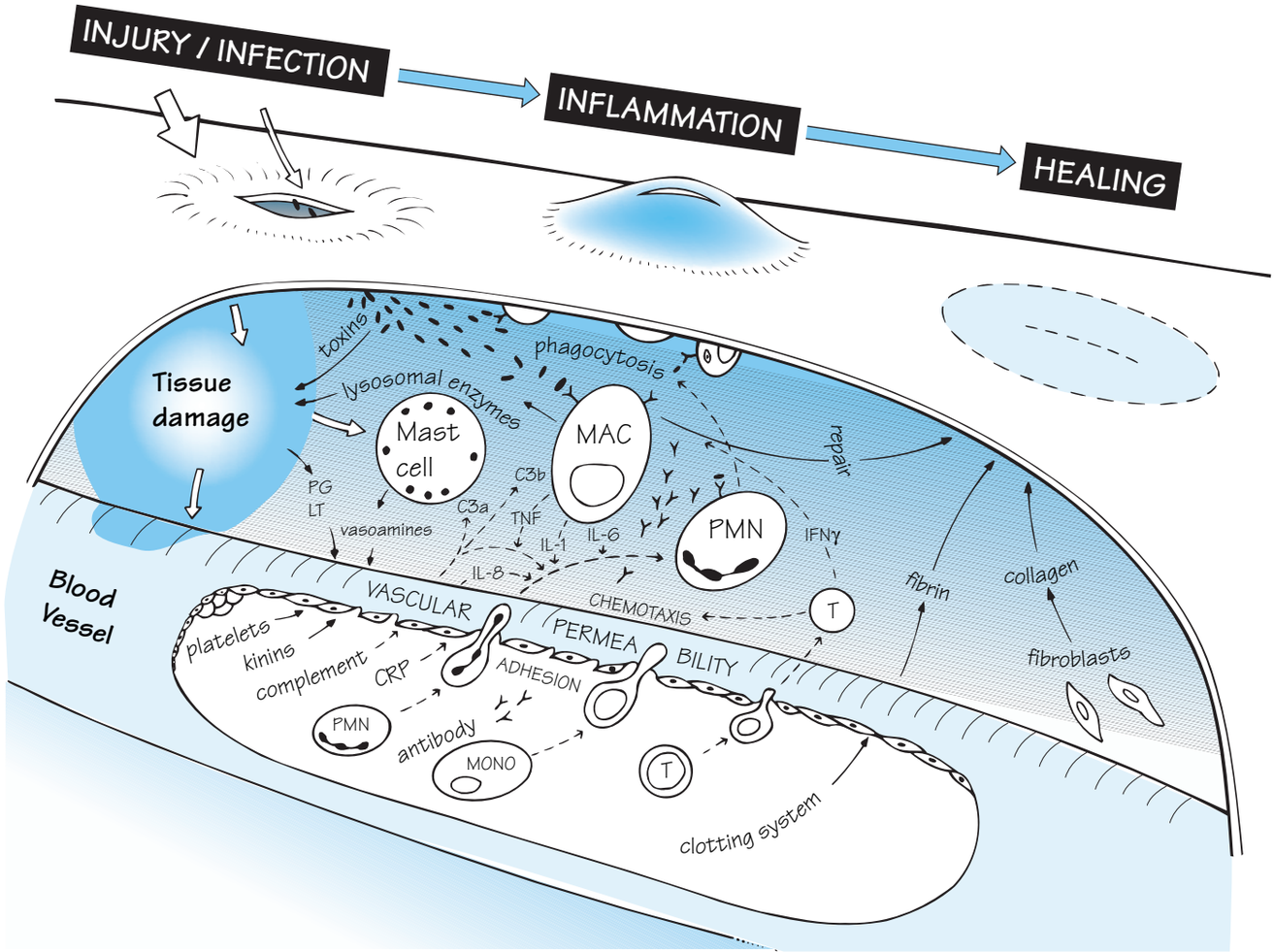
7 Acute inflammation



Whether **inflammation** should be considered part of immunology is a problem for the teaching profession not for the body, which combats infection by all the means at its disposal, including mechanisms also involved in the response to, and repair of, other types of damage.

In this simplified scheme, which should be read from left to right, are shown the effects of **injury** to tissues (top left) and to blood vessels (bottom left). The small black rods represent bacterial **infection**, a very common cause of inflammation and of course a frequent accompaniment of injury. Note the central role of **permeability of the vascular endothelium** in allowing access of blood cells and serum components (lower half) to the tissues (upper half), which also accounts for the main symptoms of inflammation—redness, warmth, swelling and pain.

It can be seen that the 'adaptive' (or 'immunological') functions of antibody and lymphocytes largely operate to amplify or focus pre-existing 'innate' mechanisms; quantitatively, however, they are so important that they frequently make the difference between life and death. Further details of the role of antibody and lymphocytes in inflammation can be found in Figs 34–38.

Note the central importance of the tissue **mast cells** and **macrophages**, and the blood-derived **PMNs**. If for any reason inflammation does not die down within a matter of days, it may become chronic, and here the macrophage and the T lymphocyte play dominant roles (see Fig. 36).

Mast cell A large tissue cell with basophilic granules containing vasoactive amines and heparin. It degranulates readily in response to injury by trauma, heat, ultraviolet light, etc. and also in some allergic conditions (see Fig. 34).

PG, LT Prostaglandins and leukotrienes; a family of unsaturated fatty acids (MW 300–400) derived by metabolism of arachidonic acid, a component of most cell membranes. Individual PGs and LTs have different but overlapping effects; together they are responsible for the induction of pain, fever, vascular permeability and chemotaxis of PMNs, and some of them also inhibit lymphocyte functions. Aspirin, paracetamol and other non-steroidal anti-inflammatory drugs act principally by blocking PG production.

Vasoamines Vasoactive amines, e.g. histamine and 5-hydroxytryptamine, produced by mast cells, basophils and platelets, and causing increased capillary permeability.

Kinin system A series of serum peptides sequentially activated to cause vasodilation and increased permeability.

Complement A cascading sequence of serum proteins, activated either directly ('alternate pathway') or via antigen–antibody interaction (see Fig. 6 for details of the individual components).

C3a and C5a, which stimulate release by mast cells of their vasoactive amines, are known as anaphylatoxins.

Opsonization C3b attached to a particle promotes sticking to phagocytic cells because of their 'C3 receptors'. Antibody, if present, augments this by binding to 'Fc receptors'.

CRP C-reactive protein (MW 130 000), a pentameric globulin (or 'pentaxrin') made in the liver which appears in the serum within hours of tissue damage or infection, and whose ancestry goes back to the invertebrates. It binds to phosphorylcholine, which is found on the surface of many bacteria, fixes complement and promotes phagocytosis; thus it may play an antibody-like role in some bacterial infections. Proteins whose serum concentration increases during inflammation are called '**acute-phase proteins**'; they include CRP and many complement components, as well as other microbe-binding molecules and enzyme inhibitors. This **acute-phase response** can be viewed as a rapid, not very specific, attempt to deal with more or less any type of infection or damage.

PMN Polymorphonuclear leucocyte; the major mobile phagocytic cell, whose prompt arrival in the tissues plays a vital part in removing invading bacteria.

Mono Monocyte; the precursor of tissue macrophages (MAC in the figure) which is responsible for removing damaged tissue as well as microorganisms. The tissue macrophages are also an important source of the inflammatory cytokines TNF-α, IL-1 and IL-6 (see below).

Lysosomal enzymes Bactericidal enzymes released from the lysosomes of PMNs, monocytes and macrophages, e.g. lysozyme, myeloperoxidase and others, also capable of damaging normal tissues.

Inflammatory cytokines The inflammatory response is orchestrated by several cytokines, which are produced by a variety of cell types. The most important are TNF-α, IL-6 and IL-1. All these cytokines have many functions (they are 'pleiotropic'), including initiating many of the changes in the vascular endothelium which promote leucocyte entry into the inflammatory site. They also induce the acute-phase response and, later, the process of tissue repair. IL-1 is one of the few cytokines that acts systemically, rather than locally; for example, through its action on the hypothalamus, it is the main molecule responsible for inducing fever. See Fig. 24 for further details of cytokines.

Chemotaxis C5a, C3a, leukotrienes and 'chemokines' stimulate PMNs and monocytes to move into the tissues. Movement towards the site of inflammation is called chemotaxis, and is due to the cells' ability to detect a concentration gradient of chemotactic factors; random increases of movement are called chemokinesis.

Chemokines These are a very large family of small polypeptides, which play a key role in chemotaxis and the regulation of leucocyte trafficking. There are two main classes of chemokines based on the distribution of conserved disulphide bonds. They bind to an equally large family of chemokine receptors, and the biology of the system is further complicated by the fact that many of the chemokines have multiple functions, and can bind to many different receptors. Although some have been called interleukins (e.g. IL-8), the majority have retained separate names. They shot to prominence when it was discovered that some of the chemokine receptors (e.g. CCR5 receptor) served as essential coreceptors (together with CD4) for HIV to gain entry into cells (see Fig. 41).

Adhesion and cell traffic Changes in the expression of endothelial surface molecules, induced mainly by cytokines, cause PMNs, monocytes and lymphocytes to slow down and subsequently adhere to the vessel wall. These 'adhesion molecules' and the molecules they bind to fall into well-defined groups (selectins, integrins, the Ig superfamily; see Fig. 13). These changes, together with the selective local release of **chemokines**, regulate the changes in cell traffic which underlie all inflammatory responses.

T T lymphocyte, undergoing proliferation and activation (**blast** transformation) when stimulated by antigen, as is the case in most infections. By releasing cytokines such as interferon (IFN)γ (see Fig. 24), T cells can greatly increase the activity of macrophages.

Clotting system Intimately bound up with complement and kinins because of several shared activation steps. Blood clotting is a vital part of the healing process.

Fibrin The end product of blood clotting and, in the tissues, the matrix into which fibroblasts migrate to initiate healing.

Fibroblast An important tissue cell which migrates into the fibrin clot and secretes **collagen**, an enormously strong polymerizing molecule giving the healing wound its strength and elasticity. Subsequently new blood capillaries sprout into the area, leading eventually to restoration of the normal architecture.