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Does serelaxin treatment alter passive mechanical wall properties in small resistance arteries?

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Running Title: Serelaxin treatment and vascular remodelling

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Abstract

The peptide hormone relaxin is recognised for its connective tissue remodelling actions in the reproductive tract during pregnancy and parturition, but it also has vascular remodelling actions independent of pregnancy. Recombinant human relaxin (serelaxin) treatment in male and non-pregnant female rodents enhances passive arterial compliance in the renal vasculature. This review focuses on serelaxin's actions on passive mechanical wall properties in small arteries and highlights the diversity of responses to serelaxin treatment in rodents. Different experimental approaches (duration of serelaxin treatment, rat strain, age) and animal models of disease (obesity, hypertension) will be considered. Most studies in young rodents demonstrate that serelaxin treatment fails to alter passive compliance in resistance-size arteries (mesenteric and femoral arteries and cerebral parenchymal arterioles), suggesting that serelaxin's beneficial effects are minimal in healthy animals. Short-term serelaxin treatment (5d) in aged, obese and spontaneously hypertensive rats (SHRs) is largely without effect on passive mechanical wall properties. However, a longer duration of serelaxin treatment in SHRs (14d) enhances passive compliance in large muscular arteries as well as resistance-size arteries. In conclusion, serelaxin is capable of vascular remodelling. Its actions are vascular bed-dependent, more prominent in disease, and likely requires a longer duration of treatment to be effective.

Keywords: relaxin, arterial compliance, RXFP1, vascular remodelling.**List of Abbreviations:**

MMP-2	matrix metalloproteinase 2
MMP-9	matrix metalloproteinase 9
RXFP1	relaxin family peptide receptor 1
SHR	spontaneously hypertensive rat
VEGF	vascular endothelial growth factor
VSMC	vascular smooth muscle cell

Introduction:

Relaxin is a 6 kDa peptide hormone that is widely recognised for its actions in pregnancy. It is predominantly produced by the corpus luteum and placenta [33], and is responsible for connective tissue remodelling within the female reproductive tract to facilitate parturition in many mammalian species [34]. Early studies indicate that the cognate receptor for relaxin, RXFP1 (relaxin/insulin like family peptide receptor 1) is also expressed in many non-reproductive tissues including the brain, heart, skin, lungs, liver, kidney and the vasculature [38]. Relaxin gene knockout mice also have distinct cardiovascular phenotypes compared with wild-type mice in the heart (increased ventricular collagen content and stiffness), small renal (increased myogenic activity, collagen content and reduced passive compliance) and mesenteric arteries (endothelial dysfunction and reduced passive

compliance) [12,15,18,22,27]. Collectively these findings demonstrate that endogenous relaxin is not only a 'pregnancy hormone' but also has important functions in a number of non-reproductive tissues. Furthermore, treatment with relaxin stimulates extracellular matrix remodelling in the heart, kidneys, lung, liver, and skin [30]. Less well characterised are the effects of relaxin treatment on vascular remodelling, largely due to contrasting findings reported in the literature. In this review we focus on vascular remodelling and passive mechanical wall properties in resistance arteries, and offer some explanations for the heterogeneous outcomes following relaxin treatment. As clinical trials and animal studies use recombinant human relaxin-2 (serelaxin) [21,25,29], we will refer to the peptide as serelaxin.

Serelaxin treatment: vascular effects

Outside of the reproductive tract, the effects of serelaxin have been most extensively studied in the kidney and its vasculature. The pioneering work of Conrad and colleagues identified that chronic subcutaneous serelaxin treatment in conscious normotensive and hypertensive male and female rats increases cardiac output and global arterial compliance and reduces systemic vascular resistance, without affecting mean arterial pressure [7,11]. These effects were dose-dependent with biphasic responses; chronic infusion of low-dose (4 µg/hr for 10 days) serelaxin increased cardiac output and global arterial compliance and reduced systemic vascular resistance, whereas higher doses (50 µg/hr for 6 days) yielded statistically insignificant changes from baseline [10]. Furthermore, serelaxin reduces mean arterial pressure in some rat models of hypertension [31,35] and increases coronary flow in rat and guinea pig hearts [1]. Serelaxin treatment improves renal function by increasing renal plasma flow, glomerular filtration rate and plasma volume and decreasing plasma osmolality [9]. These haemodynamic changes and improvements in renal function are largely attributed to the endothelium-dependent reduction in myogenic reactivity/tone in the small renal arteries (segmental and interlobar) [2,6,13,28]. Serelaxin increases matrix metalloproteinase (MMP)-2 and MMP-9 activity, which converts big endothelin to endothelin$_{1\text{-}32}$. This activates endothelial endothelin B receptors, leading to increased endothelial nitric oxide synthase II activity and production of nitric oxide, thereby reducing both vascular tone and myogenic reactivity [6].

Similar to the reproductive system, serelaxin exerts effects on the passive mechanical properties of blood vessels. In the renal vasculature serelaxin modulates the extracellular matrix. Chronic subcutaneous serelaxin infusion in rats and mice increases circumferential arterial compliance in small renal arteries [7,12]. In mice administered serelaxin for 5 days, the relative increase in small

renal artery compliance is mediated by both geometric (outward) and compositional (decreased collagen) remodelling. The outward geometric remodelling is characterised by an increase in unpressurised wall area and wall-thickness-to-lumen area ratio [12]. Serelaxin treatment also increases smooth muscle cell density and decreases total collagen content in the artery wall, without altering pro-MMP-2 and MMP-9 activity[12]. Conversely, subcutaneous serelaxin treatment (4 – 6 hours) in non-pregnant female rats increases pro-MMP-9 and MMP-9 activity in the small renal arteries [20], whereas a longer duration (5 days) of serelaxin infusion is required to increase pro-MMP-2 and MMP-2 activity in this artery [19]. As mentioned above, increases in MMP-2 and MMP-9 activity (assessed by gelatin zymography) are associated with serelaxin's actions on myogenic tone, but they may also be responsible for the reduction in collagen content [20]. This large compilation of work on the small renal artery established that serelaxin treatment has a role in vascular extracellular matrix remodelling. Compared with the renal vasculature, less is known about the remodelling effects of serelaxin in other vascular beds.

Localisation of relaxin receptors and region-specific effects of serelaxin

A key finding from our laboratory was the demonstration that relaxin receptors (RXFP1) are differentially localised within blood vessels and also throughout the vasculature. RXFP1s are localised in the atria [36], aorta [26], vena cava, small renal, mesenteric, femoral and uterine blood vessels [17,42] but are apparently absent from brain parenchymal arterioles and middle cerebral arteries [5]. In blood vessels, RXFP1s are localised to both the endothelium and vascular smooth muscle cells (VSMCs) although the relative level of expression between these cell types varies in arteries and veins in different vascular beds [17]. RXFP1s are more predominant in endothelial cells in the aorta, vena cava, mesenteric artery and vein, whereas in the femoral artery and vein and small pulmonary arteries they are more predominant in VSMCs. These data confirm that both endothelial and VSMCs are putative targets for serelaxin treatment, and reveal the potential widespread effects of serelaxin on vascular remodelling.

There is consensus that serelaxin treatment enhances agonist-induced endothelium-dependent relaxation and reduces myogenic tone in mesenteric arteries [17,23,28]. However, there is contrasting data regarding an effect of serelaxin on vascular passive mechanical wall properties in blood vessels other than those of the kidney. Subcutaneous serelaxin treatment in young (12 week old) Wistar and Long-Evans (20 – 24 week old) male rats for 3 - 5 days increases mesenteric artery compliance (circumferential and longitudinal) and passive volume compliance, and reduces passive

stiffness [17,24]. The latter is associated with outward remodelling (increased inner diameter) but not changes to the total soluble collagen or elastin content [17]. However, 5 days of serelaxin treatment failed to alter passive mechanical wall properties of young (10 - 12 week old) or old (40 - 46 week old) non-pregnant female Wistar Hannover rats [39]. Interestingly, both studies administered serelaxin at a dose of 4 μg/hr, and serelaxin plasma levels achieved in male Wistars was 40 ng/ml compared to ~85 ng/ml in female Wistar Hannover rats. Whether these differences in the effects of serelaxin are strain or sex-dependent requires elucidation. Recent unpublished data from our laboratory also demonstrated that neither 5 nor 10 days of serelaxin treatment altered passive mechanical properties of mesenteric arteries of male Wistar rats that were even younger (8 week old) than those used in abovementioned studies. There were no significant differences in any of the parameters measured including inside and outside diameter, circumferential stress-strain relationships and volume compliance. In our study the levels of serelaxin were 57 ± 12 ng/ml after 5 days and 89 ± 19 ng/ml after 10 days of treatment. Serelaxin treatment resulted in a significant decrease in plasma osmolality (brought about by actions on the renal vasculature causing vasodilation and renal hyperfiltration [8]), demonstrating that the serelaxin was biologically active in our rats. As the study was done in young rats, we concluded that the potential beneficial effects of serelaxin on vascular remodelling in these studies are hard to distinguish from normal physiological remodelling because the rats were in a growth and development phase. During this body growth phase mesenteric arteries undergo a substantial (~ 20%) amount of vascular growth and remodelling [37]. The “effectiveness’ of serelaxin in modulating passive mechanical wall properties may vary with age and between different strains of rats, and these issues require further investigation.

In arteries from vascular beds other than the kidney and mesentery, serelaxin treatment has subtle or no remodelling effects in healthy animals. For example, serelaxin, via an indirect mechanism, increases wall thickness and inside diameter of brain parenchymal arterioles, indicative of outward remodelling, without affecting passive compliance in non-pregnant female rats [4]. Serelaxin treatment (for 5 or more days) has no effect on wall properties in external iliac arteries and veins [12], middle cerebral arteries [4] or mesenteric veins [17,24]. Thus, the effects of serelaxin on passive mechanical properties appear to be highly region-specific. A summary of all the key studies (Table 1) highlights the difference between studies including animal sex, strain and age, and duration of treatment, and overall effect on vascular properties. These are all factors which could contribute to the heterogeneity in the effects on vascular remodelling in different vascular beds.

These factors need to be taken into consideration when exploring the effects of serelaxin treatment on vascular remodelling.

Disease models

The vascular remodelling that occurs with disease and aging is commonly associated with endothelial dysfunction, increased vascular stiffness, hypertrophic remodelling (thickening of the vascular wall), and increased collagen content [3,16,32] (Figure 1). As mentioned previously, the beneficial effects of serelaxin treatment on vascular remodelling appear to be minimal in healthy animals but may be augmented in disease models, particularly those with evidence of reduced arterial passive compliance. Many of the actions of serelaxin in healthy animals oppose the changes that are associated with disease and ageing (Figure 1). However, very few studies have assessed the specific vascular remodelling effects of serelaxin treatment in disease (Table 1). Again, as observed with studies on young, healthy animals, there are marked differences between vascular beds. To date, there is no evidence that serelaxin treatment (5 days) promotes vascular remodelling or alters passive mechanical wall properties in the mesenteric arteries of obese, aged (10 - 12 months old) or spontaneously hypertensive rats (SHRs) [39-41]. However, a longer duration of serelaxin treatment (14 days) with a 7-day washout period in aged (17 month old) SHRs increases vessel diameter and elastin content and reduced collagen content in the aorta and enhances passive circumferential compliance in the carotid artery [43]. Similarly, serelaxin treatment for 14 days in younger (14 – 16 week old) SHRs reverses the hypertension-induced inward remodelling to increase passive distensibility in brain parenchymal arterioles [5]. Although RXFP1 receptors are reportedly absent in brain parenchymal arterioles, serelaxin treatment is associated with increased MMP-2 and vascular endothelial growth factor (VEGF) expression in the brain cortex. Upregulation of these factors in the brain parenchyma are hypothesised to then interact with the adjacent arterioles to enhance distensibility [5]. Overall, to date there is a paucity of data in diseased arteries from different vessel beds to draw strong conclusions about the effect of serelaxin on pathological vascular remodelling. From the available evidence, it appears that a longer duration of serelaxin treatment may be necessary to alter passive mechanical properties of arteries in disease models. Research on the effects of serelaxin in diseased blood vessels are in their infancy, but are spurred on by the compelling evidence emerging from clinical studies of the beneficial effects of serelaxin treatment in heart failure patients. These beneficial effects are thought to be underpinned by the action of serelaxin on the vasculature [14,29].

Conclusions

Vascular remodelling is a process that involves modifications in both the cellular and extracellular components of the blood vessel wall to allow for changes in passive mechanical wall properties. Treatment with serelaxin appears to mediate structural changes in the vessel wall to improve arterial compliance, but these beneficial effects seem to be limited to specific vessel beds e.g. small renal arteries. The effects of serelaxin may be more prominent in diseased arteries where wall remodelling is more extensive, although this area of research has been relatively understudied at this time. From the evidence available, it appears that longer durations of serelaxin treatment are more effective, with optimal treatment duration yet to be established, and with a view to therapeutic manipulation of arterial wall properties in a clinical or disease setting.

Perspectives:

Vascular stiffness and hypertrophic remodelling are hallmarks of various cardiovascular diseases and severely impair the normal function of blood vessels. Serelaxin is likely to be a viable therapeutic in vascular disease because it improves passive compliance and reduces arterial stiffness, likely through activation of receptors localised within the vessel wall (Figure 2). Although serelaxin is capable of vascular remodelling, these actions may be limited to specific vessel beds, with relatively long durations of treatment necessary to be effective.

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Figure Legends:

Figure 1. Schematic of the vascular effects of disease / ageing and the reported actions of serelaxin treatment.

Figure 2. A working hypothesis of how serelaxin causes vascular remodelling to alter passive mechanical wall properties in resistance arteries. Relaxin is known to act on the endothelial cells (ECs) through RXFP1 to upregulate matrix metalloproteinase (MMP)-2 and -9 expression and activity. This is associated with a decrease in collagen in the media which may promote outward remodelling. It has yet to be established if serelaxin acts on RXFP1 receptors on the vascular smooth muscle cell (VSMCs) to promote outward remodelling.

Table 1. Summary of serelaxin infusion studies and effects on various types of vasculature.

Animal strain, sex, age and treatment durations vary between studies on different types of vasculature. SRA, small renal artery; MA, mesenteric artery; FA, femoral artery; FV, femoral vein; MV, mesenteric vein; BPA, brain parenchymal arteriole; MCA, middle cerebral artery; W., Wistar; WHR, Wistar Hannover rats; SHR, spontaneously hypertensive rats. [#] Kahlberg, Jelinic, Tare & Parry, 2015. [§] 7 days 'washout' period.

Animal/Strain	Sex	Age (weeks)	Treatment duration (days)	Vessel	Effect of serelaxin	Reference
Long-Evans rats	F	12-14	5	SRA	↑ passive compliance, outward hypertrophic remodelling	[7]
C57BL/6J mice	F	8-10	5			[11]
Wistar Rats	M	12	5	MA	↓ stiffness & ↑ passive compliance	[15]
Wistar Rats	M	8-12	3, 5 & 10	MA	No effect	Unpublished[#]
Wistar rats	M	12	5	FA, FV, MV	No effect	[15]
Long-Evans rats	F	20-24	3	MA	↑ passive compliance	[21]
Sprague-Dawley rats	F	14-16	10	BPA	Outward remodelling	[4]
			10	MCA	No effect	
SHRs	M	68	14 + 7[§]	Carotid	↑ distensibility, outward remodelling	[37]
SHRs	F	14-16	14	BPA	↑ distensibility, outward remodelling	[5]
			14	MCA	No effect	
W. Hannover rats	F	10-12	5	MA (young)	No effect	[33]
		40-46	5	MA (old)	No effect	
W. Hannover rats	F	10-12	5	MA (control)	No effect	[34]

			5	MA (obese)	No effect	
W. Hannover/ SHR	F	10-12	5	MA (WHR)	No effect	[35]
	F	10-12	5	MA (SHR)	No effect	

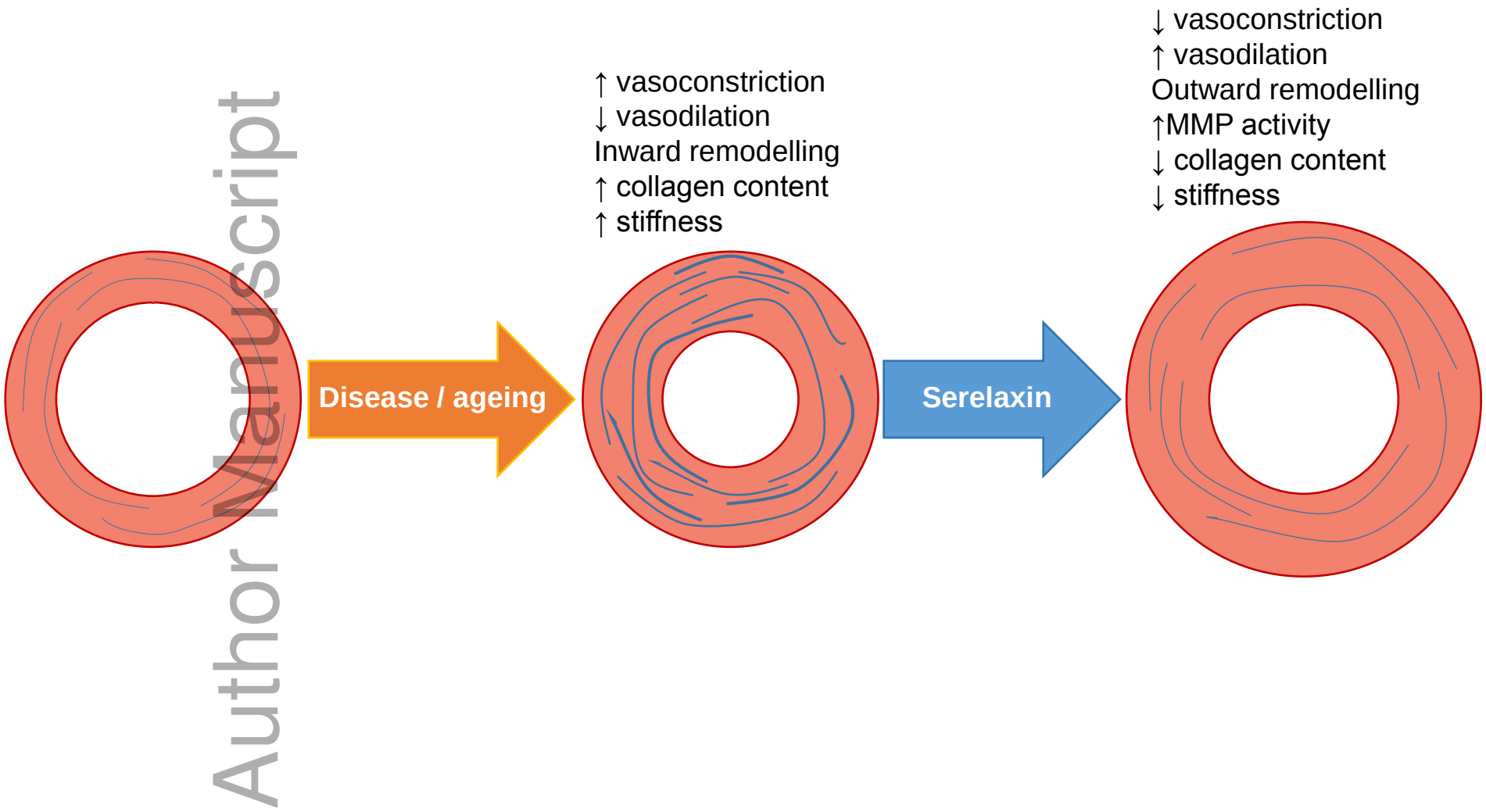

Figure 1.

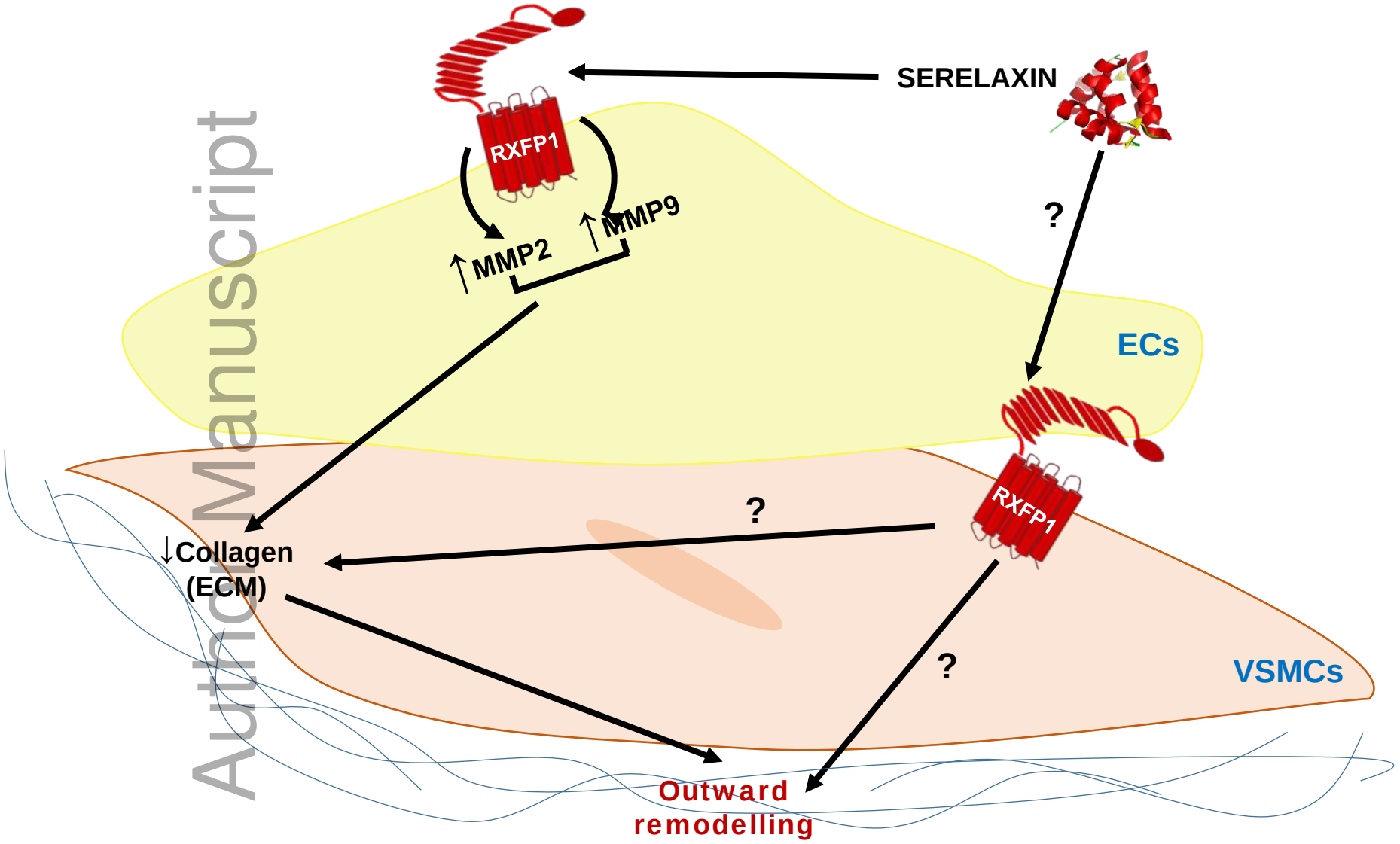

Figure 2.

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