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EDITORIAL

A Physiological Model of Cardiac Fibrosis: Changes to Maintain Function in the Cold

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Cardiac fibrosis occurs in response to several pathologies including myocardial infarction (MI) and hypertension. The increased deposition of connective tissue translates into an increase in passive stiffness, as well as impairment of electrical activation of the tissue. The result is a loss of systolic and diastolic function. Subsequent compensatory responses can lead to greater loss of function, including the development of dilated cardiomyopathy and eventual heart failure. In these disease models, fibrosis is irreversible and there is a dire lack of interventions to restore function. However, in the recent *Acta Physiologica* publication, Keen et al. [1] characterize a fibrotic response in freshwater turtles that occurs under physiological conditions that help maintain cardiac function at low temperatures. In fact, cardiac fibrosis can be induced in several ectothermic (cold-blooded) animals, including rainbow trout and freshwater turtles, in response to a decrease in physiological temperature [2, 3]. In addition, warm acclimation causes a decrease in the collagen content of the trout heart [2]. These changes are due, at least in part, to altered expression of gene transcripts for collagen monomers as well as proteins involved in regulating collagen turnover [4]. This includes matrix metalloproteinases (MMPs) and their inhibitors, tissue inhibitors of metalloproteinases (TIMPs) (Figure 1) [4]. Together, these studies suggest that the collagen content in a vertebrate heart is plastic, and that fibrosis can be reversible.

Freshwater turtles overwinter in ponds where temperatures are at least 10°C–15°C colder than in summer and there is limited oxygen [5]. With a 15°C cold acclimation, the heart rate of red-eared slider turtles has been found to decrease from ~30 bpm to ~2 bpm [5]. This bradycardia results in an increase in stroke volume and greater diastolic pressures [3]. To reduce the stress of an increase in cardiac preload, turtles have been demonstrated to decrease systemic resistance while decreasing the compliance of the ventricle [3]. The increase in cardiac collagen with cold acclimation is thought to be responsible for this increase in passive stiffness [3].

Keen et al. [1] characterize the remodeling of the turtle heart with cold acclimation as well as the associated modifications to metabolic function. In this study, an increase in tissue stiffness was measured after 8 weeks of cold acclimation using atomic force microscopy, and it is suggested that this was due to an increase in the density of stiff collagen fibers throughout the myocardium. Histological methods confirmed the increase in collagen and demonstrated an increase in fiber alignment with cold acclimation. To identify the mechanisms responsible for the increase in collagen, the authors examined changes in the expression of relevant genes, the levels of MMPs, and the activity of endogenous MMPs. These results suggest that the rise in collagen with cold acclimation was due to a decrease in MMP activity caused by an increase in TIMP abundance. Importantly, the results from the in situ gelatinase zymography indicate that there is inactivation of MMPs across the ventricle with cold acclimation. This would translate into a decreased capacity to catabolize collagen.

Based on Fourier transform infrared imaging spectroscopy, Keen et al. [1] suggest that cold acclimation increased the level of protein, including collagen, as well as lactate and glycogen in the myocardium, but decreased lipid content. The increase in glycogen and decrease in lipid is thought to reflect a switch from fatty acid oxidation (FAO) to increased usage of glycolysis and may have contributed to the rise in circulating lactate levels. A switch from FAO to glycolysis is required as oxygen

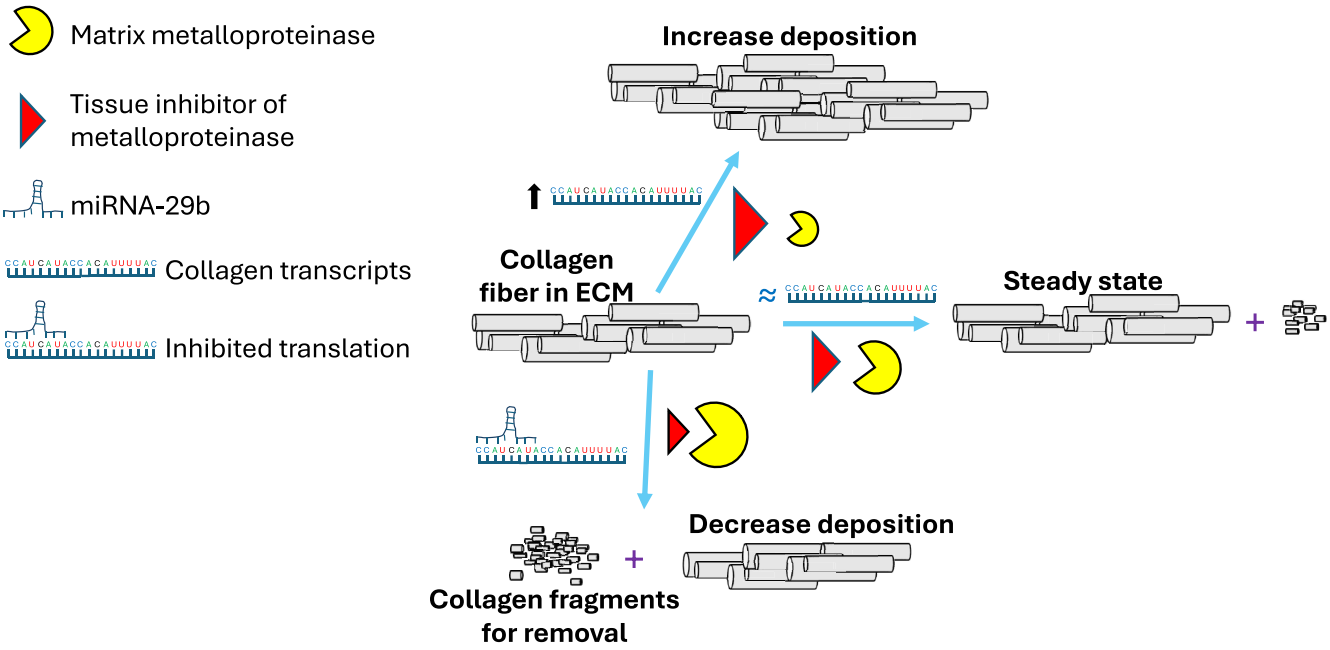

FIGURE 1 | Regulation of collagen in the mammalian heart. Changes in the relative sizes of the symbols represents a change to the levels of the associated component that can lead to a change in deposited collagen in the tissue. ECM, extracellular matrix.

levels become limiting in winter [6]. This switch also parallels the metabolic dysregulation that occurs in the mammalian heart following an MI where there is increased use of glycolysis as oxygen delivery to the tissue is impaired [7]. Importantly, this increase in glycolysis is associated with the onset of cardiac fibrosis and may contribute to the activation of fibroblasts that drive this process.

It has been proposed that the remodeling induced with cold acclimation is due to an increase in hemodynamic load on the heart activating cellular processes that trigger fibrosis. The increase in load is thought to result from an increase in blood viscosity caused by a stiffening of the erythrocyte membranes. In mammals, an increase in blood pressure is a trigger of fibrosis through the activation of mechanically gated G-coupled membrane proteins in fibroblasts and initiating the release of transforming growth factor β1 (TGF-β1) from myocytes with increased biomechanical stimulation [8]. Each of these activates the p38-JNK-ERK mitogen-activated protein kinase (MAPK) pathway in fibroblasts that leads to collagen deposition [8]. Work by Johnston et al. [9] demonstrates that exposure of trout cardiac fibroblasts to TGF-β1 causes an increase in collagen deposition and that mechanical stimulation of trout cardiac fibroblasts activates p38-JNK-ERK MAPK signaling involved in the regulation of collagen deposition. Together, these studies illustrate the parallels between the induction of cardiac fibrosis in mammals and the activation of temperature-induced cardiac remodeling in turtles and fish.

As suggested by Keen et al. [1], the remodeling response caused by cold acclimation of the turtle may be a useful model to increase our understanding of pathological cardiac fibrosis and to develop strategies to reverse it. It is likely that the fibrotic response in turtles is reversible as their temperatures increase with the arrival of spring and they become active in O_2-rich water. One potential avenue to gain insight into the regulation of collagen deposition is the role of microRNA 29b (miR-29b). This microRNA prevents translation of the mRNA for collagen 1a1 (col1a1) [10]. In mammalian models, a decrease in the expression of miR-29b following MI coincides with the onset of cardiac fibrosis [10] and work by Johnston et al. [9] demonstrates that increased expression of miR-29b in trout cardiac fibroblasts causes a decrease in collagen deposition. There is also complete sequence identity between human miR-29b and trout miR-29b [9]. Comparing the regulation of miR-29b expression during MI with that in ectothermic models during temperature change may prove fruitful.

This work by Keen et al. [1] is a very good example of the benefit of studying comparative models. Because of their capacity to increase collagen deposition in the heart under physiological, not pathological conditions, these animals are a good model, as would be suggested by Krogh, to "conveniently study" its regulation, and perhaps learn how to reverse it.

Author Contributions

The author takes full responsibility for this article.

Conflicts of Interest

The author declares no conflicts of interest.

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