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VASCULAR-MESENCHYMAL CHANGES AS THE MAIN LINK IN THE INFLAMMATORY PROCESS

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Abstract
Inflammation is a highly dynamic process. After just 4 hours, changes begin to occur in the inflammatory infiltrate and vascular bed: the number of neutrophils decreases and the number of mononuclear cells, mainly monocytes and lymphocytes, increases. These changes correlate with a change in the phenotype of adhesive molecules expressed by endothelial cells.

Keywords: Inflammation, cytokines, expression, cells, molecule, synthesis.

Introduction

Thus, 6-8 hours after the action of inflammatory cytokines, the expression of E-selectin (ELAM-1) begins to decrease due to both a reduction in its synthesis and an intensification of internalisation and degradation processes. ICAM-1 synthesis, on the contrary, constantly increases and reaches a stable level of expression 24 hours after the onset of inflammation. Parallel to the increase in ICAM-1 expression, another adhesive molecule, VCAM-1, appears on the surface of endothelial cells, which, like ICAM-1 and ICAM-2, belongs to the immunoglobulin superfamily. The ligand for VCAM-1 is a molecule of the beta-1 integrin family, VLA-4, which is expressed on mononuclear leukocytes but not on neutrophils. T lymphocytes migrating to the site of inflammation are memory cells, i.e. cells that have been previously stimulated by an antigen. Along with VLA-4, they express another adhesive molecule, CD44, which also mediates the binding of memory T cells to the endothelium. Similar to neutrophils, T cells appear in response to IL-8, which enhances the interaction of CD11aalpha\CD18 (LFA-1) with ICAM-1.

Unlike lymphocytes, monocytes appear later in the site of inflammation. Monocytes are insensitive to IL-8, but respond to the product of the human JE gene or monocyte chemotactic protein (MCP-1). IL-1 and TNF-α stimulate endothelial cells to synthesise JE\MCP-1. Activated monocytes express beta-1 (VLA-4) and beta-2 (LFA-1, Mac-1) integrin molecules on their surface, which bind to ICAM-1 and VCAM-1. IL-1 and TNF-α serve as activators of adhesive molecule expression on both leukocytes and endothelial cells in this process. In addition to these cytokines, IFN-γ is produced in the site of expression. It enhances ICAM-1 expression, especially

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webofjournals.com/index.php/5

in the late stages of inflammation (24-72 hours), induces JE\MCP-1 production, and increases the ability of TNF-α to induce ELAM-1 and ICAM-1 expression on endothelial cells.

During migration, as in the adhesion process, interaction between leukocytes and the endothelium is also observed. Although leukocytes are capable of synthesising enzymes that destroy the basement membrane, endothelial cells also contribute to increasing the permeability of the barrier. Cytokines such as IL-1, TNF-α, IFN-γ, and TGF-β alter the protease/antiprotease balance, leading to damage to the proteins of the basement membrane by the enzymatic system of endothelial cells.

The strengthening or weakening of the expression of various cytokines and adhesive molecules has a temporal dependence that regulates the evolution of the inflammatory process. Changes in the avidity of some adhesive molecules, the appearance or disappearance of others, and the synthesis and production of various mediators lead to the migration of certain cell pools at different time intervals.

Burns in the area of thermal damage cause the formation of large amounts of biologically highly active substances, known as mediators (Yeo-Kyu Youn et al., 1992), which trigger local vascular-mesenchymal changes that are the essence of inflammation. These include histamine, serotonin, kinins, oxidants, arachidonic acid metabolites, cytokines, etc. Histamine, which is released from mast cells, and serotonin, which is released from platelets damaged by thermal exposure, appear earliest. Among oxidants, oxygen radicals play an important role. These are unstable oxygen metabolites with an unpaired electron and therefore have powerful oxidative potential. One of the main such radicals is the hydroxyl anion (OH-).

It is formed as a result of enzymatic reactions. Immediately after a burn, the formation of (OH-) occurs in tissues during ischaemia and deterioration of their perfusion due to microcirculation disorders in the affected area. As a result of the action of xanthine oxidase on xanthine and hypoxanthine substrates in the presence of oxygen, oxygen superoxide (O2-) and hydrogen peroxide (H2O2) are formed. Histamine released from mast cells in the affected skin enhances local xanthine oxidase activity.

Later, hydroxyl anions are formed by neutrophils. Oxygen superoxide and hydrogen peroxide are produced by white blood cells under the action of myeloperoxidase. Subsequently, in both cases, hydrogen peroxide reacts with iron ions to form (OH-). The hydroxyl anion actively interacts with unsaturated fatty acids in membranes, primarily arachidonic acid, forming lipid peroxides and damaging cell membranes, thereby disrupting their function.

They also exacerbate inflammation by producing chemoattractants and can impair white blood cell function. In burns, oxidants play a major role in triggering various reactions. Under their influence, vascular permeability is disrupted, cell function is damaged as a result of lipid peroxidation processes, local and systemic inflammatory responses are initiated and sustained, the interstitial matrix is disrupted, the phagocytic ability of macrophages is weakened, cellular DNA is damaged, and the arachidonic acid metabolic cascade is initiated.

There are also many systemic responses caused by oxidants: 1) an increase in lipid peroxides in circulation; 2) haemolysis of red blood cells; 3) a systemic inflammatory response after a local burn, also caused by the activation of complement by hydroxyl anions. In addition, immediately after a burn, lipid peroxidation begins in the lungs, liver, kidneys, and other tissues. Antioxidants

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webofjournals.com/index.php/5

reduce the intensity of systemic reactions. Experimental studies have shown that increased permeability in local burns can be reduced by xanthine oxidase inhibitors. Their use in infusion therapy reduces the need for fluid therapy, as well as the level of oxidants.

As the local inflammatory process develops in the area of thermal injury, the production of local and systemic mediators increases. As a result of the release of phospholipase A2 in the area of thermal injury, a cascade of arachidonic acid transformations is triggered, resulting in the formation of products of the cyclooxygenase and lipoxygenase reaction pathways (thromboxanes, prostacyclins, prostaglandins and leukotrienes), which have a strong vasoactive effect and contribute to an increase in membrane permeability by damaging it. The use of the leukotriene inhibitor ICI-198,615 in the experiment contributed to a reduction in membrane permeability and extravasation; however, this result was observed only when the drug was administered no later than 15 minutes after the burn (Santos X. et al. 2000). Aspirin and other non-steroidal anti-inflammatory drugs reduce the intensity of enzymatic transformations of arachidonic acid and, consequently, decrease the amount of vasoactive mediators in the area of thermal injury. These drugs are readily available for use in first aid and mutual aid in the event of burns. However, a positive result can only be achieved if they are taken immediately after the burn occurs.

Cytokines, primarily tumour necrosis factor (TNF) and interleukin-1 (IL-1), play an important role in the development of inflammation in burns. It has been established that immediately after extensive deep burns, the level of TNF-alpha in the blood serum increases, with this increase being greater in deceased patients than in survivors. Tissue fluid taken from under the burn scab has the ability to activate macrophages and thereby increase the production of TNF-gamma and IL-1.

IL-1 is one of the first to influence T-lymphocyte activation, promoting increased adhesion of neutrophils and lymphocytes to endothelial cells. It has been established that serum levels of TNF-alpha, IL-1-beta, and IL-6 increase significantly immediately after a burn, then decrease by the 2nd-3rd week after the burn, but increase again by the time the wounds are completely healed, without, however, reaching the level that was immediately after the burn. The peak of spontaneous proliferation and cytokine production, particularly IL-1, IL-2, and IL-6, in lymph node cells draining the thermal injury area is observed on the third day after the burn.

The magnitude and dynamics of changes in TNF-alpha, IL-1-beta, and IL-6 reflect the severity of burn disease and the nature of burn healing, while changes in circulating IL-8 levels can be used to assess the extent of damage to the respiratory system. Subsequently, in cases of extensive deep burns complicated by organ failure and infection, the level of IL-1 in the blood decreases, which is apparently due to the depletion of monocytes that produce this cytokine (X-S. Lin et al., 1994). Conversely, the levels of TNF-alpha, IL-6 and IL-8 in such patients increase and reach very high values in systemic inflammatory response syndrome (sepsis).

These cytokines stimulate the production of adhesive molecules CD 11alpha, CD 11beta, CD 18, which appear in large quantities in patients with extensive deep burns in cases of multiple organ failure and septic shock. High levels of these cytokines were found in the blood of all burn victims who died.

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