ESC European Society of Cardiology

Cardiovascular Research (2020) **116**, 1654–1655
doi:10.1093/cvr/cvaa113

EDITORIAL

Thioredoxin-1: a cardioprotector against stress

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Online publish-ahead-of-print 28 April 2020

This editorial refers to 'Thioredoxin-1 maintains mitochondrial function via mTOR signaling in the heart' by S.I. Oka *et al.*, pp. 1742–1755.

Oxidative stress is central in several cardiac pathological conditions, contributing to the maladaptive process of myocardial remodelling.[1,2] Furthermore, progression of heart failure is usually characterized by a deficit of energy with a shift in the use of substrates. In fact, mitochondrial metabolism, redox regulation, and energy transport are unbalanced in the failing heart. During progression to cardiac dysfunction, change of metabolism results in cytosolic accumulation of toxic intermediates.[3] Actually, oxidative stress in myocardial cells determines structural and functional changes leading to cell death.[4]

Endogenous antioxidant pathways, such as Thioredoxin-1 (Trx1), protect from the increase of oxidative stress. Trx1 has been reported as a cornerstone in maintaining the cellular redox status and regulation of signalling mechanisms.[5]

Trx1 is a redox protein with five cysteine residues and two, Cys32 and Cys35, positioned in the catalytic centre. Trx1 mainly carries out its activity by cleaving disulfide bonds of oxidized proteins thus affecting intracellular scavenging of oxidative stress. This action relies on cell survival, cell growth, and gene transcription. From the point of view of the cardiac myocyte, Trx1 performs a cardioprotective activity against ischaemia and reperfusion damage, reducing the infarct size.[6] In addition, Trx1 acts as a negative regulator of cardiac hypertrophy, as shown by Yamamoto *et al.* that generated a whole-body Trx1-dominat negative mutant mice, finding that they developed enhanced cardiac hypertrophy in response to chronic pressure overload induced by transverse aortic coartation.[7]

Trx1 has several cellular targets. In particular, Nagarajan *et al.*[8] described nuclear targets, such as NF-κB, AP1, and p5, and target protein kinases that inhibit apoptosis through an interaction with apoptosis signal-regulating kinase 1 (ASK1). Furthermore, Trx1 modulates the activity of other targets, like the class II histone deacetylases (HDACs),[9] AMP-activated protein kinase (AMPKα),[10] and mechanistic target of rapamycin (mTOR), through mechanisms depending on the reduction of specific cysteine residues.[11]

The article by Oka *et al.*[12] in this issue adds another piece of knowledge about the endogenous role of Trx1, previously uncharacterized by a whole-body loss of function mutation. In fact, the authors generated cardiac-specific conditional Trx1 knockout (Trx1cKO) mouse model. In the homozygous mutant mice, they evidenced increased oxidative stress and morphological mitochondria anomalies, associated with enhanced cardiac fibrosis and apoptotic cell death, development of spontaneous heart failure and reduced survival. The dramatic cardiac phenotype observed, clearly emphasizes the key homeostatic role of the Trx1 in cardiomyocytes. On the other hand, heterozygous Trx1cKO mice, characterized by a modest mitochondrial dysfunction and a reduced ejection fraction, showed an enhanced hypertrophic response to pressure overload featuring traits of transition towards heart failure, suggesting that a moderate reduction of thioredoxin activity is not sufficient to protect the heart during haemodynamic stress (*Figure 1*).

An additional interesting result of the study presented in this issue was to identify mTOR as a cardiomyocyte-specific substrate of Trx1. In particular, the authors showed that Trx1cKO mice have increased oxidation of mTOR and inhibited phosphorylation levels of its substrates (S6K and 4EBP1), thus suggesting that Trx1 maintain a functional level of activation of mTOR signalling in cardiomyocytes. On this issue, the similar cardiac phenotype (heart failure and early death) observed in mTOR knockout mice[13] and Trx1cKo mice further supports the molecular link between the two intracellular signallings. Nevertheless, it should also be taken into account that the oxidation of mTOR may not be the only mechanism for the development of heart failure and death observed in the absence of Trx1. A rescue of Trx1cKO cardiac phenotype through targeting selectively mTOR oxidation would be an interesting possibility to definitively demonstrate that the Trx1-mTOR signalling is a master regulator of cardiac function.

The development of cardiac hypertrophy in both constitutively Trx1 and mTOR cardiac KO[14] suggests that genetic hypertrophic programme can be sustained through different molecular mechanisms independent by both pathways. On this issue, Class II HDACs could be the main candidates[15] and further work will be necessary to better dissect this interesting question and how Trx1 regulates class II HDACs.

In conclusion, the study of Oka *et al.* adds mechanistic and cell-specific information on the role of Trx1 and its molecular relationship with mTOR to protect from developing heart failure. Some issues are still open, such as the dealing of Trx1 and mTOR with other molecular

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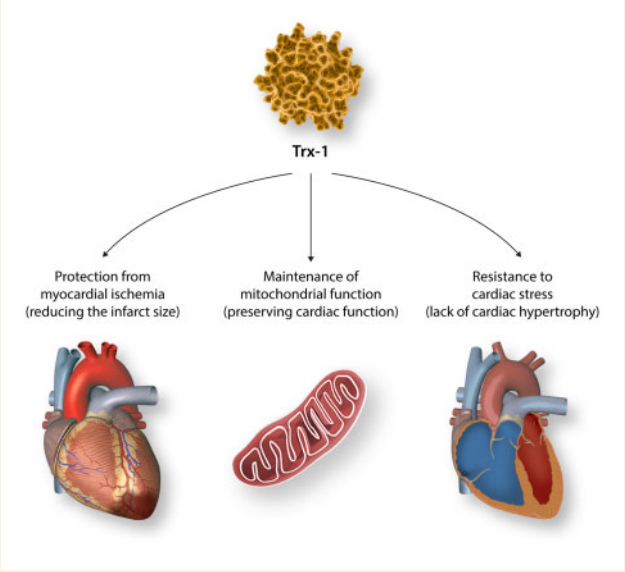

Figure 1 Cardioprotective roles of Thioredoxin-1. Trx-1 regulates the intracellular signal of cardiomyocytes and, by counteracting oxidative stress, plays a cardioprotective role. In the context of current knowledge, Trx-1 performs its protective action in various settings. In fact, it protects from myocardial ischaemia, reducing the infarct size in case of ischaemia and reperfusion damage. Furthermore, it maintains mitochondrial function in the heart and cardiac pump function in basal conditions and after stress, preventing the development of cardiac hypertrophy and heart failure.

targets that have been demonstrated to be involved as well in cardiac structural and functional remodelling.

Funding

This work was supported by Ricerca Corrente (Italian Ministry of Health) to G.L.

Conflict of interest: none declared.

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