species (ROS) which activates ADAM-17/TACE [25].

**Protein kinases**—Protein kinase C (PKC) may play a key role in metalloproteinase activation. PKC is allosterically activated by diacylglycerol (DAG) which is made by GPCR agonist-activated phospholipase C. Both DAG and its phorbol ester analogs trigger ADAM-12 activity and subsequent HB-EGF shedding in cardiomyocytes [26,27]. Active ADAM-12 is a major mediator of cardiac hypertrophy induced by angiotensin II, phenylephrine and pressure overload [28]. Cardiac PKC may modulate intracellular MMP-2 activity by phosphorylation at multiple sites including Ser and Thr residues. Indeed,

mammalian MMP-2 contains 29 potential phosphorylation sites and mass spectrometry reveals that at least five of these sites are phosphorylated [21]. The kinase activity of extracellular signal-regulated kinase, ERK, leads to phosphorylation of the Thr<sup>735</sup> of ADAM-17/TACE rendering ADAM-17 able to shed tumor necrosis factor (TNF)- $\alpha$  [29]. ADAM-17 activation can thus be pro-inflammatory, prohypertrophic and profibrotic.

**Protein–protein interactions**—A recently discovered mechanism of MMP and ADAM activation independent of proteolytic cleavage, oxidative stress, or kinase activity involves metalloproteinase interaction with protein interaction modules in other proteins. Binding of Src homology 3 (SH3) domains in PACSIN-3 and eve-1 to proline-rich domains of ADAM-12 enhances ADAM-12 proteolytic activity [30,31]. PKC- $\epsilon$  domains C1 and C2 bind to ADAM-12 enabling ADAM-12 translocation to the cell membrane and subsequent activation [32]. Protein–protein nonproteolytic interactions could explain the activation of ADAM-9, -12 and -17 in models where proteolytic activation and oxidative stress play a little or no role in activating MMPs such as GPCR agonist stimulation at subpressor doses.

### **Metalloproteinases regulate vasoactive peptides, contractile proteins, growth factors and cytokines as well as cell surface receptors**

For many years, the cardiovascular effects of GPCR agonists were interpreted as a direct consequence of Ca<sup>2+</sup> release from intracellular stores and Ca<sup>2+</sup> uptake from the extracellular milieu. These two events are triggered rapidly following the allosteric binding of G $\alpha_q$  to phospholipase C which releases a Ca<sup>2+</sup> channel agonist, inositol 1,4,5-trisphosphate (IP3), from membrane-anchored phosphoinositols. Induction of Ca<sup>2+</sup> signaling by agonists can successfully explain how agonists evoke contractile responses in the cardiovascular system. However, to explain the maintenance of contraction over prolonged periods of agonist stimulation or the mitogenic effects induced by agonists, it is necessary to consider additional pathways such as the transactivation of growth factor receptor signaling by agonist-activated metalloproteinases.

Originally thought to degrade only components of the extracellular matrix (ECM) during the long-term process of tissue remodeling, MMP and ADAM family members also cleave and regulate many non-ECM substrates in an acute fashion. Excessive GPCR signaling thus translates into pathological metalloproteinase cleavage of ECM and non-ECM substrates. This section will focus on two classes of non-ECM substrates of metalloproteinases: ligands of receptors and cell surface receptors.

#### **Cleavage of receptor ligands**

The cleavage of receptor ligands can explain many acute actions of metalloproteinases and those of their pharmacological inhibitors such as modulation of vascular contractile responses. For instance, MMP-2 and MMP-9 can acutely enhance vascular tone through the cleavage of vasoactive peptides such as adrenomedullin, calcitonin gene-related peptide and big endothelin-1 [16,33–35]. Another non-ECM acute action of MMPs and ADAMs is shedding of membrane-anchored ligands of receptors such as epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) to transactivate intracellular signaling of growth

via the MAPK cascade. Thus, metalloproteinases modulate MAPK signaling to help maintain agonist-induced vascular tone and signaling of hypertrophic growth [36].

Acute cleavage of non-ECM substrates can affect immunity. MMP-2 cleaves monocyte chemoattractant peptide, MCP-3, turning it into a chemokine antagonist [37]. Agonist-activation of MMP-2 may thus dampen inflammation in hypertensive cardiac disease.

The remodeling of the contractile machinery of the cell is yet another novel action of MMPs. Recent work suggests that MMP-2 cleaves myofilament proteins such as titin and myosin light chain in models of ischemia–reperfusion in isolated perfused working hearts [24]. Unchecked cleavage of contractile components by metalloproteinases may be deleterious for cardiac muscle function.

Some metalloproteinases share substrates [38]. For instance, activation of TNF- $\alpha$  as well as shedding of HB-EGF can follow activation of either MMP-7 or ADAM-17/TACE. As such, these metalloproteinases have redundant roles with regards to inflammation and cardiac hypertrophy.

### Cell surface receptors as substrates of metalloproteinases

This novel paradigm can help explain some features of the co-occurrence of hypertension and other morbidities [39]. MMPs have been found to cleave and inactivate vascular endothelial growth factor receptor (VEGFR)-2 to enable endothelial apoptosis and capillary rarefaction – a feature of malignant hypertension in humans and rodent models of disease. MMP cleavage of  $\beta$ 2-adrenoceptor may impair vascular smooth muscle relaxation and increase peripheral resistance in spontaneously hypertensive rats. MMP-mediated degradation of the insulin receptor in the same model provides a novel explanation for why insulin resistance sometimes accompanies hypertensive disorders. Pathologically high levels of GPCR agonists in these models may trigger the observed MMP- and ADAM-mediated destruction of cell surface receptors.

### GPCR signaling through MMPs and ADAMs: a clock for disease development?

The working hypothesis that has served as foundation for this review states that hypertensive cardiac disease can develop as a common pathological response to high levels of multiple GPCR agonists. MMPs and ADAMs are mediators of multiple GPCRs. However, it remains unclear whether metalloproteinases are central to cardiovascular regulation *all* the time or only in some stages of disease development.

Ongoing research from our laboratory is directed at answering this question. We have identified MMP-2, MMP-7, ADAM-12 and ADAM-17/TACE as mediators of angiotensin II-induced hypertensive cardiac disease. We have also found that gene expression of these metalloproteinases changes throughout disease development [16,36,40–42]. Moreover, some MMPs and ADAMs (such as MMP-7 and ADAM-17) appear to regulate others (such as MMP-2 and ADAM-12). In addition to the transient expression of individual MMPs and ADAMs, we observe the emergence of a novel specialization of functions: MMP-7 and



MMP-2 may regulate vascular tone whereas ADAM-17 and ADAM-12 may signal cardiac hypertrophy and fibrosis under transcriptional control of MMP-7 and ADAM-17. This functional specialization is determined by temporal differences in expression and hierarchical relationships among MMPs and ADAMs [16,36,40–42].

Although we expect some MMPs and ADAMs to contribute to disease through overlapping mechanisms, their unique substrates and different time windows of expression will probably dominate their unique functions. The emerging functional specialization of metalloproteinases suggests new ways to manipulate and normalize specific processes such as signaling of vascular contractile responses, hypertrophy and fibrosis.

From a clinical translation point of view, studies are warranted to establish the impact of timely inhibition of specific metalloproteinases for effective treatment of hypertension and the associated damage of target organs such as the heart. As hypertension often goes undetected for years, currently it is unclear how timely inhibition of metalloproteinases can be achieved for the treatment of hypertension. In addition to timing, other areas of potential intervention include metalloproteinase activation mechanisms (such as oxidative stress), metalloproteinase-specific activities or expression, metalloproteinase substrates and the mechanisms elicited by these substrates after cleavage.

## Conclusions

Metalloproteinases have emerged as key and common mediators of multiple GPCR agonists, which makes them candidate therapeutic targets for treatment of hypertensive cardiac disease when the etiology is complex or unknown. This type of global therapeutic concept would have potential for treatment of hypertensive cardiac disease in metabolic syndrome patients and perhaps also for treatment of populations where ethnic diversity might result in significant differences in the responses to current antihypertensives.

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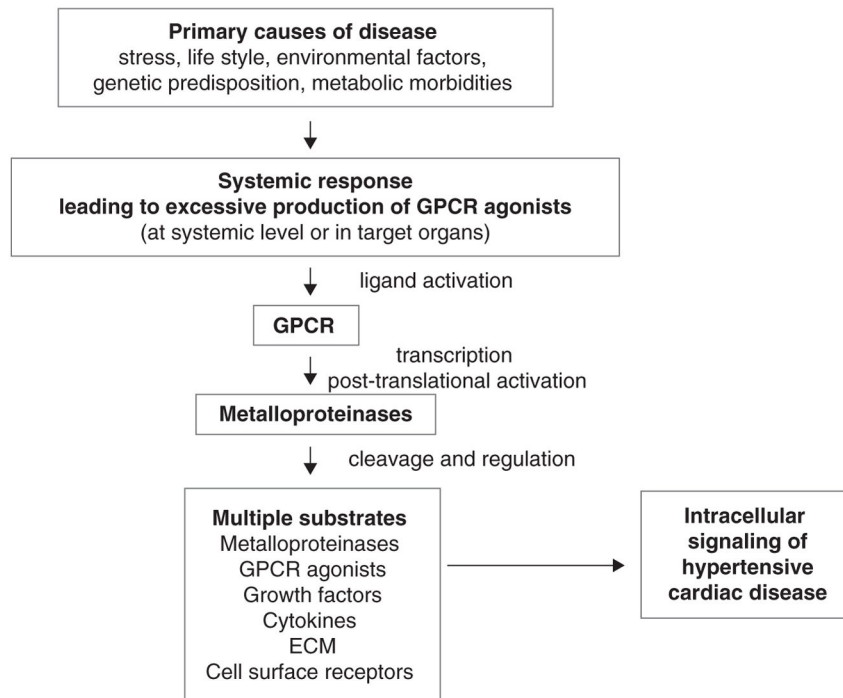
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**Figure 1.**

Hypertensive cardiac disease is a consequence of diverse conditions and morbidities. Conditions such as chronic stress, environmental factors, genetic predisposition and metabolic morbidities trigger responses systemically and locally (on target cardiovascular organs) which lead to excessive signaling by GPCR agonists. This translates into unchecked proteolytic activity of metalloproteinases that regulate many substrates including growth factors, cytokines and cell surface receptors. Uncontrolled cleavage of these substrates contributes to the development of hypertensive cardiac disease.