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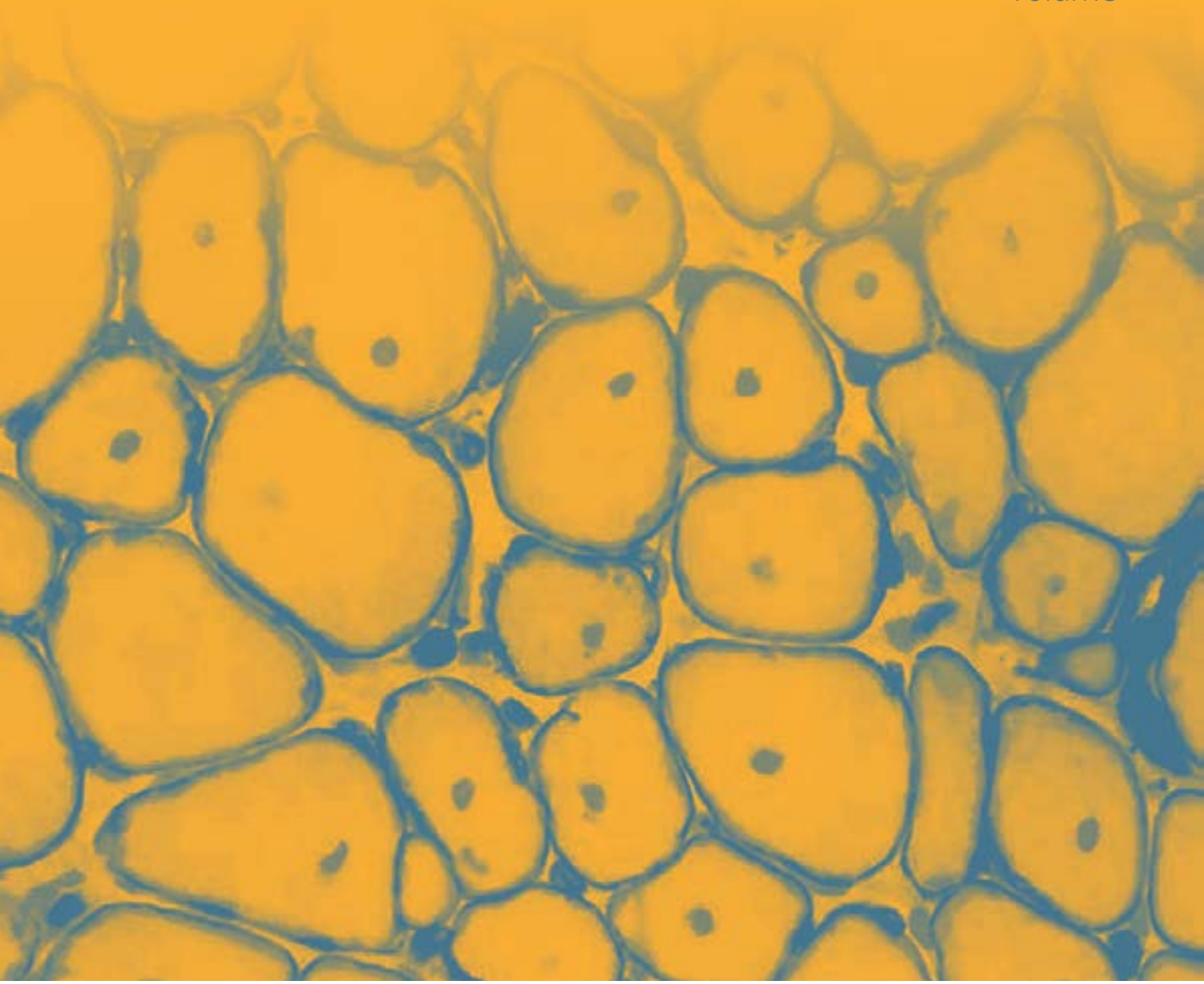

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OXIDATIVE STRESS AND CARDIAC CONTRACTILITY: A DOUBLE EDGE SWORD?

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ABSTRACT

The stretch of cardiac muscle increases developed force in two phases. The first phase occurs immediately after stretch and is the expression of the Frank–Starling mechanism, while the second one or slow force response (SFR) occurs gradually and is due to an increase in the calcium transient amplitude. Previously, we have shown that the SFR is the mechanical manifestation of an autocrine/paracrine mechanism activated by wall stretch involving growth factors-triggered reactive oxygen species (ROS) formation, and followed by redox-mediated cardiac Na^+/H^+ exchanger (NHE1) activation leading to an increase in the Ca^{2+} "transient" amplitude. Recent own experiments assigned a role to thioredoxin-1 ("TRX1", an important cellular antioxidant enzymatic system) in the development of the SFR. Interestingly, cardiac hypertrophy and failure, two of the most important health problems in western societies, are both triggered by intracellular signals triggered by myocardial stretch, being oxidative stress a critical step for its progression. Remarkably, experimental evidence has revealed that TRX1 overexpression negatively regulates cardiac hypertrophy. In this scenario, this short review was meant to briefly discuss the physiological, but potentially pathological, role of oxidative stress following myocardial stretch.

Keywords: TRX1, SFR, NHE1, oxidative stress, cardiac hypertrophy.

RESUMEN

El estiramiento miocárdico produce una respuesta contráctil en dos fases: un aumento rápido inmediato que es la expresión del mecanismo de Frank-Starling, y uno lento posterior denominado segunda fase de fuerza (SFF). En trabajos anteriores hemos mostrado que la SFF es la manifestación mecánica de un mecanismo autocrino/paracrino disparado por el estiramiento, que involucra liberación de factores de crecimiento seguida de la activación redox-dependiente del intercambiador Na^+/H^+ cardíaco (NHE1) que conduce a un aumento Na^+-dependiente del Ca^{2+} intracelular. Experimentos más recientes de nuestro grupo han demostrado además que la tioredoxina-1 ("TRX1", importante sistema enzimático antioxidante a nivel celular) es capaz de modular la magnitud de la SFF. Interesantemente, la hipertrofia y la insuficiencia cardíaca, dos de los problemas de salud más importantes en sociedades occidentales, se desencadenan por señales intracelulares que ocurren después del estiramiento miocárdico e incluyen estrés oxidativo como factor clave para su progresión patológica. En conexión, se ha demostrado que la sobreexpresión de TRX1 regula negativamente la hipertrofia cardíaca. En este escenario, esta revisión tiene como objetivo discutir brevemente el papel fisiológico, pero potencialmente patológico, del estrés oxidativo disparado por el estiramiento del miocardio.

Palabras claves: TRX1, SFF, NHE1, stress oxidativo, hipertrofia cardiaca.

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Introduction

The heart possesses a powerful intrinsic capacity to adapt cardiac output to abrupt changes in hemodynamic conditions. The stretch of ventricular wall is the mechanical stimulus that triggers such adaptation. Seminal experiments by Otto Frank at the end of the 19th Century and Ernest Starling at the beginning of the 20th Century served to describe the well-known "Frank-Starling Law", which describes a mechanism that explains how force increases after stretch. However, the adaptive response of force to wall stretch actually occurs in two consecutive phases. In this regard, the less known slow force response to stretch (SFR) that gradually develops just after the Frank-Starling mechanism took place, constitutes an important additional adaptive mechanism that deserves special attention. While the abrupt Frank-Starling mechanism is attributed to enhanced myofilament Ca^{2+} responsiveness, the gradual SFR is due to an increase in Ca^{2+} transient amplitude. Identification of the mechanism that underlies the increase in intracellular Ca^{2+} was the area of investigation of our laboratory group during more than twenty years. We described a complex sequence of events where hormones-triggered reactive oxygen species (ROS)-mediated Na^{+}/H^{+} exchanger (NHE1) activation plays a critical role [1]. These findings reinforced the notion that ROS increase would not be necessarily linked to deleterious effects, but instead, it can be part of physiological responses [2]. However, it is important to remark that critical events leading to the physiological SFR (hormones release-oxidative stress-NHE1 hyperactivity-increase in Ca^{2+} transient) are also involved in the progression of severe cardiac pathologies like hypertrophy and heart failure [1, 3, 4], whose mechanical trigger is ventricular wall stretch. Actually, we may conceivably affirm that wall stretch initiates intrinsic heart mechanisms to adapt cardiac force to different hemodynamic conditions, but also would lead to the development of cardiac pathology if the stimulus continues during more time. In this scenario, interventions leading to prevent ROS increase beyond its physiological limits appear to be promissory tools to treat severe cardiac pathologies fueled by chronically increased oxidative stress. Based on a recent discovery about the role of thioredoxin-1 (TRX1) in the SFR development [5], we will briefly discuss in the following sections the physiological but potentially pathological role of ROS in the stretched myocardium.

The Slow Force Response to Myocardial Stretch: A Redox-Sensitive Phenomenon

As stated before, the SFR is a second increase in force following myocardial stretch that gradually occurs after the expression of the Frank-Starling mechanism. Although Allen and Kurihara [6] were the first to identifying that an augmented Ca^{2+} transient underlies the SFR development, the exact genesis of this increase remained rather elusive during several years. A comprehensive revision of the main conclusions raised by different study groups about this important issue can be found in an elegant recent review by Kaur et al. [7]. In our hands, more than twenty years of research allowed us to propose that the SFR results from a stretch-triggered autocrine/paracrine mechanism where ROS increase plays a critical role [8].

In 2006, Sudgen and Clerk [2] provided evidence that myocardial ROS are part of the intracellular signaling pathway fired by Angiotensin II (AngII) and Endothelin (ET), well-known mediators of the SFR development [9]. Contemporarily, we demonstrated that AngII through a dose that mimics the increase in force observed during the SFR, increases sarcomere shortening

of isolated cardiomyocytes through an autocrine crosstalk with endogenous ET [9], being this effect dependent on ROS production. Interestingly, these ROS were from mitochondrial origin but triggered by a small amount of NADPH oxidase-derived ROS, clearly resembling the so-called "ROS-induced ROS-release" phenomenon described some years before [10]. In 2007, we described the crucial role of ROS in the SFR development [11]. We showed that the SFR and the NHE1-dependent increase in intracellular Na^+ concentration that follows myocardial stretch are both abolished when ROS increase is blunted. In addition, we reported that myocardial stretch induced an AT1-triggered increase in ERK1/2-p90RSK phosphorylation, recognized redox-sensitive kinases upstream NHE1 [11], indirectly reinforcing the notion that myocardial stretch activates the exchanger. Interestingly, either NADPH oxidase inhibitors or mKATP channel blockers abolished both the SFR and the NHE1-mediated increase in Na^+_i, suggesting that the ROS-induced ROS-release mechanism also lies beneath the SFR development [11]. These and other subsequent results served us to unveil a complex sequence of events underlying the SFR that can be summarized as follows: 1) release of pro-hypertrophic factors (AngII-ET) with the consequent sequential activation of their respective receptors (AT1-ETA), 2) activation of the mineralocorticoid receptor (MR, probably a membrane-bound subpopulation), 3) transactivation of the epidermal growth factor receptor (EGFR), 4) NADPH oxidase activation, 5) mitochondrial ROS production, 6) activation of redox-sensitive kinases, 7) NHE1 hyperactivity, 8) increase in Na^+_i, 9) increase in Ca^{2+} transient amplitude through the Na^+/ Ca^{2+} exchanger in reverse (see [8] for review). It is important to highlight that previous own results showed that the increase in ROS induced by AngII, ET or aldosterone is prevented by NADPH oxidase inhibition [1, 9, 12], suggesting that its activation would participate in different steps downstream hormone receptors in the signaling cascade triggered by myocardial stretch.

Interestingly, it is possible to speculate that in addition to lead to the SFR, this mechanism would probably be the foundation stone for cardiac hypertrophy development and eventually heart failure if the mechanical stimulus persists over time. We will address this issue in following sections.

Thioredoxin and the Slow Force Response

TRX1 is one of the most important cellular antioxidant molecules [13]. This enzyme belongs to the "TRX/TRX reductase" system that together with the "glutathione/glutathione reductase" system represents most of the antioxidant power of cells. This ubiquitously expressed cytosolic protein owns the main function of maintaining the intracellular medium in a reduced state, therefore playing a critical protective role against oxidative stress, primary stimulus to inducing enzyme transcription and hence cardiac remodeling [13]. There are at least three isoforms in mammals among which TRX1 is the most studied one. The TRXs have captured the interest of the scientific community due to its potentiality as a therapeutic target in clinical medicine [14]. In cardiac tissue, TRX1 functions as a major antioxidant enzyme, but also interacts with important signaling molecules and transcription factors, thereby modulating various cellular functions [13]. Interestingly, it has been reported that overexpression of this protein negatively regulates cardiac hypertrophy [15, 16]. Furthermore, TRX1 inhibits Ras activation induced by oxidative stress during α-adrenergic receptor stimulation, therefore suppressing cardiac

hypertrophy development [17]. Conversely, inhibition or downregulation of the enzyme amplified the hypertrophic response to pressure overload [15] or contributed to negative cardiac remodeling [18]. All these evidences led us to explore the possibility that TRX1 overexpression could affect the SFR after myocardial stretch, results that are reproduced in Figure 1. The upper left panel shows the typical contractile behavior of a papillary muscle from a wild type mouse before and after stretch. As expected, an initial rapid increase in force due to the Frank-Starling mechanism was followed by a SFR that stabilized after ~10 minutes. Interestingly, myocardial TRX1 overexpression did not affect the initial rapid phase, but completely abolished the SFR as shown in the representative experiment of the upper right panel of the Figure 1 [5]. The latter result strengthened previous own findings demonstrating the critical role of ROS in the SFR development [11], but this time evidenced by a different experimental approach which consisted in potentiating cardiomyocyte antioxidant power.

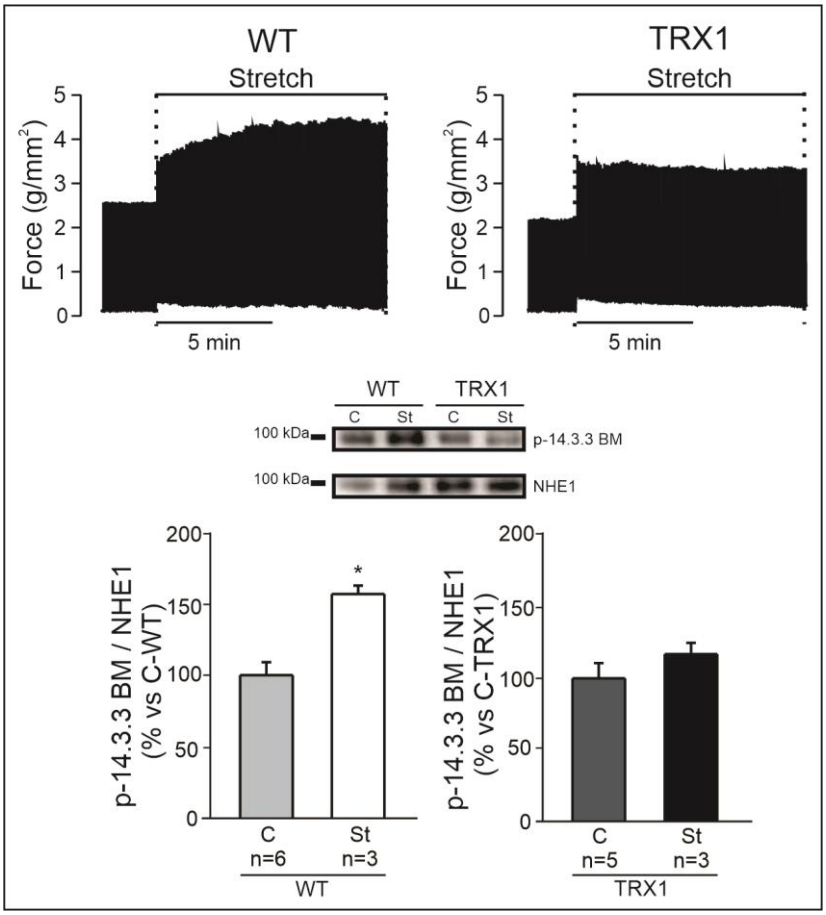

Figure 1. Upper panel: Original force record of isolated papillary muscles from both mouse strains that were suddenly stretched from ~92 to ~98% of their maximal length. The characteristic two-phase increase in force that follows myocardial stretch can be observed in the WT papillary muscle (left), while a complete cancelation of the SFR was observed in the TRX1-overexpressing one (right). **Lower panel:** Myocardial stretch promoted a significant increase in NHE1 phosphorylation in WT mice ("St-WT") compared to the corresponding non-stretched controls ("C-WT") (left), effect that was not observed in TRX1 overexpressing muscles (right). A representative immunoblot is shown in the inset (top). *Indicates $p < 0.05$ vs. C-WT. *Adapted from Zavala et al.* [5].

As stated before, we [11, 12] and others [19] previously showed that the SFR depends on the activation of NHE1, which is a target for the redox sensitive kinases ERK1/2 and p90RSK. In line, we have previously demonstrated that stretch-triggered ERK1/2-p90RSK-mediated NHE1 phosphorylation at Serine 703 (an indirect but confident indicator of NHE1 activation [20]) is a critical step in the chain of events leading to the SFR development [11, 21]. Interestingly, TRX1 overexpression completely abrogated the increase in Serine 703 NHE1 phosphorylation that accompanied the SFR development in wild type mice (Figure 1, bottom panel). Neither basal NHE1 expression or basal ERK1/2-p90RSK phosphorylation were altered by TRX1 overexpression [5]. We did not measure ROS production or TRX1 activity under the experimental conditions, but previous results demonstrated that mice overexpressing TRX1 exhibit similar basal enzyme activity than wild type animals as reported by Pérez et al. [22]. These authors also showed a correlation between ROS production and TRX1 activity, suggesting that the model requires a stimulus to be switched-on. In this regard, we could speculate that in our experimental conditions the stretch-triggered ROS production would be the initiator of the signalling cascade. Whatever the case, it is possible to conclude that if endogenously ROS production is prevented either pharmacologically [11] or by potentiating antioxidant defense [5], the SFR will be abolished.

Another interesting issue to address is the possible link between TRX1 and p38-MAPK. On one hand, we have recently demonstrated that activation of p38-MAPK after myocardial stretch negatively regulates the SFR [23], effect that was assigned to limitation of NHE1 phosphorylation/activation after stretch, through a mechanism that involves dual specificity phosphatase 6 activation-mediated decrease in ERK1/2-p90RSK phosphorylation. On the other hand, while the reduced form of TRX1 interacts with the apoptosis-signaling kinase 1 (ASK1) inhibiting its activity [24], its oxidation form destabilizes this complex and promotes ASK1 activation, leading to p38-MAPK activation [25]. The latter mechanism would certainly be activated after myocardial stretch. Further studies will be necessary to unveil a possible link between TRX1 overexpression and ASK1, and therefore, its possible relationship with p38MAPK and the SFR development.

In summary, overactivation of TRX1 appears to prevent stretch-triggered ROS formation, avoiding a possible phosphorylation/activation of ERK1/2-p90RSK, and therefore precluding NHE1 phosphorylation/activation. These novel findings demonstrate that exacerbation of myocardial antioxidant power impedes the SFR development, further supporting the notion that ROS formation is crucial for the heart to confront changes in hemodynamic conditions. A simplified scheme of these novel findings is depicted in Figure 2.

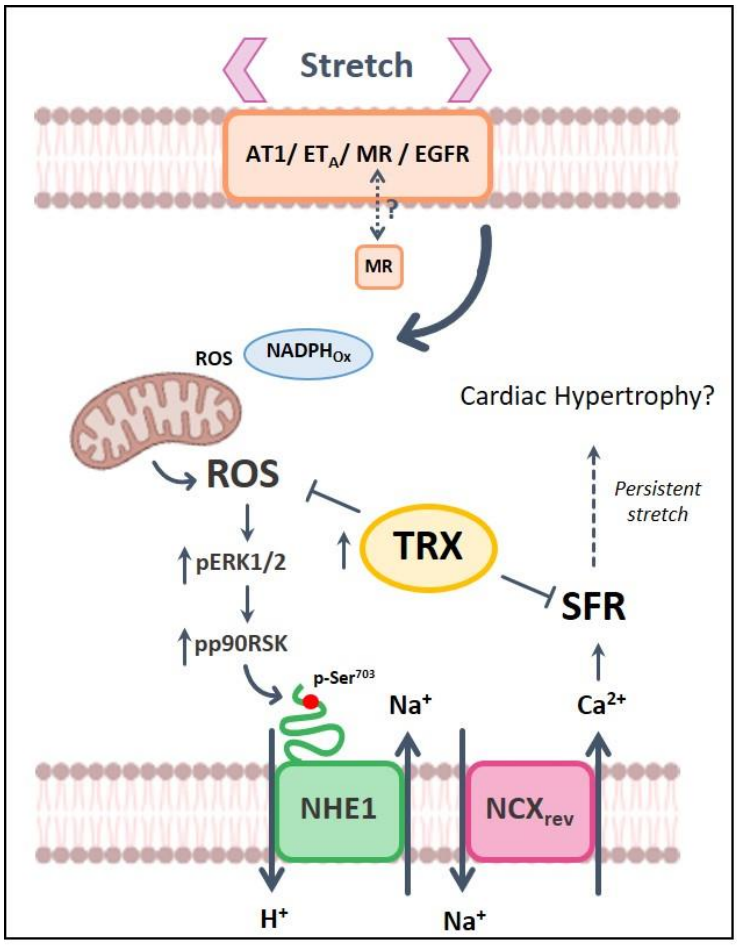

Figure 2. Simplified scheme of the intracellular signaling pathway triggered by myocardial stretch. A ROS-dependent ERK1/2-p90RSK phosphorylation mediates Serine 703 NHE1 phosphorylation, crucial step to promote a Na^+-dependent increase in Ca^{2+} transient amplitude (through reverse Na^+/Ca^{2+} exchanger, "NCX") responsible of the SFR development. TRX1 overexpression exacerbates myocyte antioxidant defense, therefore preventing stretch-induced ROS accumulation, NHE1 activation and SFR development.

Myocardial stretch and oxidative stress: From Physiology to Pathophysiology

The striking similarity between molecular mechanisms leading to the SFR and intracellular signals triggering cardiac hypertrophy suggests that like a double-edged sword, mechanical stress may not only trigger immediate intrinsic heart mechanisms to adapt cardiac output to changes in hemodynamic conditions, but also would constitute the keystone toward dysfunction if initial events are perpetuated in time. Therefore, the interest in deciphering the subcellular basis of the SFR is beyond its physiological role, given that oxidative stress, NHE1 hyperactivation, and augmented Ca^{2+} concentration, are pathognomonic hallmarks of cardiac hypertrophy and heart failure [3, 4], highly prevalent cardiac pathologies of western societies.

The role of NHE1 activation early after stretch leading to the SFR development has been detected in different species [11, 26, 27, 28, 29, 30]. Our contribution was to demonstrating that regulation of the phosphorylation state of the exchanger is critical for the final modulation of the contractile response to stretch. This is not unanimously recognized [31, 32, 33], despite we showed that silencing of NHE1 by interference RNA cancels the SFR [34], maneuver that on the other hand

also prevents cardiac hypertrophy development in spontaneously hypertensive rats [35]. It is important to highlight that NHE1 hyperactivity has been identified as the main responsible for the development of cardiac hypertrophy from different origins [36, 37, 38]. In fact, NHE1 overactivation in the heart is sufficient to induce cardiac hypertrophy and heart failure [39]. Furthermore, interventions known to cancel the SFR are also effective for the treatment of this pathology [36, 40, 41, 42, 43], giving support to the hypothesis that the sequence of events triggered by stretch and leading (immediately) to the SFR, could trigger hypertrophy if the mechanical stimulus persists over time. In this context, the contribution of our most recent results demonstrating that exacerbation of cardiac antioxidant defense precludes stretch-induced NHE1 activation, encourages to suggest that modulation of TRX1 activity would be a suitable target to develop novel therapeutic strategies against these severe diseases.

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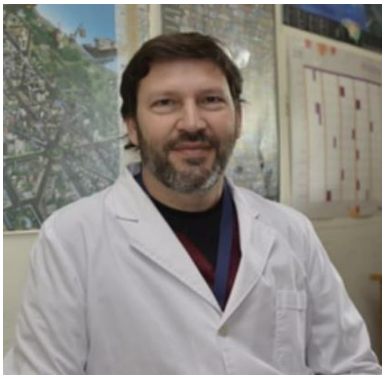

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