

The balance between the production of tumor necrosis factor- α and interleukin-10 determines tissue injury and lethality during intestinal ischemia and reperfusion

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A major goal in the treatment of acute ischemia of a vascular territory is to restore blood flow to normal values, i.e. to "reperfuse" the ischemic vascular bed. However, reperfusion of ischemic tissues is associated with local and systemic leukocyte activation and trafficking, endothelial barrier dysfunction in postcapillary venules, enhanced production of inflammatory mediators and great lethality. This phenomenon has been referred to as "reperfusion injury" and several studies demonstrated that injury is dependent on neutrophil recruitment. Furthermore, ischemia and reperfusion injury is associated with the coordinated activation of a series of cytokines and adhesion molecules. Among the mediators of the inflammatory cascade released, TNF- α appears to play an essential role for the reperfusion-associated injury. On the other hand, the release of IL-10 modulates pro-inflammatory cytokine production and reperfusion-associated tissue injury. IL-1 β , PAF and bradykinin are mediators involved in ischemia and reperfusion injury by regulating the balance between TNF- α and IL-10 production. Strategies that enhance IL-10 and/or prevent TNF- α concentration may be useful as therapeutic adjuvants in the treatment of the tissue injury that follows ischemia and reperfusion.

Key words: inflammatory response - tumor necrosis factor- α - interleukin-10 - neutrophil - ischemia and reperfusion

Intestinal ischemia and reperfusion injury

Ischemia contributes to the pathophysiology of many conditions, including myocardial infarction, peripheral vascular insufficiency, stroke, and hypovolemic shock. Ischemia-reperfusion injury of the intestine is a significant problem in abdominal aortic aneurysm surgery, small bowel transplantation, cardiopulmonary bypass, strangulated hernias, and neonatal necrotizing enterocolitis (Collard & Gelman 2001). It can also occur as a consequence of collapse of the systemic circulation, as in hypovolemic and septic shock (Moore et al. 1994, Swank & Deitch 1996). It is associated with a high morbidity and mortality. Among the internal organs, the intestine is probably the most sensitive to ischemia and reperfusion injury (Granger et al. 1986). The intestine is composed of labile cells that are easily injured by episodes of ischemia. Subsequent reperfusion of the intestine results in further damage to the mucosa (Takeyoshi et al. 1996).

There is substantial evidence that the mucosa of the intestine becomes the site for the production of various acute-phase proteins (Molmenti et al. 1993, Wang et al. 1998), gut hormones (Zamir et al. 1992) and cytokines (Souza et al. 2000a, 2001). These not only influence the intestine but also may affect the function and integrity of distant organs (Schemeling et al. 1989, Souza et al. 2000a, b). The initial site of abnormality in ischemia has been

emphasized on the cellular mitochondria, which is particularly important in producing ATP for organ recovery (Jassem et al. 2002). The damage, however, is dramatically magnified by a large number of events, such as oxygen free radical formation, release of iron storage and damage of the microvasculature of organs (Carden & Granger 2000). Then, a major goal in the treatment of ischemia of a vascular territory is to restore blood flow to normal values, i.e. to "reperfuse" the ischemic vascular bed (Carden & Granger 2000). However, reperfusion of ischemic tissues is associated with local and systemic leukocyte activation and trafficking (specially neutrophil), endothelial barrier dysfunction in postcapillary venules, enhanced production of inflammatory mediators and great lethality (Lefer & Lefer 1996, Granger 1999, Carden & Granger 2000). This phenomenon has been referred to as "reperfusion injury" and several studies have demonstrated that injury is dependent on neutrophil recruitment (Jaeschke et al. 1990, Weight et al. 1996, Xiao et al. 1997, Kyriakides et al. 1999, Souza et al. 2000a, b, Baxter 2002, Kohtani et al. 2002, Merchant et al. 2003). Activated neutrophils contribute to tissue damage through several mechanisms: (i) release of free radicals following the respiratory burst of the NADPH oxidase system; (ii) release of proteolytic enzymes; (iii) stimulation of cytokine release from local cells, thus promoting further neutrophil recruitment and, finally (iv) plugging of capillaries by neutrophils contribute to the no-flow phenomenon (Ambrosio & Tritto 1999, Jordan et al. 1999, Vermeiren et al. 2000).

From the brief exposition above, it is clear that understanding the pathophysiology of the inflammation that occurs after reperfusion may be useful in the development of novel therapeutic strategies that limit the injury caused by the reperfusion process. Here, we review the

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role of cytokines, especially TNF- α and IL-10, that influence neutrophil recruitment and, consequently, lesions and lethality associated with ischemia and reperfusion injury.

The cytokine cascade

Ischemia and reperfusion injury is associated with the coordinated activation of a series of cytokines and adhesion molecules. A critical element in the regulation of these genes involves the complex formed by NF- κ B and I κ B. NF- κ B is activated by a vast number of agents, including cytokines (such TNF- α and IL-1 β) and free radicals. The genes regulated by the NF- κ B family of transcription factor are diverse and include those involved in the inflammatory response, cell adhesion and growth control. NF- κ B activation has been demonstrated in various models of experimental ischemia and reperfusion, including after intestinal ischemia and reperfusion (Chen et al. 2003, Zou et al. 2003). Additionally, Chen et al. (2003) demonstrated that inhibition of NF- κ B activation in intestinal epithelial cells prevented the increase in systemic TNF- α concentrations after intestinal ischemia and reperfusion.

In a model of reperfusion injury following a prolonged period of ischemia (120 min) of the superior mesenteric artery, there is a massive local, remote and systemic inflammatory response and significant lethality (Souza et al. 2000a, b, 2001, 2002a, b). Previous studies have shown an important role of TNF- α for reperfusion-induced tissue injury and lethality (Welborn et al. 1996, Carden & Granger 2000, Granger et al. 2001, Souza et al. 2001, 2002c, Yamamoto et al. 2001). Indeed, treatment of rats with anti-TNF antibodies prevented neutrophil influx, tissue injury and lethality after intestinal ischemia and reperfusion (Souza et al. 2001). In addition, in TSG-14 transgenic mice, a TNF- α -inducible protein, there is greater production of TNF- α and greater lethality as compared to their wild type counterparts (Souza et al. 2002c). The enhanced lethality correlated with greater and earlier TNF- α in serum and was blocked by treatment of animals with a soluble chimeric form of the TNF- α receptor, confirming the essential role of TNF- α for enhanced neutrophil influx, tissue injury and lethality in the experimental system (Souza et al. 2002c).

Although the studies above suggest that TNF- α is essential for neutrophils to migrate, we have also previously shown that the local influx of neutrophils plays an important role in the cascade of events leading to tissue, but not systemic, TNF- α production (Souza et al. 2000a, b, 2004a). As such, the blockade of neutrophil recruitment with a selectin inhibitor (fucoidin) or a CXCR2 antagonist (repertaxin) virtually abolished the TNF- α production in tissue. Interestingly, fucoidin treatment was capable of inhibiting reperfusion-induced neutrophil influx and tissue lesions, without decreasing systemic TNF- α and lethality (Souza et al. 2000a). On the other hand, repertaxin treatment inhibited inflammatory parameters in tissue, prevented the increase in the concentration of TNF- α in serum and lethality (Souza et al. 2004a). Indeed, systemic concentrations of TNF- α appear to be the best correlate of lethality in our system (Souza et al. 2001, 2002c). One unproven possibility to explain the difference between

these results, is that repertaxin, but not fucoidin, prevented the activation of circulating neutrophils and, consequent, systemic production of TNF- α and TNF- α -dependent lethality.

It is difficult to reconcile the observation that in one hand TNF- α is essential for neutrophils to occur with the observation that neutrophils are essential for tissue TNF- α production. One possibility to explain these findings stems from the work of Frangogiannis et al. (2002) who showed that mast cells are an important early source of TNF- α during ischemia and reperfusion. In this regard, an initial tissue release of TNF- α , possibly mast cell-derived, may be essential and sufficient for an early wave of neutrophil influx to occur. An amplification circuit is then installed in which neutrophil influx facilitates TNF- α production and TNF- α production facilitates neutrophil influx (Souza et al. 2001, 2002c). Pharmacological strategies which modulate this amplification circuit may be of interest for the treatment of ischemia and reperfusion injury.

Several studies have now demonstrated that IL-10 modulates pro-inflammatory cytokine production and tissue injury following ischemia and reperfusion injury (Lane et al. 1997, Frangogiannis et al. 2000, 2002, Zingarelli et al. 2001, Souza et al. 2003a). For example, studies in IL-10-deficient mice suggested that endogenous IL-10 exerted anti-inflammatory role during reperfusion injury, possibly by regulating an early stress genetic response (c-Jun kinase activation), neutrophil influx and cytokine production (Zingarelli et al. 2001). Exogenous administration of IL-10 reduced the systemic inflammatory response in a rodent model of intestinal reperfusion injury, an effect associated with inhibition of cytokine production and neutrophil accumulation (Lane et al. 1997, Souza et al. 2003a, 2004c). Moreover, treatment with anti-IL-10 was associated with increased TNF- α concentration, tissue injury and lethality, demonstrating a role for endogenous production of IL-10 in modulating exacerbated tissue pathology and lethality (Souza et al. 2003a). Additionally, IL-10 appears to be involved with preconditioning. Oreopoulos et al. (2004) showed that hypertonic saline pretreatment prevented liver enzyme release concomitant with a reduction in liver neutrophil sequestration. This effect appeared to be secondary to inhibition of TNF- α generation and enhancement of IL-10 expression. Most importantly, in IL-10 knockout animals, hypertonic saline pretreatment was unable to prevent the liver enzyme release, TNF- α generation, or neutrophil sequestration induced by liver ischemia and reperfusion (Oreopoulos et al. 2004).

From the discussion above, it is clear that strategies which favor IL-10 production and/or prevent TNF- α production or function are effective at preventing reperfusion-induced tissue injury and lethality. As it will be discussed below, several mediators of the inflammatory process impart on the reperfusion process by affecting the balance between TNF- α and IL-10.

Interleukin (IL)-1 β

As IL-1 β may be involved in the induction of TNF- α during acute and chronic inflammatory conditions, we assessed the ability of IL-1 β to modulate TNF- α production, tissue injury and lethality during intestinal ischemia

and reperfusion injury (Souza et al. 2003a). Two strategies were used to block the action of IL-1 β - neutralization of the protein with anti-IL-1 antiserum and administration of IL-1ra, a natural antagonist of IL-1 receptors. Our results clearly showed that the use of both strategies were associated with an overall enhancement of tissue injury, pro-inflammatory cytokine expression and lethality. These were surprising results as previous studies have suggested a role for IL-1 β during models of less severe ischemia and reperfusion injury (Welborn et al. 1996, Shito et al. 1997, Suzuki et al. 2001, Yamamoto et al. 2001). Interestingly, neutralization and/or antagonism of IL-1 β were associated with a marked prevention of the reperfusion-induced increase of IL-10 (Souza et al. 2003a). The latter results suggest that IL-1 β is a major inducer of IL-10 during severe intestinal ischemia and reperfusion injury. On the other hand, administration of anti-IL-1ra, which antagonizes endogenous IL-1ra, and exogenous administration of recombinant IL-1 β suppressed tissue pathology, increased pro-inflammatory cytokines and lethality that followed reperfusion of the ischemic superior mesenteric artery. Of note, there was a marked inhibition of the elevation of TNF- α levels in tissue and serum and enhancement of tissue and serum concentrations of IL-10 (Souza et al. 2003a). One possibility to explain the inhibitory effects of IL-1 β in our system was raised by the demonstration that endogenous or exogenous IL-1 β modulated the production of IL-10. This possibility was proven by demonstration that anti-IL-10 reversed the protective effects of IL-1 β on reperfusion-associated lethality. Thus, in the present model of intestinal ischemia and reperfusion injury, IL-1 β appeared to be a major inducer of IL-10 production and modulated tissue injury and lethality in an IL-10-dependent manner.

Platelet-activating factor

Among the mediators of the inflammatory cascade released and thought to be important for the reperfusion-associated injury is platelet-activating factor (PAF) (Kubes et al. 1990 a, b, Montrucchio et al. 2000, Souza et al. 2000a). The latter results are consistent with the ability of PAF to induce TNF- α production (Buke et al. 2004, Seo et al. 2004). To ascertain the role PAF in modulating the cascade of cytokines following ischemia and reperfusion we evaluated tissue injury and lethality in PAFR^{-/-} mice and their wild-type controls (Souza et al. 2003c). There was no increase in vascular permeability, neutrophil accumulation and haemorrhage in the intestine and lungs of reperfused PAFR^{-/-} mice. These results were in agreement with other studies using PAFR antagonists that demonstrated a role for PAFR in models of ischemia and reperfusion injury in several other vascular territories, including the heart, gut, kidney and lung (Canale et al. 1994, Carter et al. 1996, Riera et al. 1997, Qayumi et al. 1998, Morgan et al. 1999, Kecskemeti & Balogh 2000, Kim et al. 2000, Sun et al. 2001, 2002). In PAFR^{-/-} mice, the reperfusion-associated increases in serum concentration of TNF- α were significantly suppressed and this was associated with an increase in the concentrations of IL-10. Additionally, there was a significant delay in reperfusion-associated lethality in PAFR^{-/-} mice (Souza et al. 2003c). These results

strongly corroborate the role of PAFR during ischemia and reperfusion injury. In addition, the pharmacological antagonism of PAFR prevented tissue injury and lethality, as observed in PAFR^{-/-} mice. Similarly to the observations in PAFR^{-/-} mice, the inhibition of reperfusion-associated increases in serum TNF- α concentration and lethality was associated with an enhanced production of IL-10 in animals treated with PAFR antagonists (Souza et al. 2003c). Overall, the results demonstrate a role for PAFR during ischemia and reperfusion and support our hypothesis that the role of this receptor may be secondary to its ability to modulate the reperfusion-associated TNF- α /IL-10 balance.

Kallikrein-kinin system

As ischemia and reperfusion injury is a process which occurs very acutely, it is likely that mediators which can be rapidly generated, such as those derived from the kallikrein-kinin system, may participate in the initial events that lead to cytokine production and reperfusion injury. After intestinal ischemia and reperfusion, the activity of tissue kallikrein in the duodenum and lung was greatly enhanced (Souza et al. 2003b). More importantly, the *in vivo* treatment with a tissue kallikrein-specific inhibitor was accompanied by marked inhibition of the reperfusion injury (Souza et al. 2003b). Thus, in this system there is activation of tissue kallikrein, which is functionally relevant for reperfusion-associated injury. Additionally, the pretreatment with B₂ receptor antagonist markedly inhibited inflammatory response (Souza et al. 2003b, 2004b). The inhibitory effects of B₂ receptor antagonists are in line with previous studies demonstrating the capacity of this class of drugs to suppress leukocyte recruitment and activation in acute models of inflammation (eg. Abraham et al. 1991, Bandeira-Melo et al. 1999, Perron et al. 1999). Interestingly, our studies clearly demonstrated that the blockade of B₂ receptors was accompanied by virtual abolishment of TNF- α production and, conversely, enhancement of IL-10 in tissues of reperfused animals (Souza et al. 2003b, 2004b). Thus, it is clear that B₂ receptor activation plays an important role in the cascade of events leading to local (intestine), remote (lungs) and systemic injury following intestinal ischemia and reperfusion. The mechanisms by which B₂ receptor activation facilitates inflammatory injury appears to be multiple, including the direct induction of leukocyte migration and degranulation, and the induction of the secondary release of pro-inflammatory mediators, such as cytokines and PAF (Koyama et al. 1998, 2000, Calixto et al. 2000). One interesting possibility to explain the effects of bradykinin acting on B₂ receptors in the system is that this mediator may activate sensory nerves to release neuropeptides and potentiate the inflammatory response further (Averbeck & Reeh 2001, Madeddu et al. 2001). We have previously shown that neuropeptides acting via NK1 receptors are important for intestinal ischemia and reperfusion injury (Souza et al. 2002a).

Several studies have now shown that B₂ receptor activation or B₂-induced mediators released (eg. TNF- α) may enhance B₁ receptor expression during inflammatory re-

ogenous IL-10 to prevent lethality and tissue injury was clearly correlated with the concentrations of local or systemic TNF- α . It is interesting to note that the innate ability of germ-free to produce IL-10 and, possibly, other molecules, was an active process that prevented the inflammatory phenotype, ie. animals not exposed to an intestinal microbiota have an innate ability to produce molecules with anti-inflammatory properties that suppress the development of an inflammatory response (Souza et al. 2004c).

Mice that have a normal intestinal microbiota are capable of responding to inflammatory stimulation, suggesting that the presence of microorganisms in the gut induce a "state of alert" that is characterized by the loss of the innate ability to produce IL-10 and, possibly, other molecules (e.g. TGF- β). Recently, we have observed that the greater ability of germ-free mice to produce lipoxins and annexin-1 appears to underlie their greater capacity to produce IL-10 and to prevent acute inflammation (DG Souza, MM Teixeira, unpublished data). Studies are now in progress to examine the fundamental question as to why germ free mice produce more antiinflammatory molecules that lead to IL-10 production which, in turn, prevents inflammation.

Concluding remarks

The restoration of blood flow, ie. reperfusion, is the treatment of choice to save viable tissue following acute ischemia of a vascular territory. Nevertheless, reperfusion of ischemic tissues can be accompanied by significant local, remote and systemic inflammatory events that may limit the beneficial effects of blood flow restoration. Experimental evidences reviewed by this article showed an important role for TNF- α in amplifying reperfusion injury. On the other hand, this amplification process is suppressed by IL-10, which is produced as an endogenous brake for the process. Thus, strategies that enhance IL-10 and/or prevent TNF- α concentration may be used as therapeutic adjuvants in the treatment of the tissue injury that follows ischaemia and reperfusion.

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