The double-edge sword of TNF-α in ischemia-reperfusion injury

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Inflammation has been recognized for several years as an underlying factor in the initial responses to ischemia-reperfusion (I/R) (1). The microcirculation constitutes the initial barrier in I/R in all tissues, and thus it represents an important target for therapeutic interventions. While a large body of research on myocardial I/R has focused on understanding the bases of the deranged metabolism of myocytes (13), it is important to realize the significance of the impact of microvascular disease in the heart. In fact, endothelial dysfunction, characterized, in part, by a reduction in the ability of endothelial nitric oxide (NO) synthase-associated signaling cascade to initiate appropriate vasodilating responses, plays a causal role in myocardial disease (16).

The basic factors leading to microvascular dysfunction in the pathophysiology of I/R involve a series of events, resulting in inadequate oxygen supply, reduction in cellular energy stores, accumulation of noxious metabolites, and reperfusion injury mediated by reactive oxygen species (ROS), including peroxynitrite, which is derived from reactions between NO and superoxide anion. While it is difficult to determine accurately the differential contributions of ischemia and of reperfusion to microvascular dysfunction, it seems plausible that reperfusion exaggerates cellular damage caused during ischemia.

It is usually understood that the formation of oxygen-derived free radicals depends on the generation of superoxide anion through endothelium and leukocyte-stimulated biochemical reactions. This understanding is based on the facts that endothelial cells contain xanthine oxidase, whereas leukocytes feature membrane-bound NADPH oxidase. While leukocyte-endothelial interactions are nearly universally established in inflammatory processes (7) and in the increased microvascular permeability to macromolecules in I/R (1), the results of Zhang et al. (4) demonstrate that their activation is not a relevant mechanism of action for tumor necrosis factor-α (TNF-α)-induced derangement of vasodilation. These authors show that TNF-α produced enhanced generation of superoxide and the same deleterious microcirculatory results in control and in leukopenic animals, an observation that supports an important direct action of TNF-α on microvascular cells, which leads to the generation of ROS and a decrease in the vasodilating capacity of coronary arterioles.

TNF-α is a prominent element in the “cytokine hypothesis” of heart disease (11) and has been the focus of research in myocardial ischemia. TNF-α displays beneficial as well as detrimental actions on myocardial health. Experimental evidence indicates that it protects myocytes against apoptosis following I/R (6) and contributes to maintain tissue homeostasis (15). The significance of TNF-α in the development of I/R damage is illustrated by the significantly reduced infarct size in postischemic heart of mice lacking the gene encoding for TNF-α (8). Interestingly, while activation of neutrophils is not necessary for TNF-α impact on microvascular function, lack of TNF-α or inhibition of TNF-α reduces leukocyte infiltration into the myocardium (4, 5, 8).

TNF-α is produced locally in the heart. Myocytes, mast cells, resident macrophages, as well as vascular smooth muscle (but apparently not endothelium) are able to synthesize TNF-α (4, 9). Myocardial ischemia is sufficient to generate enough TNF-α, leading to myocardial dysfunction (12). Thus great care must be exercised upon reperfusion of ischemic myocardium, as TNF-α can trigger a positive feedback mechanism, which will initiate the systemic synthesis of TNF-α (10, 14) and compound the already compromised condition of the postischemic myocardium.

Zhang and colleagues explored the microvascular benefits of neutralizing TNF-α (via specific antibodies) before reperfusion, but after ischemia, in the mouse heart (4). These studies represent a continuation of Zhang’s laboratory efforts in elucidating and understanding the endothelial pathology initiated by TNF-α in the coronary microcirculation (3, 17). Administration of neutralizing anti-TNF-α antibodies contributed to partial restoration of NO-associated coronary vasodilation, confirming that TNF-α-induced microvascular dysfunction works via NO-associated signaling cascades. In addition, neutralizing anti-TNF-α led to a reduction in superoxide generation by inhibiting the activity of NAD(P)H oxidase and of xanthine oxidase. Importantly, administration of neutralizing anti-TNF-α antibodies before reperfusion reduced the expression of TNF-α mRNA in the postischemic mouse myocardium. This finding is significant as the TNF-α antibodies efficaciously broke a key step, the feedback mechanism of synthesis of TNF-α. Even though not tested in the study by Zhang’s laboratory, this strategy may also contribute to blocking remote organs or systemic synthesis of TNF-α.

Restoration of flow and function in postischemic organs is a challenge faced by vascular as well as cardiac and general surgeons in situations of nonelective surgery. For such cases, the strategy of administering antibodies before or at reperfusion appears to be quite attractive. In experimental models, administration of specific antibodies leads to successful results that ameliorate I/R damage in skeletal muscle (2), as well as in coronary arterioles (4). However, one must evaluate carefully the specific conditions in the translation of experimental findings to clinically relevant cases. We need to assess how well or how closely the experimental interventions, such as duration of ischemia, period of reperfusion, doses administered, potential secondary systemic effects of the antibodies or agents, etc., apply to patients. Because, as stated earlier, we do not know how much of the I/R damage is due to ischemia and how much is due to exacerbation of preexisting damage by reperfusion, it seems appropriate to suggest that the strategy of administering agents (such as specific antibodies) before or at the time of...
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reperfusion is likely to be beneficial, as such intervention would contribute to block or inhibit the synthesis or release of noxious metabolites upon reoxygenation by restoration of blood flow.

It is plausible that the outcome of TNF-α impact on function depends on its tissue concentration and on the tissue physiological state. The report by Zhang’s laboratory indicates that modulation of TNF-α by way of selective inhibition at reperfusion represents an attractive treatment modality when the tissue concentration of TNF-α is likely to be harmful. Indeed, the work of Zhang and colleagues (4) provides exciting evidence that should serve as a trigger for stimulating renewed interest in therapeutic approaches targeting TNF-α in myocardial I/R.

GRANTS

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REFERENCES


