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Editorial

Pathogenic role of mitochondrial calcium uniporter upregulation in the failing heart: Ca^{2+} mishandling or what else?

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A highly efficient cardiac mitochondrial function is crucial to guarantee energy supply to an organ characterized by the staggering turnover of its entire ATP pool every 10 s, even at rest [1]. Interestingly, the same organelles that function as the principal cellular power plants can also initiate cell death mechanisms under pathological conditions, hence have been long considered as potential targets for therapies [2]. Both processes, mitochondrial energy production and death pathways activation, require Ca^{2+} signaling. In the healthy, normo-oxygenated cardiomyocyte, Ca^{2+} stimulates energy production by activating pyruvate dehydrogenase, i.e. the rate limiting step of carbohydrate oxidation [1], as well as two enzymes of the Krebs cycle and the ATP synthase, all located in the mitochondrial inner membrane and matrix [3]. The channels that permit Ca^{2+} influx in the mitochondrial matrix and their relative importance are still being defined; however, solid evidence indicate that, at least during acute increases in cardiac metabolic demand, a major role is played by the mitochondrial calcium uniporter (MCU) [4,5], the core component of the multi-protein MCU holocomplex. MCU is also responsible for the excessive Ca^{2+} influx in mitochondria under pathological conditions such as myocardial ischemia and reperfusion: rather than modulating energy production, in this case Ca^{2+} overload triggers the formation of mitochondrial permeability transition pores, powerful initiators of cell death processes [3]. This pathogenic mechanism is supported by experimental models in which MCU blockade or genetic inactivation limits myocardial damage after ischemia-reperfusion [3,5].

Ischemia-reperfusion…and? It was recently shown that physiological and pressure overload-induced pathological cardiac hypertrophy are both associated with MCU upregulation in animal models and in humans [6]. In this issue of the Journal, Yu and collaborators [7] went further on testing whether MCU inhibition can improve cardiac function and remodeling during the transition from pressure overload-induced cardiac hypertrophy to failure. As the authors mention in the discussion, they were prompted by evidence of MCU upregulation in cardiac tissue from heart failure dogs and patients (data not shown in their paper). To test their hypothesis, they utilized a mouse model of cardiac hypertrophy and failure induced by transverse aortic constriction (TAC). Some animals were treated for seven weeks with daily intraperitoneal injections of Ruthenium Red (RR), an established MCU blocker, while the control TAC group received physiological solution. TAC + RR animals displayed markedly preserved ejection fraction, shortened QRS duration -both indicating improved cardiac contractile function and synchronization- and lower death rate compared to control TAC. Consistently, positron emission tomography showed a higher percentage of viable myocardium in TAC + RR. Molecular analyses confirmed the up-regulation of mitochondrial and, interestingly, also cytoplasmic MCU (Fig. 1) after TAC, an alteration that could not be prevented by RR administration. In both non-treated TAC and TAC + RR hearts, the levels of microtubule-associated proteins 1A/1B light chain 3B ratio (LC3B II/I) were high, indicating a strong activation of the autophagosome formation process (Fig. 1). However, cardiac levels of sequestrosome1/p62 were reduced only in TAC + RR, indicating that RR administration favored the effective completion of the autophagic process. These findings were consistent with the higher number of autophagosomes and mitophagosomes and the reduced mitochondrial morphological alterations in TAC + RR. Further evidence of improved autophagy was provided in vitro using H9c2 cells stressed with isoprenaline and exposed to RR or short interfering RNA directed against MCU.

Taken together, these results suggest that the beneficial effects of MCU inhibition can be attributed at least in part to restored autophagy and mitophagy, essential housekeeping processes for cell survival, which are impaired in the failing heart [8]. On the other hand, the improved ventricular synchrony was likely due to the restored expression of connexin-43. Therefore, it is safe to conclude that MCU inhibition exerted curative effects in a model of non-ischemic heart failure.

Nonetheless, several aspects deserve more in depth investigation. The most evident limitation of this study is the lack of experiments testing possible direct mechanistic links between MCU inhibition and autophagy restoration. Similarly, there is no direct evidence of altered

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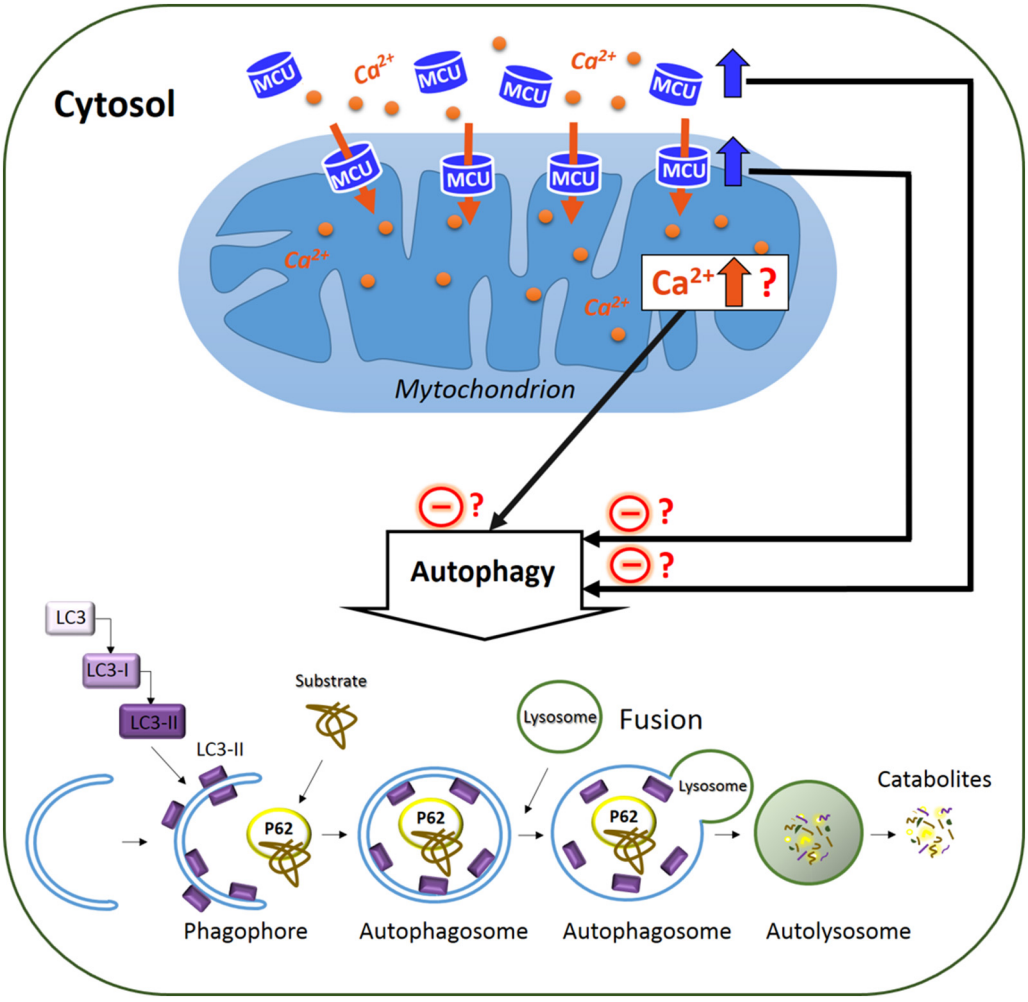

Fig. 1. MCU upregulation and autophagy in cardiac pathological hypertrophy and failure. Cytosolic and mitochondrial MCU upregulation in cytosol and mitochondria is associated with decreased autophagy, although the mechanistic links have not been determined. LC3 (microtubule-associated proteins 1A/1B light chain 3B) is key for autophagosome formation and maturation. After entrapping a substrate, phagophores form autophagosomes and the conversion LC3-I to LC3-II is a good indicator of this process. However, the accumulation of autophagosomes does not necessarily reflect effective autophagy. Sequestrosome1/p62 is an ubiquitin-binding scaffold protein accompanying the substrate for autophagy, hence its concentration is widely used as an indicator of effective autophagic flux.

Ca^{2+} concentration in mitochondria, hence the pathogenic role of this cation remains uncertain (Fig. 1). Moreover, it has been previously shown that RR blocks not only MCU, but also Ca^{2+} fluxes through ryanodine receptor 1 (RyR1) and L-type Ca^{2+} channels [9], which might have been involved in the protective action found in TAC mice. Another major question regards the persistence of beneficial effects of MCU inhibition in the long term, considering that heart failure is a chronic condition. While studies in cardiac specific MCU knockout indicate the essential role of this channel for enabling mitochondria to meet the metabolic demand of the fight or flight response [4] such indispensable function was not confirmed in global MCU knockouts and the difference between two types of MCU deletion was no longer detectable after prolonged catecholamine stimulation [5]. RyR1 and TRPC3 (the transient receptor potential canonical 3) may serve as alternative MCU-independent Ca^{2+} entry ports in mitochondria [9,10], which prompts the question on whether prolonged MCU blockade in TAC + RR mice might induce compensatory mechanisms. Subsequent preclinical studies in diverse animal models will be necessary to confirm short and long term beneficial effects and rule out the toxicity of RR or other MCU inhibitors, to identify molecular mechanisms and to test more clinically relevant routes of administration.

Notwithstanding the above mentioned limitations and others, the study by Yu and collaborators has the merit of providing the first proof of concept that MCU inhibition is a potential strategy for the treatment of heart failure. One more possible weapon against this seemingly undefeatable syndrome.

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