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Research update

Activation of common signaling pathways during remodeling of the heart and the bladder

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ABSTRACT

The heart and the urinary bladder are hollow muscular organs, which can be afflicted by pressure overload injury due to pathological conditions such as hypertension and bladder outlet obstruction. This increased outflow resistance induces hypertrophy, marked by dramatic changes in the organs' phenotype and function. The end result in both the heart and the bladder can be acute organ failure due to advanced fibrosis and the subsequent loss of contractility. There is emerging evidence that microRNAs (miRNAs) play an important role in the pathogenesis of heart failure and bladder dysfunction. MiRNAs are endogenous non-coding single-stranded RNAs, which regulate gene expression and control adaptive and maladaptive organ remodeling processes. This Review summarizes the current knowledge of molecular alterations in the heart and the bladder and highlights common signaling pathways and regulatory events. The miRNA expression analysis and experimental target validation done in the heart provide a valuable source of information for investigators working on the bladder and other organs undergoing the process of fibrotic remodeling. Aberrantly expressed miRNA are amendable to pharmacological manipulation, offering an opportunity for development of new therapies for cardiac and bladder hypertrophy and failure.

1. Introduction

Although the heart and the urinary bladder serve distinct functions in the body, both are designed to undergo repeated cycles of filling and emptying, albeit with remarkably different kinetics. The heart ensures a constant supply of blood to all other organs, contracting and relaxing continuously from early embryogenesis until death. The bladder on the other hand stores urine as it is being produced by the kidneys and empties when an appropriate opportunity arises, usually once every few hours. Contraction and relaxation of the heart and the bladder are governed by different mechanisms. However when there is a resistance interfering with liquid outflow, their respective contractile units, cardiomyocytes and bladder smooth muscle cells (SMCs), can be subjected to pressure and volume overload.

Notwithstanding the structural and functional differences between the bladder and the heart, both organs respond to the pathological pressure overload by hypertrophy and fibrotic remodeling leading to the loss of contractility [1,2]. Due to the immediate life-threatening nature of these processes in the heart, the wealth of experimental and clinical data far surpasses that of the bladder. Although not all observations are immediately transferable from one organ to the other, there are striking parallels in the cellular and molecular mechanisms, which we will discuss in this Review. We will regard the processes, occurring during pressure overload-induced organ remodeling in the heart and the bladder in the context of the role of miRNAs, important epigenetic regulators of stress signaling pathways.

2. Dysfunction of the heart and the bladder caused by sustained pressure overload

Normally, the heart responds to an increase in blood flow by adjusting the stroke volume and rate. Increased filling pressure and volume intensify the stretching force on the myocardium leading to a pressure overload. Because the adult mammalian myocardium

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has negligible regenerative capacity, it responds to this mechanical stress by producing additional sarcomeres leading to an increase in myocyte size. In the heart volume overload occurring due to mitral regurgitation or arteriovenous fistulas causes increased diastolic stress and results in eccentric hypertrophy. The heart is enlarged, but the wall is thin with big cavities; cardiomyocytes are elongated due to the serial insertion of new sarcomeres [3]. In contrast, hypertension, aortic stenosis and other stimuli, resulting in pressure overload, induce parallel insertion of sarcomeres and an increase in myocyte width, characteristic of concentric hypertrophy [4]. Both pressure overload and stretching of the cardiomyocytes activate growth signaling pathways, which lead to organ remodeling [5]. Cardiac hypertrophy can be physiological, when it is induced by prolonged exercise or during pregnancy, or pathological, when it develops in response to hypertension, aortic stenosis, heart valve insufficiency or myocardial infarction [6]. While both types of hypertrophy provoke increased myocardial mass, pathological hypertrophy is accompanied by extensive fibrosis, cardiac dysfunction and ultimately heart failure. Physiological hypertrophy, in contrast, is characterized by normal cardiac structure and function, and is reversible [7]. Not surprisingly, in each type of cardiac hypertrophy involve different signaling pathways [8]. Pressure overload-induced cardiac hypertrophy initially is an adaptive response aiming to maintain output. However, when the underlying cause is not eliminated, an extensive organ remodeling program is initiated, resulting in increased myocardial stiffness due to fibrosis, diastolic dysfunction and eventually ventricular dilation and combined diastolic and systolic heart failure [9]. The pathological mechanisms of an isolated volume overload marked by eccentric left ventricular remodeling and dysfunction are less clearly defined, although many parallels are emerging [10]. It has been shown that chronic volume overload is a stimulus for myocardial fibrosis in human patients [11] and animal models [12], with similar signaling pathways activated in both in concentric and eccentric hypertrophy [12].

The lower urinary tract (LUT) comprises the bladder and urethra. The bladder is a musculo-membranous hollow organ, which stores and expulses urine. Prerequisite for normal storage and voiding is a coordinated interaction between the muscle components of the bladder wall (detrusor) and its outlet (urethra and sphincter). During the filling phase the bladder wall maintains a certain degree of tension, which is caused by myogenic contractile activity, while detrusor pressure remains low without detectable muscle contractions [13]. Activation of the sphincter in the absence of detrusor contractions during the filling phase preserves continence [14].

When this process is impaired, lower urinary tract dysfunction (LUTD) with the symptoms of urgency, frequency and incomplete emptying can occur. LUTD is caused by various pathologies including neurologic disorders and bladder outlet obstruction (BOO) [15]. BOO caused by benign prostatic hyperplasia (BPH), which affects the majority of men as they age [16], or urethral strictures, leads to an increased resistance during voiding and is more commonly observed in men than in women [17]. BOO necessitates an increased intravesical pressure to void completely and results in profound structural and functional changes in the bladder wall, bladder hypertrophy, which resemble those of concentric myocardial hypertrophy. The increase in wall thickness corresponds to the severity of obstruction [18], with a significant correlation between the two observed in men with BPH [19]. In contrast, volume overload injury in the bladder of human patients is a rare occurrence, and is usually prevented by catheterization [20]. Bladder hypertrophy is characterized by changes in the expression profile of SM contractile and signaling proteins, modification of extracellular matrix (ECM) proteins, and an increase in bladder innervation [21,22]. Although relief of obstruction is a traditional form of therapy for this disorder, many storage and voiding symptoms, including urgency, frequency and incomplete emptying, persist after surgery, indicating that timing of the surgical intervention may be critical for complete recovery of bladder function. As bladder outlet obstruction progresses from inflammation to hypertrophy to fibrosis [23], early identification of structural changes can guide therapeutic decisions that might prevent further damage to the bladder and optimize the timing of treatment. Reliable markers of bladder function are urgently needed in order not to surpass the “point of no return”, leading to bladder decompensation/failure.

3. Regulatory miRNAs and their impact in disease

Since their discovery in the early 1990s [24], miRNAs have emerged as central regulators of many biological processes, including proliferation, differentiation and cell death [25]. MiRNAs are endogenous non-coding single-stranded RNAs of approximately 22 nucleotides which regulate gene expression by post-transcriptional mechanisms upon sequence-specific binding to the 3′ untranslated regions (3′ UTRs) [25,26] or, occasionally, the 5′ UTRs [27,28] or coding regions [29–31] of their mRNA targets. The short “seed” sequences (nucleotides 2–8) at the 5′ ends of miRNAs are most critical and often sufficient for target selection. MiRNAs exhibit imperfect complementarity with mRNAs, allowing them to regulate multiple genes and thus complicating efforts to predict and functionally validate their targets [32]. Each miRNA target is regulated in the range of a 2-fold change, therefore the additive effect of simultaneous regulation of a large number of transcripts is believed to bring about strong phenotypic effects [33]. The details of miRNA synthesis are well characterized and extensively reviewed elsewhere [34–36].

MiRNAs are produced in a wide range of species, with more than 1000 encoded by the human genome [37]. Changes in their expression profiles, occurring concomitant with emerging pathologies, have led to the notion that in addition to their developmental function, they might influence the responses of already differentiated tissues to physiologic and pathophysiologic stress [38]. This suggests a role of miRNAs in disease states, and indeed dysregulation of their synthesis contributes to fibrotic diseases of the lung, liver and the heart [39–41]. The first miRNA profiling of a LUTD was performed for bladder pain syndrome (BPS) in our laboratory. We identified several miRNAs, which affect the expression of signaling and adhesion molecules known to be relevant for the pathogenesis of bladder pain [42], suggesting a regulatory role of miRNAs. Follow-up experiments established the role of miRNAs in the regulation of urothelial permeability [43] and bladder SMC proliferation and morphology [44]. More recent studies implicated miRNAs in the regulation of bladder contractility [45,46].

4. The cellular effectors of cardiac and bladder fibrosis

Although cell types comprising the heart and the bladder are different, their response to pathologic pressure bears a lot of similarity. The contractile cells of both organs, cardiomyocytes and detrusor SMCs (dSMC), are capable of a considerable morphologic and proliferative plasticity. Initially, both cardiomyocytes and dSMCs undergo an increase in size as a result of increased synthesis and incorporation of contractile elements. In the heart, this is associated with structural remodeling including changes in fibrillar collagen network and angiogenesis [8]. Chronic pressure overload, unlike physiologic hypertrophy, may then activate pro-fibrotic pathways leading to cell death (apoptosis, necrosis) and the replacement of the lost myocytes with excessive collagen. Fibrosis