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EDITORIAL COMMENT

A new weapon in the armamentarium to tackle inflammation associated with myocardial infarction

Uma nova arma para o armamento de combate à inflamação associada ao enfarte do miocárdio

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Despite the investments and progress witnessed in recent years in alleviating its damaging consequences, myocardial infarction (MI) is still the leading cause of mortality worldwide. It is normally associated with the occlusion of a coronary artery that blocks blood flow to the underlying regions of the heart, leading to myocardial ischemia. In this situation, oxygen and nutrient deprivation trigger a myriad of mechanisms that culminate in cardiomyocyte dysfunction and death.

Currently, the principal treatment for myocardial ischemia is primary percutaneous coronary intervention (PCI), which reopens the obstructed vessel, restoring blood flow. Although reperfusion is necessary to replenish the energy supply to cardiomyocytes, it also triggers additional cellular events, such as increased mitochondrial permeability, oxidative stress, calcium overload and neutrophil activation, which can exacerbate cardiac muscle and microvascular dysfunction.[1,2] Thus, besides the damage inflicted by the lack of nutrients and oxygen during ischemia, MI is also characterized by reperfusion injury. Despite increased knowledge and improved technical interventions for myocardial reperfusion, mortality and morbidity associated with the development of heart failure following MI remain high.[3] Hence, it is vital to devise additional cardioprotection strategies that can attenuate the damage caused by reperfusion. Accordingly, various non-pharmacological approaches, such as ischemic conditioning, stem cell therapies and aerobic exercise, have been developed to reduce ischemia-reperfusion injury, and pharmacological therapies aiming to prevent the production of reactive oxygen species and/or improve the antioxidant defenses of cardiomyocytes have also been investigated.

The targeting of inflammatory events for the prevention and treatment of cardiovascular diseases including MI has gained increasing attention.[4,14] Immediately after ischemia-reperfusion, oxygen free radicals and pro-inflammatory factors are released that activate neutrophils, which enhance expression of adhesion molecules, promoting the adhesion and infiltration of inflammatory cells, resulting in damage to cardiomyocytes. It is therefore conceivable that suppression of the inflammatory response may be an effective therapeutic pathway. In line with this cardioprotective view, the study by Liu et al. published in this issue of the *Journal*[5] provides evidence suggesting that alprostadil, a synthetic form of prostaglandin E1, may have cardioprotective effects against myocardial ischemia-reperfusion injury, through the down-regulation of serum expression of soluble intercellular adhesion molecule (sICAM), soluble vascular adhesion molecule (sVCAM), CD11b and CD18. This is not the first study aiming to unveil the protective effects of alprostadil in ischemia-reperfusion. It has been reported that alprostadil exhibits a therapeutic effect on

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hepatic ischemia-reperfusion injury in rats.[6] Moreover, in a rat model of ischemia-reperfusion sciatic nerve injury, alprostadil attenuated peripheral nerve injury by reducing serum malondialdehyde content and increasing serum nitric oxide levels.[7] Additionally, Zhang et al. demonstrated that alprostadil has cardioprotective effects that are, at least in part, due to promotion of antioxidant activity and activation of endothelial nitric oxide synthase (eNOS).[8] However, in the paper by Liu et al., they suggest that alprostadil attenuates myocardial ischemia-reperfusion injury through an anti-inflammatory pathway. Thus, it is plausible that other molecules play a similar role, acting as protective players in myocardial ischemia-reperfusion injury. Considering that ICAM-1 is an early acute inflammation marker, related to leukocyte recruitment and adhesion, therapies that decrease its expression may reduce inflammation and tissue damage.[9]

Interestingly, the authors of this study demonstrated that *Salvia miltiorrhiza*, a herb used in traditional Chinese medicine, can reduce levels of sICAM and sVCAM as well as of CD11b and CD18, although alprostadil has a more pronounced effect. Furthermore, lithospermic acid, a catechol derivative extracted from *S. miltiorrhiza*, can alleviate myocardial ischemia-reperfusion injury by promoting eNOS activation.[10] Additionally, microRNA-141 (miR-141) was demonstrated to target and suppress ICAM-1 expression, hence overexpression of miR-141 may also ameliorate myocardial ischemia-reperfusion injury.[11] Interestingly, a recent study reported an administration technique to deliver a small interfering RNA targeting ICAM-1 into injured rat cardiac microvascular endothelial cells, providing a promising approach for the anti-inflammatory treatment of myocardial ischemia-reperfusion injury.[12] The study by Liu et al. sheds new light on the molecular mechanisms behind the cardioprotective effect of alprostadil, and suggests that anti-inflammatory strategies offer a therapeutic approach for myocardial ischemia-reperfusion injury. However, although targeting inflammation is emerging as a strategy for cardioprotection, some limitations can already be discerned. Considering that ischemia-reperfusion injury is a multifactorial process, a combined targeting approach, combining anti-inflammatory agents with therapies targeting mitochondrial dysfunction, constitutes a promising strategy to successfully tackle the disorder.[13]

Overall, the paper by Liu et al. is a valuable contribution, since it demonstrates that both alprostadil and *S. miltiorrhiza* decrease levels of adhesion molecules, and can thereby reduce the inflammatory response and attenuate myocardial ischemia-reperfusion injury, highlighting the importance of anti-inflammatory therapies to treat myocardial ischemia-reperfusion injury.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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