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PATHOPHYSIOLOGIC ROLE OF SELECTINS AND THEIR LIGANDS IN ISCHEMIA REPERFUSION INJURY

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1. ABSTRACT

Research findings are unveiling the potential role of leukocytes and leukocyte adhesion molecules such as selectins in ischemia-reperfusion injury (IRI). "Anti-adhesion" therapy using selectin blocking agents may represent a new approach to treatment of the many diverse clinical disorders in which ischemia-reperfusion occurs, including transplantation, reperfusion after thrombotic events and shock. In this paper we review the pathophysiology of IRI, the different types of selectins and selectin ligands, the clinical implications of selectin blockade in different organs with IRI, and new insights into mechanism of action.

2. INTRODUCTION

Recent developments in immunology and cell biology have demonstrated the importance of inflammation in the pathogenesis of post-ischemic organ dysfunction. Whereas prolonged ischemia causes anoxic cell death, recent evidence suggests that sublethal injury may be amplified by inflammatory and cytotoxic injury cascades activated during the reperfusion period.

Ischemia is a state of tissue oxygen deprivation accompanied by a reduced washout of the resulting metabolites (1). Reperfusion is the restoration of blood flow to the ischemic tissue. Despite the unequivocal benefit of reperfusion of blood to an ischemic tissue, reperfusion itself can elicit a cascade of adverse reactions that paradoxically injure tissue (2). Indeed, reperfusion injury has been well described in the literature to cause organ damage in the brain, heart, lungs, liver, kidneys and skeletal muscle. The susceptibility of tissue to ischemia reperfusion injury (IRI) is a major obstacle to both reperfusion after an infarct and successful organ transplantation.

The incidence and implications of ischemic injury are enormous: ischemia occurs in myocardial infarction, stroke, organ procurement injury, and many other situations. In 1995, ischemic cardiovascular events alone were the diagnosis in 5 million (16.2%) hospital patient discharge records and were the leading cause of death in the United States (38.7%) (3).

A growing body of evidence, primarily from animal models of IRI and preliminary human studies has revealed that inflammatory mechanisms play a major role in the pathogenesis of IRI. Interest in the inflammatory response to IRI has led to the identification of multiple inflammatory mediators, including leukocytes, leukocyte adhesion molecules and cytokines.

In the following review we will focus on the pathophysiology of ischemia-reperfusion, the role of leukocytes in the post-ischemic inflammatory cascade, and the crucial role of the selectin family and their ligands in mediating leukocyte induced post-ischemic injury.

3. PATHOPHYSIOLOGY OF ISCHEMIA-REPERFUSION INJURY

The pathophysiology of the IRI is complex. The inflammatory aspect of IRI includes both the cellular and humoral components (Figure 1). Moreover, mechanisms of IRI may be organ-dependent, with similar but distinct pathways involved in different organs. During the last decade there has been an explosion of research

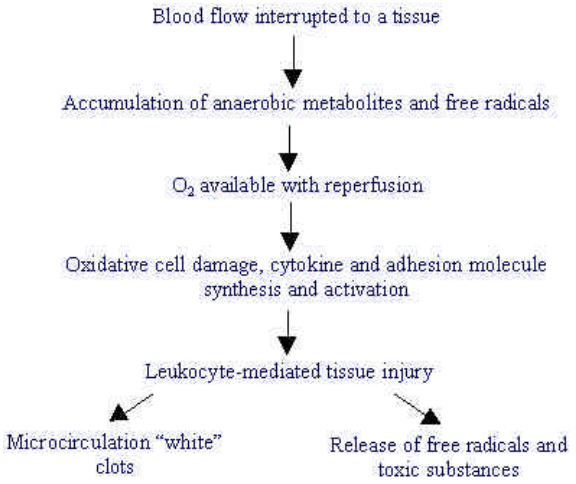

Figure 1. Proposed inflammatory cascade in ischemia-reperfusion injury.

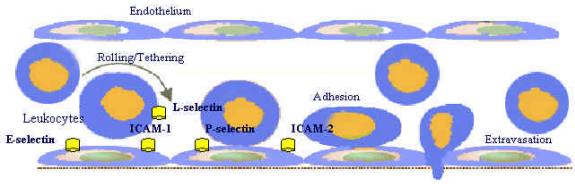

Figure 2. Current model of leukocyte migration to inflammed tissue.

documenting the role of leukocytes and leukocyte adhesion molecules in IRI (4). Multiple mechanisms have been postulated for the leukocyte-mediated tissue injury that occurs after ischemia-reperfusion. Microvascular occlusion (5), release of oxygen free radical (6), cytotoxic enzyme release (7), increased vascular permeability (8) and increased cytokine release (9) have all been demonstrated to contribute to leukocyte-induced tissue injury.

Leukocyte adhesion molecules (LAMs) are expressed on leukocytes and other cell types and regulate many leukocyte functions. LAMs function in various biological processes such as development, signaling, inflammation and apoptosis. There currently exists a multi-step paradigm of leukocyte emigration to inflamed tissue that involves specific leukocyte adhesion molecules (Figure 2). To emigrate into tissue, leukocytes initially tether to and roll on the vascular endothelium. This relatively loose adhesion is mediated by the selectin family of adhesion molecules and their ligands (10-12). Subsequent activation of leukocytes and the endothelium leads to firmer adhesion mediated through integrin adhesion molecules (e.g., CD18) and their receptors (e.g., intercellular adhesion molecule-1, ICAM-1). Leukocyte transmigration is the final stage and occurs between endothelial cells. Leukocytes then travel through the extracellular matrix to the source of tissue injury, guided by a concentration gradient of cytokines and chemokines produced at the site of injury.

Because selectin engagement of leukocytes precedes CD11/CD18 binding to ICAM-1, targeting selectins is an attractive way to block inflammation at an even earlier step. In addition, selectin blockade might cause less susceptibility to bacterial infections than does CD11/CD18 blockade (13).

3.1. SELECTINS

The selectin family of leukocyte adhesion molecules consists of three known members: L-, P-, and E-selectin (table 1). These molecules are involved in the initial adhesion of leukocytes to activated endothelium at a site of tissue injury (14-19). L-selectin is a cell surface glycoprotein expressed constitutively on a wide variety of leukocytes (15). L-selectin plays a role in the emigration of lymphocytes into peripheral lymph nodes and sites of chronic inflammation and of neutrophils into acute inflammatory sites. P-selectin is a cell surface glycoprotein that also plays a critical role in the emigration of leukocytes into tissues (17). P-selectin is constitutively stored in the Weibel-Palade bodies of endothelial cells and in the alpha granules of platelets. It is expressed on the cell surface within minutes after exposure to stimuli such as thrombin. E-selectin expression is largely restricted to endothelial cells activated by different stimuli such as endotoxin and the pro-inflammatory cytokines interleukin-1 (IL-1) and tumor necrosis factor (TNF) (19). E-selectin expression peaks within 4-8 hours of tissue injury and returns to baseline by 24 hours (16). E-selectin expression, as with P-selectins, requires *de novo* messenger RNA and protein synthesis, and involves the translocation of the transcription factor NF-kappaB onto nuclear promoter sites (20).

In the first 10-20 minutes after tissue injury, leukocyte rolling on the vascular endothelium is mainly mediated by P-selectin, with minimal L-selectin contribution (14). This is consistent with the rapid mobilization of P-selectin from intracellular stores after tissue injury. After approximately 20 minutes, the role of P-selectin diminishes secondary to internal degradation, and L-selectin becomes the principal mediator of leukocyte rolling. There is little appreciable role for E-selectin in leukocyte rolling during the early response (<2 hrs) to tissue injury. While E-selectin expression on stimulated endothelial surfaces is detectable at 2 hrs after injury, the delay in peak surface expression precludes the contribution of E-selectin to the early rolling and leukocyte recruitment in acute inflammation. Rather, initial interactions between leukocytes and the vascular endothelium, mediated via P- and L-selectins, are followed by a stronger interactions, probably involving E-selectin and subsequently integrins, that lead eventually to extravasation through the blood vessel wall into lymphoid tissues and to sites of inflammation (16).

3.2. Selectin ligands

While initial studies suggested that all three selectins recognize carbohydratescontaining the sialyl Lewis x antigen (NeuAcα2→3Galß1→4[Fucα1→3] GlcNAcß1→R) (sialy vl Le^x), however, recent studies have now shown that each selectin demonstrates higher affinity binding to specific macromolecular ligands expressing

Table 1. Structure and expression of selectins

Selectin	Expressing Cells	Ligands	Expression	Structure
L-selectin	Leukocytes	Sialylated Lewis X	Constituent of cellular surfaces	NH2=L=E=CC==COOH .
P-selectin	Platelet & Endothelium	PSGL-1, sialylated Lewis X	Constituent of cellular surface & induced	NH2=L=E=CC==COOH .
E-selectin	Endothelium	ESGL-1, PSGL-1, sialylated Lewis X	Induced	NH2=L=E=CC==COOH .

PSGL-1 = platelet selectin glycoprotein ligand; ESGL-1 = endothelial selectin glycoprotein ligand; L= lectin; E= Epidermal growth factor-like molecule; C= Complement-binding protein-like.

sialylated and fucosylated glycans. To date the best characterized cell adhesion ligand for selectins is the P-selectin glycoprotein ligand-1 (PSGL-1). Although PSGL-1 is expressed on the membrane surfaces of all leukocytes, with respect to binding of P-selectin, it is only functional on granulocytes and subclasses of lymphocytes. Interestingly, PSGL-1 may also serve as a ligand for both E- and L-selectin (21).

Treatment of purified PSGL-1 with sialidase abolishes its binding to P-selectin, confirming cell studies that indicate a role for sialic acid in P-selectin recognition (22,23). Interestingly, treatment of neutrophil-derived PSGL-1 with peptide N-glycosidase F, which removes most of the N-glycans of the molecule, does not affect its recognition by P-selectin, suggesting that O-glycans, but not N-glycans, are important determinants of selectin binding (22). PSGL-1 may also be an important signaling molecule in neutrophils. Upon activation of polymorphonuclear leukocytes there is a redistribution of PSGL-1 resulting in a lowering of affinity of activated cells for P-selectin (23). Incubation of neutrophils with either P-selectin or the monoclonal antibody PL1 to PSGL-1 stimulates tyrosine phosphorylation of several proteins and production of IL-8 (24).

In vivo approaches to studying the importance of glycans in selectin ligand function have recently provided exciting new insights and have partly confirmed predictions about the importance of sialyl Le^x and core-2 O-glycans for PSGL-1 recognition by P-selectin. Neutrophils from null mice lacking the myeloid enzyme fucosyltransferase VII bind poorly to P-, E- or L-selectin, and neutrophil efflux in experimentally induced inflammation in such mice is dramatically reduced (25). Another approach to studying PSGL-1 function during *in vivo* inflammation has been to explore its role in ischemia/reperfusion injury models, in which blood flow is blocked and subsequently restored, thereby stimulating P-selectin expression by endothelial cells. In a rat model of hepatic ischemia/reperfusion injury (26), animals treated with 100 µg of recombinant PSGL-1 had significantly enhanced recovery of liver function and higher survival. PSGL-1 may also be important for lymphocyte recruitment to sites of inflammation *in vivo*, since intravenous administration of antibodies to the extreme N-terminus of mouse PSGL-1 blocks migration of Th1 T-lymphocytes into skin undergoing cutaneous delayed-type hypersensitivity reactions (27).

While all three selectins can bind to simple glycans containing the sialyl Le^x determinant, as demonstrated for P-selectin and PSGL-1, such binding is relatively weak and macromolecular ligands bind with higher affinity. Although several glycoproteins are recognized by L- and E-selectin, whether these ligands serve physiologically to support selectin-mediated cell adhesion is still not clear. Interestingly, evidence is accumulating that indicates that PSGL-1 may be a physiological ligand for L-selectin and may participate in some E-selectin-dependent adhesion.

4. CLINICAL IMPLICATIONS

Adhesion molecules are vital for the physiological processes of leukocyte trafficking and are critically involved in the enhanced leukocyte emigration that is a key feature of all inflammatory and immune diseases. The studies on selectins and their ligands have yielded an insight to potential therapies for many diseases. Indeed, interference with selectin function is an attractive way to potentially block inflammation at a very early step. Although most intervention studies to date have been performed in animal models, human studies also have indicated a significant role for selectins and their ligands in the inflammatory response. In the following section we review select studies demonstrating a role for selectins in inflammatory injury in different organs.

4.1. Brain

Human studies have shown increased selectin levels in ventricular cerebrospinal fluid (CSF) from children with severe traumatic brain injury (Glasgow coma score < 8) (28) and in patients with relapsing-remitting multiple sclerosis (29). Middle cerebral artery occlusion in non-human primates is associated with upregulation of E-selectin (30). Selectins are also thought to contribute to tissue injury in stroke. In multiple murine models of stroke, the use of selectin ligands to block selectin function has reduced infarct size (31-33) (Table 2).

4.2. Heart

Leukocyte adhesion to damaged endothelium is enhanced in the presence of platelets by a mechanism involving platelet P-selectin. Thrombus formation may also be enhanced by this interaction. In human studies, P-selectin levels were shown to be significantly increased in plasma in patients with acute myocardial infarct (34). The use of a selectin blocker (CY-1503), an analogue of sialyl Lewis X selectin ligand, inhibited leukocyte and platelet interaction after arterial injury produced by angioplasty in pigs (35). Other studies have shown that the selectin blocker fucoidin provides cardioprotection in rats and dogs with coronary artery occlusion (36). These promising results may be the precursors of clinical trials of selectin blockers in humans (Table 3).

Table 2. Selectin studies in brain

Specie	Selectin measured/targeted	Intervention	Injury/Model	Results	Ref
Human	P-selectin, E-selectin, L-selectin		Traumatic brain injury	P-selectin was increased	28
Human	L-selectin		Relapsing-remitting multiple sclerosis	Increase in soluble L-selectin	29
Non-human primate	E-selectin		Middle cerebral artery occlusion	E-selectin significantly upregulated	30
		sLex-glycosylated complement inhibitory protein	Stroke	Reduced cerebral infarct volumes.	31
Rats	E-selectin	Synthetic oligopeptide corresponding to lectin domain of selectin.	Transient cerebral ischemia	Decreases the size of ischemic injury.	32
Rats	P-selectin, E-selectin	tPA and anti-ICAM-1	Middle cerebral artery occlusion	Significant reduction in stroke volume	33

4.3 Kidneys

Unlike in heart and muscle, L-selectin alone does not appear to mediate leukocyte recruitment to postischemic kidney (37). P-selectin, however, is upregulated in renal ischemia-reperfusion injury (38). Initial results with P-selectin antibody were protective in rats post renal ischemia (39). A soluble P-selectin glycoprotein ligand, which blocks P and E-selectins, has been shown to decrease renal injury secondary to ischemia-reperfusion in mice models (40). Blocking initial selectin-mediated events that accompany renal ischemia-reperfusion has also been shown to reduce late renal dysfunction and tissue damage (41). Thus, selectin blockade might be a potential therapeutic intervention in the transplantation of kidneys from non-heart-beating donors and in kidneys subjected to prolonged ischemic times. Recently small molecule blockade of selectin ligands substantially reduced renal injury and improved mortality in rats. Interestingly, this occurred independent of neutrophils infiltration (42) (Table 4).

4.4. Lungs

In a sheep model of ischemia-reperfusion, antibodies directed against both L- and E-selectin significantly reduced pulmonary leakage and neutrophil accumulation (43). In a lung transplant model, anti-E- and anti-L-selectin antibodies improved post-transplant pulmonary function tests (44). Similarly, an analog of sialyl lewis X was found to reduce allograft rejection and reperfusion injury in a lung transplant model (45) (Table 5).

4.5. Liver

Studies of selectin involvement in liver ischemia-reperfusion injury have focused primarily on P-selectin and its ligands. Rat studies have shown that P-selectin is the primary determinant of leukocyte adhesion to endothelial cells (46). Other studies have shown reduced liver injury and improved survival in rats treated with anti P-selectin antibodies during hepatic ischemia-reperfusion injury produced by uncontrolled hemorrhagic shock (47) (Table 6).

5. NOVEL PERSPECTIVES

There is now ample evidence that selectins are important mediators of ischemia-reperfusion injury in a number of different organs. Recent data also suggest that targeting selectin ligands may be a valuable therapeutic approach in the treatment of ischemia-reperfusion injury. The mechanisms underlying the protective effect of selectin antagonism in organ ischemia-reperfusion appear to be more complex than merely reducing neutrophil migration into reperfused tissue. Indeed, recent studies have suggested that blocking leukocyte adhesion molecules, including selectins, can protect against inflammatory injury independent of blocking tissue leukocyte infiltration. Interfering with the leukocyte adhesion molecule very late antigen-4 (VLA-4) on eosinophils and lymphocytes was found to attenuate late airway responses in an asthma model despite little effect on the migration of leukocytes into airway tissues (48).

It is possible that selectin antagonism may exert a protective effect during ischemia-reperfusion by interfering with cell signaling. Intriguingly, it has recently been reported that administration of glycyrrhizin, a licorice plant (*Glycyrrhiza radix*) derivative, decreased renal ischemia-reperfusion injury in a rabbit model (49). Moreover, the authors proposed that the protective effect of glycyrrhizin was due to selectin antagonism, which has been reported for glycyrrhizin (50). Glycyrrhizin inhibits 11β-hydroxysteroid dehydrogenase, the enzyme that converts cortisol to cortisone. Thus, could the protective role of selectin blockade in organ ischemia-reperfusion injury be somehow related to modulation of glucocorticoid activity?

It is clear that further investigation is warranted to elucidate the mechanisms by selectins mediate ischemia-reperfusion injury, beyond simply promoting leukocyte recruitment. In addition, given the ample evidence that now exists regarding efficacy of selectin antagonism in treating

Table 3. Selectin studies in Heart

Specie	Selectin measured/targeted	Intervention	Injury/Model	Results	Ref
Human	P-selectin		Coronary recanalization therapy after AMI.	P-selectin significantly higher in AMI than in stable angina pectoris.	34
Pigs	P-selectin	CY-1503	Arterial injury by angioplasty	CY-1503 reduced neutrophil adhesion but not platelets.	35
Rats		Fucoidin	No-flow ischemia to rats hearts.	Fucoidin significantly reduced leukocyte accumulation in capillaries and venules	36

Table 4. Selectin studies in Kidneys

Specie	Selectin measured/targeted	Intervention	Injury/Model	Results	Ref
Rats		P-selectin antibody	Renal artery cross-clamping for 60 min.	Role for P-selectin in renal ischemic injury.	39
Mice		P-selectin-deficient mice.	Renal artery cross-clamping.	Mice protected from I/R injury.	40
Rats		Soluble ligand for P- and E-selectin.	Clamping of renal pedicle 45 min.	Function and structure remained at relative baseline.	41

Table 5. Selectin studies in Lungs

Specie	Selectin measured/targeted	Intervention	Injury/Model	Results	Ref
Sheep	L-selectin	Anti-L-selectin (EL-246)	Infrarenal aortic ischemia (3h) followed by reperfusion.	Significant reduction in pulmonary leakage by 59% and neutrophil accumulation by 84%	43
Sheep	L- and E-selectins	L- and E-selectins antibody	Left lung autotransplant	Improved pulmonary function tests..	44
Rats	P-selectin	Analog of Sialyl-Lewis X (SLX).	Lung transplant.	Reduction in allograft rejection and reperfusion injury.	45

Table 6. Selectin studies in Liver

Specie	Selectin measured/targeted	Intervention	Injury/Model	Results	Ref
Mice	P-selectin		Left hepatic lobe ischemia for 30 min	P-selectin is the primary determinant of leukocyte-endothelial cell adhesion	46
Rats		P-selectin antibody	Uncontrolled hemorrhagic shock	Decreased hepatocellular injury and increased survival	47
Rats		PSGL-1	Cold ischemia	Significant increase in liver isograft survival	26

organ ischemia-reperfusion injury, clinical trials are justified to translate these basic research findings to clinical utility. However, there are crucial questions to be answered before any human clinical trials, including: (1) What are the effects of selectin interventions on the immune system?, and (2) Is it possible to selectively block just the detrimental effects of leukocyte adhesion molecules without leaving an individual immunocompromised?

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