

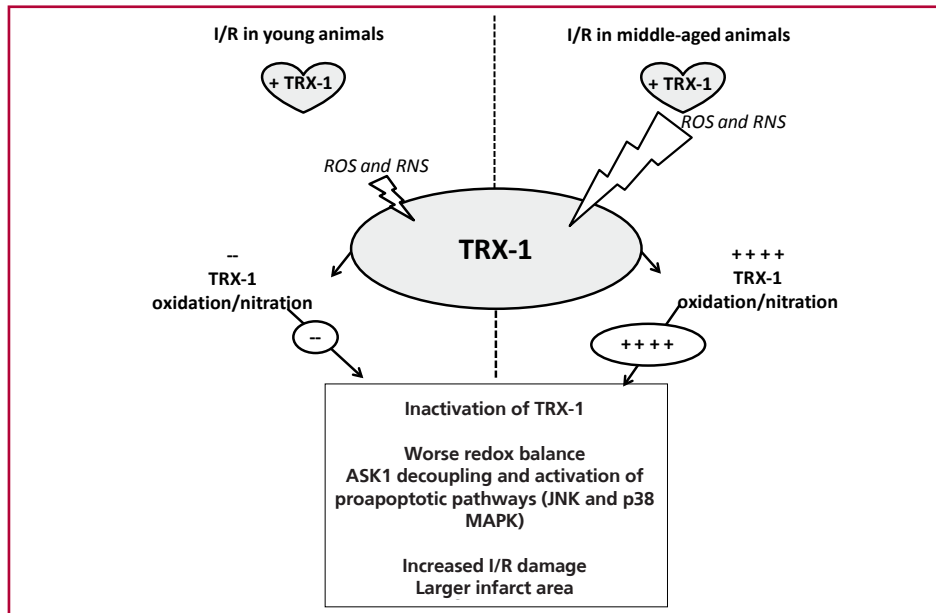
## Protection of Thioredoxin-1 Against Myocardial Ischemia and Reperfusion... Is Not the Same as With Good Wines!

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“The older, the better”, so the popular saying goes when it comes to good wines. However, it does not seem to be the case when it comes to reduction-oxidation (redox) balance. Some authors suggest that there is an increase in concentration of reactive oxygen species (ROS) during aging, leading to increased use of endogenous antioxidants and to an imbalance of the cellular redox state (1). Under these physiological aging conditions, ischemic injury leads to additional ROS production, exceeding the response of antioxidant systems. In the myocardium, this response may be crucial to maintain tissue integrity in cases of increased ROS production, as in the event of an ischemic episode followed by reperfusion (I/R). In this scenario, cardiomyocyte survival largely depends on the ability to support the reduced environment. In the elegant study by Pérez et al published in this issue of the Argentine Journal of Cardiology (2) the powerful tool of genetic engineering was used to analyze the impact of cardiac thioredoxin-1 (TRX-1) overexpression on I/R injury. Their results showed reduced infarct size in young animals overexpressing TRX-1 compared to their wild controls. However, this effect was not seen in middle- age animals where no changes were found neither in left ventricular function parameters nor in infarct size. This is a novel and striking finding, since although the deleterious mechanisms associated with aging are not totally established at middle-age TRX-1 already appears as a possibly altered factor. It is known that the homeostatic response to improve redox balance depends on the combined action of various antioxidants, so that the increased expression of TRX-1 would only represent a part of this complex defense mechanism, not enough in middle-age to promote an improvement in structural remodelling. Conversely, overexpression of TRX-1 in young animals protected the myocardium against ischemic injury, an effect that might be due to a more favorable redox environment as a result of a preserved endogenous antioxidant reserve (Figure 1).

Together with glutathione, the thioredoxin system

is considered important to maintain a reduced intracellular environment. It promotes ROS detoxification and is consequently a key regulator of cardiovascular homeostasis.(3) Thioredoxin is a protein involved in the antioxidant thioredoxin/peroxiredoxin system, which also has an antiapoptotic effect.(4) Its antioxidant effect is due to its ability to reduce the oxidized thiol groups of peroxiredoxin in the process of detoxification of hydrogen peroxide (5). It is postulated that ROS would act as signaling molecules (6). The control of ROS concentrations, particularly of hydrogen peroxide, can then be significant in that signaling process (6). Therefore, in addition to controlling ROS levels, thioredoxin, by acting directly on proteins involved in apoptotic signaling (such as ASK1, apoptosis signal-regulating kinase-1) (3), would have a key role in controlling maladaptative cardiac remodelling, by modulating cell death pathways. Myocardial infarction resulting from an I/R episode is a consequence of cell death due to necrosis and apoptosis, and ROS are important signaling molecules in this process (7, 8). ROS molecules may cause both necrosis and apoptosis, but the regulatory mechanisms have not been fully clarified yet (9). Any stimulus blocking pro-apoptotic signaling pathways can significantly reduce myocardial infarction and improve cardiac function (10). This protection occurs when the heart has effective antioxidant and antiapoptotic systems to prevent damage from ROS (3). In a previous study from our lab, Schenkel et al showed in a rat model that TRX-1 significantly contributes to early reduction of hydrogen peroxide concentrations in the myocardium of infarcted animals during post-infarction remodelling. This effect was shown to be associated with a reduction of the pro-apoptotic protein JNK expression. It also demonstrated that during the transition from myocardial infarction to cardiac failure, cardiac hydrogen peroxide concentration increased while TRX-1 concentration remained low, and apoptotic signaling was activated without changes in the infarct area. In the article by Pérez et al., (2) reduced infarct size



**Fig. 1.** Possible mechanisms involved in loss of protection against I/R injury in middle-aged TRX-1 animals

following I/R, observed in young animals with overexpression of TRX-1, was not found in middle-age transgenic mice. The authors postulate that inactivation of TRX-1 might explain this phenomenon. In fact, reduced TRX-1 is associated with ASK1, inhibiting its activity. But under oxidative stress conditions, TRX-1 undergoes changes in its catalytic site and dissociates from ASK1, which is phosphorylated and activated (12, 13). Activated ASK1 moves pro-apoptotic downstream signaling molecules, such as JNK or p38 MAPK (3). Post translational changes in TRX-1 due to nitration or interaction with its endogenous inhibitor, TXNIP (thioredoxin interacting protein), also reduce TRX-1 activity and could represent mechanisms related to loss of protection of TRX-1, possible increase in apoptosis (14) and larger infarct area, all effects observed in middle-age TRX-1 mice. It would be interesting to carry out additional experiments to confirm whether the loss of protection of TRX-1, observed in middle-age animals, is due to changes in TRX-1 expression and/or activity associated with increased ROS or reactive nitrogen species (RNS) (Figure 1).

The present work (2) addresses current issues and highlights the crucial importance of thioredoxin in the response to I/R in an ex vivo model that simulates the changes in acute myocardial infarction. The perfusion model described by Langendorff represents an excellent study model for cardiac function in different experimental situations. Perfusion flow and heart rate remained constant in this work (2). These conditions ensure more homogeneous workload and, therefore, oxygen consumption, thus balancing ROS production. An interesting finding was that overexpression of TRX-1 did not change the parameters of post-ischemic ventricular function, despite reduction in infarct size. As the authors very well discussed, protective effects on cardiac function may not have been observed due to the type of experimental protocol

used, which analyzes functional response only during two hours after reperfusion. The authors also point out that in this context, there are areas of stunned myocardium, masking functional improvement up to 72 hours following ischemia. In this regard, it would be interesting to perform in vivo experiments of ischemia-reperfusion, and observe the time course of possible changes in cardiac function at different ages in transgenic animals.

TRX-1 has been described as a negative modulator that suppresses both hypertrophy and apoptosis during heart failure, and is thus ideal to consider as a potential therapeutic target (5). It would be interesting to conduct additional studies to verify the mechanisms involved in myocardial protection and to clarify the causes of loss of protection against post-ischemic injury in middle-age shown in this work. Certainly, this study by Perez et al (2) highlights an important means of protection against I/R, targeting cardiac overexpression of TRX-1 as a promising therapeutic strategy for myocardial protection and integrity preservation after I/R episodes.

Who knows if, once the phenomena leading to the loss of such effect in middle-aged subjects are identified and controlled, this would result in better health at the age of "Grand Reserve", and not just of "Young" wines...

#### Conflicts of interest

None declared

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