ICAM-1: role in inflammation and in the regulation of vascular permeability

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the endothelium is a semipermeable barrier that regulates the exchange between blood and peripheral tissues. The regulation of vascular permeability is an essential and critical function that is effectively carried out by the endothelium (12). This function is important since endothelial cells will regulate or prevent the specific infiltration of molecules and cells into organs such as the brain. Vascular permeability has been shown to be affected in a number of disease states such as cancer and atherosclerosis as well as in infections. Molecules can be transported via two major pathways across the endothelium. They can be transferred from the lumen of blood vessels via a pathway termed transcytosis. This pathway allows the transfer of molecules across endothelial cells and has been shown to be regulated by caveolae (4, 15). In addition, transport across the endothelium can occur via a paracellular pathway that involves the transport of molecules between endothelial cells (15). Both transport modes have been shown to involve complex signaling pathways (10).

In normal tissues, microvascular permeability is usually a function of the radius of the molecules to be transferred (11). Molecules of the diameter of albumin or smaller are usually transferred via a paracellular pathway. Under basal conditions, larger molecules cannot be transferred via this system but are transferred via a transcytotic pathway involving the cellular component caveolae (4). Increased microvascular permeability can be observed acutely or chronically in inflamed tissues. In response to proinflammatory signals, the modification of interendothelial junctions is observed. In that case, proteins involved in the formation of tight junctions will regulate the permeability for a given macromolecule. Modifications of plasma membrane proteins as well as a reorganization of cytoskeletal and filament proteins will eventually be responsible for the modification of endothelium permeability. These changes have been shown to be mediated by protein kinase C (PKC) activation and via tyrosine-kinase-regulated pathways (9, 10).

Vascular adhesion molecules have been shown to play an important role in atherosclerosis (5) and have also been proposed to play important roles in cancer (8). TNF-α has been shown to play an important function in the initiation of inflammation (14). The TNF-α signaling pathway is mediated by NF-κB and is responsible for the expression of adhesion molecules such as VCAM-1 and ICAM-1 in the endothelium (1). TNF-α was previously shown to induce ICAM-1 expression (2), possibly via PKC-ζ (7). These adhesion molecules allow the attachment of leukocytes to the endothelium and may permit their subsequent transmigration into peripheral tissue. At the same time, microvascular permeability is increased.

Intravital microscopy has been a tool of choice to study the modifications of vascular permeability. It is an in vivo technique that allows for the measurement of small vascular permeability changes with the use of fluorescently labeled albumin as a molecule undergoing transport from the blood vessel to peripheral tissues (6).

In their paper, Sumagin et al. (16) have examined the role of ICAM-1 and the possible role of a leukocyte-endothelium interaction in the regulation of vascular permeability. During inflammation development, two major events occur. Leukocytes will interact with the endothelium in a process that will allow these cells to cross the barrier created by endothelial cells. This cellular migration will result in modifications of the vascular permeability that will permit the transfer of solutes to peripheral tissues. Sumagin et al. (16) show that both arterioles and venules can respond to a proinflammatory stimulus. In addition, their data also demonstrate that, under basal conditions, vascular permeability alterations are linked to ICAM-1 expression in a PKC-dependent manner. Increased vascular permeability usually observed with TNF-α is ablated in ICAM-1-deficient mice and is dependent on a Src-related kinase signaling pathway.

Taken together, these data suggest that there is a change in the mode of transport of albumin during inflammation and that its movement is highly influenced by ICAM-1. Under basal conditions, albumin is mainly transcytosed via caveolae, across endothelial cells. However, upon ICAM-1 activation via leukocyte binding, the modification of cytoskeletal proteins and/or tight junction proteins lead to a redirection of albumin transport to peripheral tissues via a paracellular pathway.

These findings imply that increased ICAM-1 expression in tumors could play an important role during cancer development as it has been suggested (3). In vascular disease such as atherosclerosis, the same observation could be made. In that case, it was shown that ICAM-1 is upregulated sites prone to atherosclerosis development (13). Therefore, regulating the inflammation process and ICAM-1 function could open a new avenue for the treatment of these illnesses.

GRANTS

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