1

Inflammation

Definition

Inflammation is by definition a defensive reaction of the body with the aim of eliminating the trigger of the inflammation and repairing the damage caused, either by restoring the tissue of origin (restitutio) or by a replacement tissue, the scar (reparatio).

Trigger

Inflammation is triggered by any stimuli, called 'noxae', that overcome the organism's defence-compensation mechanisms. By definition, a *noxious agent* is a substance or event that causes damage to a biological organism. The noxious agent can be divided according to its origin into internal and external, and according to its structure into physical, chemical or biological triggers (Table 1.1).

Defence Cascade of the Body

Numerous defence mechanisms exist to protect an organism. These are particularly effective at the 'contact surfaces' between the organism and the environment. There, the penetration of the noxious agent is prevented by mechanical as well as biological defence mechanisms.

The **skin** prevents the penetration of the noxious agent under physiological conditions due to its structural design. For this purpose, the skin consists of different layers with different functions (Figure 1.1).

The outer layer of the skin, the epidermis, is made up of the layers – stratum corneum, lucidum, granulosum, spinosum and basale from the outside inwards. The main cell type in the epidermis is the keratinocyte. This differentiates in the stratum basale from epidermal stem cells. In the stratum spinosum, the cells begin to remodel with an increase in volume and a change in shape and width. In the further course, keratohyalin grains are formed in the stratum granulosum, and further remodelling processes take place. The cells become flattened, the nucleus is lost, shrinkage occurs due to fluid loss, and finally cornification takes place. Eventually, no more keratinocytes can be detected in the stratum corneum. Keratinocytes become corneocytes. The cornification process builds up a mechanical protection for the skin. In addition, penetration of a noxious substance is ensured by a close connection between the keratinocytes through tight-junctions. The tight-junctions consist of connections of transmembrane proteins, such as claudin and occludin. Intracellularly, these proteins are connected to the cytoskeleton. The tight-junctions connect the cells into a bandage that forms a barrier to the paracellular penetration of a noxious agent.

In addition, defence cells such as Langerhans cells are localised in the epidermis.

These are tissue macrophages that are capable of phagocytosis but also differentiate into antigen-presenting cells after contact with an antigenically active noxious agent, which can initiate an immune response.

Finally, the extracellular matrix in the epidermis forms a molecular association that can prevent the penetration of a noxious agent. The molecules of the extracellular matrix include, for example, keratins and collagens as structural proteins

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Table 1.1 Common causes of inflammation in dogs and cats.

Physical	Chemical	Biological	Infectious agents
Heat	Environmental toxins		Viruses
Cold	Endogenous toxins	Tumours	Bacteria
		Degenerations	Fungi
			Parasites

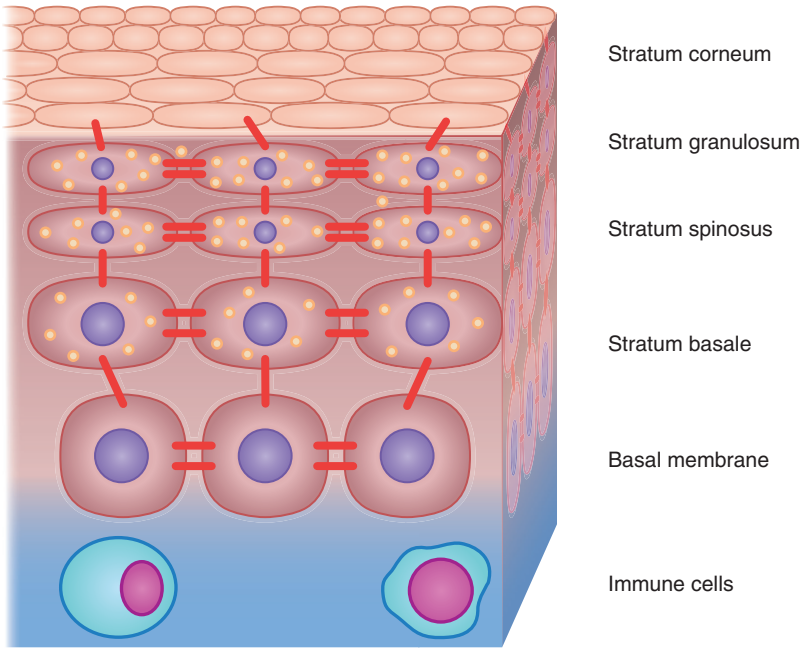

Figure 1.1 Structure of the outer skin and development of keratinocytes.

Table 1.2 Components of the epidermal extracellular matrix with function.

Molecule	Function
Keratin	Intermediate filament, structural element of keratinocytes
Collagen	Tight protein of the ECM, adhesion molecule
Elastin	Elastic protein of the ECM
Fillagrin	Structural protein
Ceramide	Hydrophobic protection

and ceramides, which are lipids composed of a sphingosine molecule and fatty acids that provide protection against hydrophilic noxae (Mitamura et al. 2021) (Table 1.2).

The **mucous membranes** of the body form the inner boundary layer between the organism and the environment. The microscopic structure of the mucous membranes already reflects defence competences. This includes the contact of the mucosal cells through tight-junctions. These form a tight connection between the cell membrane of neighbouring cells through proteins such as occludin. This prevents the paracellular penetration of extracorporeal noxae.

Another superficial defence mechanism is the synthesis of mucins. Mucins are glycoproteins that are synthesised by goblet cells and form a protective layer several micrometres thick on the mucosa. In the process, defence functions of the mucins develop due to their gel-like structure, which enables mechanical protection of the underlying mucosal cells. Chemically, for example, bicarbonate residues of the mucins can bind and inactivate acids, and biologically, mucins can prevent bacteria from invading by binding them.

Cells localised in the mucosa (Paneth cells) secrete lysozyme or defensins to inactivate germs. The latter are differentiated into α-, β- and θ-defensins based on their molecular structure (Lehrer and Ganz 2002).

The effects of defensins are antimicrobial and immunomodulatory. The former effect is based on their positive molecular charge, which enables a charge-dependent interaction with the negatively charged bacterial cell wall, especially the lipopolysaccharides (Scott and Hancock 2000). The binding of the defensins results in pore formation. The consequence is a depolarisation of the bacterial cell membrane and thus a breakdown of the membrane potential and lysis of the cell (Scott and Hancock 2000; Sahl et al. 2005).

In addition, defensins show immunomodulatory functions. Defensins have a chemotactic effect on dendritic cells and memory T cells, and thus represent a link between innate and adaptive immune responses. In addition, some defensins act chemotactically on monocytes and macrophages, and in some cases induce mast cell activation and degranulation. As a result, histamine and prostaglandins are released, which promote the migration of neutrophilic granulocytes. Degranulation of the recruited neutrophilic granulocytes in turn releases defensins again, resulting in a positive feedback loop (Yang et al. 2002).

The secretion of lysozyme is another defence mechanism against bacterial invasion of the mucous membranes. Lysozyme is an enzyme that cleaves murein. Murein is a peptidoglycan and a component of the bacterial cell wall. Due to the hydrolytic cleavage of murein, the bacterial cell wall loses its selective permeability and rupture of the bacterial cell wall occurs due to increased water influx.

Another defence mechanism in the mucosa is the mucosa-associated lymphoid system located in the lamina propria, which is called 'gut associated lymphoid tissue' (GALT) in the gastrointestinal tract and bronchial associated lymphoid tissue (BALT) in the respiratory tract. This system includes numerous cells of the non-specific and specific defence response, such as macrophages and lymphocytes (Figure 1.2).

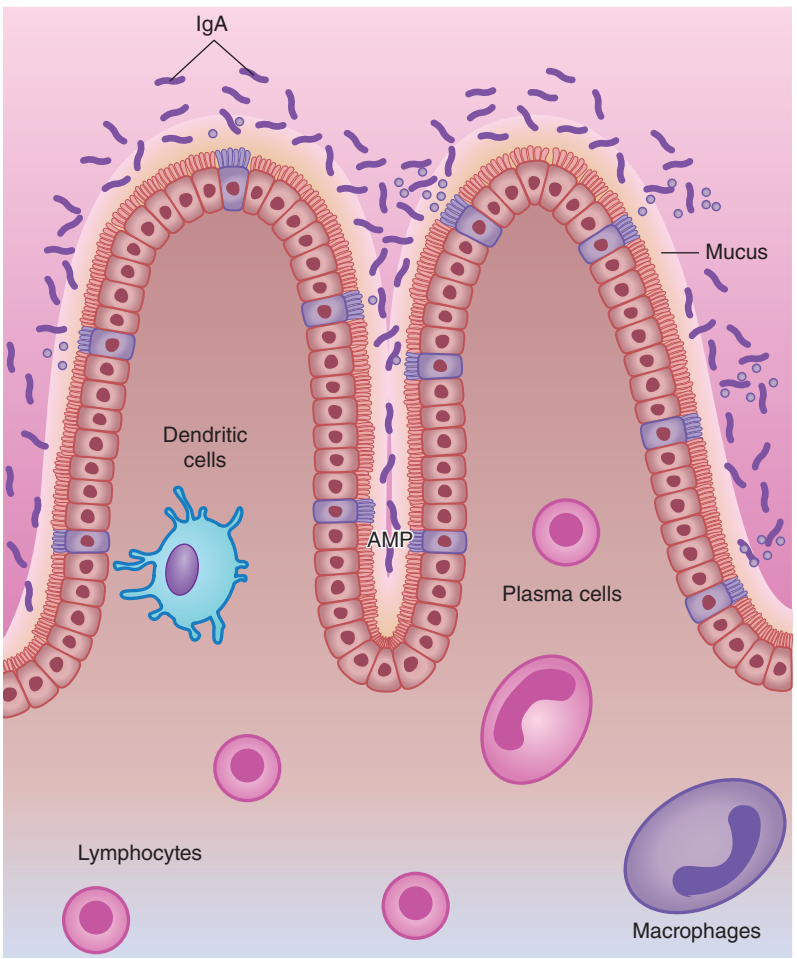

Figure 1.2 Building up the defence system of the mucous membrane.

Player of the Inflammation

The inflammatory process is maintained by some so-called 'inflammatory cells'. These combine some properties that predispose them to fulfil the definitional task of inflammation. This states that inflammation is a reaction of the body that serves to eliminate a noxious agent and its consequences.

The following cells are involved in the inflammatory process:

Neutrophilic granulocytes originate from the leukocyte pool of the bone marrow and are distributed throughout the blood. The residence time in the blood is a few hours (6–12 hours). Subsequently, the neutrophilic granulocytes leave the blood capillaries under the influence of chemoattractive substances. These are released as part of the local inflammatory process. The process of neutrophilic granulocyte emigration from the blood vessels takes place via adhesion and transmigration. Integrin-mediated, the neutrophilic granulocytes adhere to the surfaces of the endothelial cells. In the process, the cells change their shape from roundish to an amoeboid cell shape. The cells can now migrate trans- and paracellularly through the vascular endothelial layer.

In the area of inflammation, the neutrophilic granulocytes have different functions. The ability to phagocytose allows the cells to take up and lyse the noxious agent (e.g. bacteria). For this process, the noxious agent is taken up by membrane invagination and the resulting vesicle combines with the granular structures of the granulocyte. In particular, molecules of the so-called 'primary granules' are responsible for the process of phagocytosis; these include myeloperoxidases, defensins and lysozyme.

Beyond the process of phagocytosis, neutrophilic granulocytes are able to maintain the inflammatory process through the secretion of prostaglandins, leukotrienes and proinflammatory cytokines (TNF-α, IL-1, IL-6). At the same time, they link the innate immunity with the adaptive immunity e.g. via macrophage-inflammatory-protein 1 (MIP-1) (Salazar-Mather and Hokeness 2003). Antigen presentation by neutrophilic granulocytes has also been described, underlining that neutrophilic granulocytes link the two immune systems (Appelberg 2007). A special form of defence by neutrophilic granulocytes occurs when they form neutrophilic extracellular traps (NETs) as part of specialised cell death (NETosis). These are networks formed by neutrophilic granulocyte chromatin and proteins such as elastase, cathepsin or histones. All NETs have an antibacterial effect by binding and inactivating bacteria (Muñoz et al. 2019) (Figure 1.3).

Monocytes and tissue macrophages represent the mononuclear phagocyte system and are part of the innate immune system. Monocytes are distributed throughout the blood and differentiated into macrophages with different functions after emigration into the surrounding tissue. The process of emigration is comparable to that of neutrophilic granulocytes and is composed of rolling, adhesion and para- or transcellular migration (Gerhardt and Ley 2015).

Macrophages are capable of phagocytosis and they link the innate and acquired immune systems by presenting antigen. In addition, they control the course of the inflammatory response.

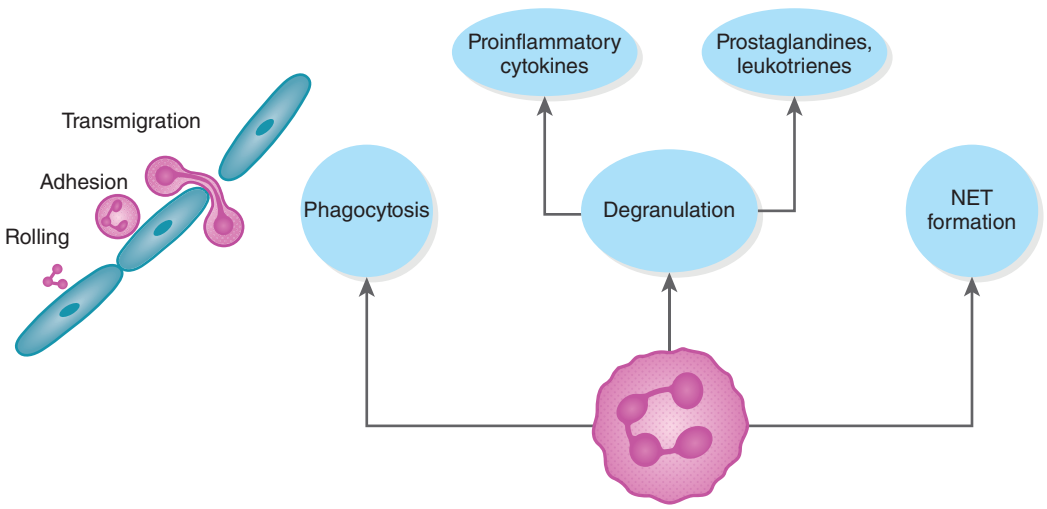

Figure 1.3 Defence mechanism by neutrophilic granulocytes.

Phagocytosis is a process in which particles in the form of large molecules (e.g. proteins), prokaryotic or eukaryotic cells are taken up and 'digested' by the phagocytosing cells. Of the inflammatory cells, primarily macrophages and neutrophilic granulocytes are capable of phagocytosis. The phagocytosis process can take place after prior opsonisation of the particle or without it. If opsonisation takes place, the particle is opsonised before phagocytosis, e.g. by IgG or complement (C3). Particles labelled in this way react with specific receptors (FcR, CR) of the phagocyte. In non-opsonised phagocytosis, a reaction takes place through the particle's own surface molecules (e.g. saccharides). Phagocytosis begins with the attachment of the particles to receptors on the cell membrane. The particle–receptor connection initiates the signal transduction for phagocytosis. Subsequently, polymerisation of cytoskeletal actin occurs, causing the cell membrane to develop pseudopodial protrusions, enclosing the particle and invaginating it into the cell interior. The invagination process results from depolymerisation of the basal actin filaments. Eventually, the particle is pinched off and a vesicle is formed. In this process, part of the cell membrane is used for vesicle formation and after the vesicle is strangulated, the lipid double membrane closes again. Inside the cell, the vesicle is now called a 'phagosome', which fuses with a primary lysosome released from the Golgi apparatus to form a secondary lysosome. The lysosome contains an acidic environment inside with numerous digestive enzymes. Proteins and polysaccharides are broken down into amino acids and monosaccharides by the lysosomal enzymes and can diffuse out of the secondary lysosome into the cell interior. The remaining, indigestible components of the secondary lysosome can fuse with the cell membrane again and be released into the environment (Rosales and Uribe-Querol 2017).

In addition, protein components of the antigen will be bound to molecules of the major histocompatibility complex II (MHC II). These complexes reach the cell surface, are attached to the cell membrane and can be presented to other cells in this way (Savina and Amigorena 2007; Roche and Furuta 2015).

The control of the inflammatory process by macrophages is governed by numerous cytokines secreted by the macrophages. These include proinflammatory cytokines such as IL-1, IL-6 and TNF-α. But anti-inflammatory cytokines such as IL-10 or TGF are also synthesised. Through their diverse functions and the formation of numerous mediators, macrophages essentially control the local inflammatory process (Figure 1.4).

Eosinophilic granulocytes are easily recognised by their eosinophilic cell granules. Their formation takes place predominantly in the bone marrow. In circulation, the eosinophilic granulocytes only move for a few hours before emigrating into the tissue. This process is similar to the processes already described for neutrophilic granulocytes and monocytes. The preferred tissues for emigration are those of the gastrointestinal tract and the respiratory tract. In the tissues, the eosinophilic granulocytes undergo apoptosis after a few days, unless they are previously activated by cytokines (e.g. IL-5).

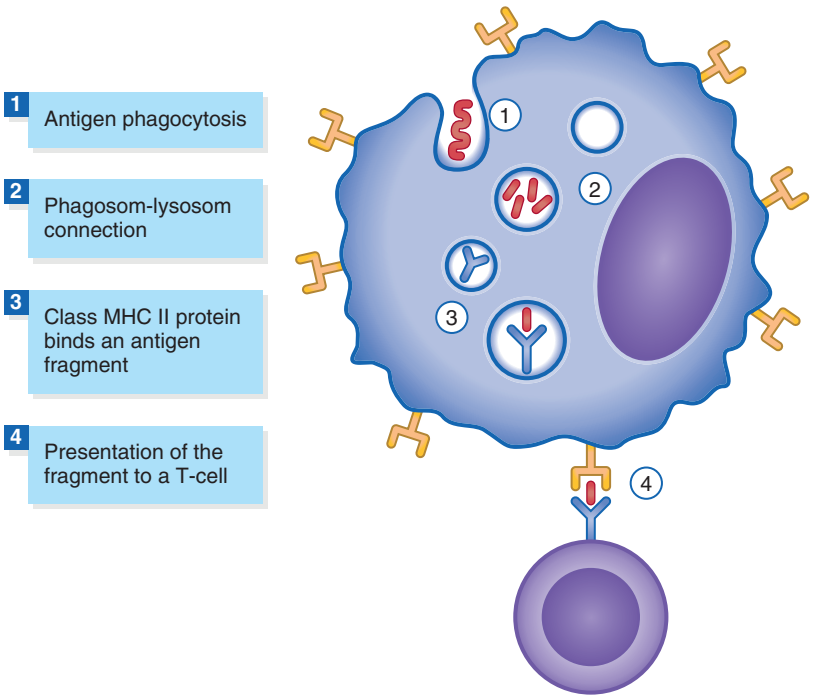

Figure 1.4 Antigen presentation by macrophages.

The functional roles of eosinophilic granulocytes are cytotoxic effects, tissue remodelling and immune cell interaction. Eosinophilic granulocytes are capable of phagocytosis of e.g. bacteria or antigen–antibody complexes. However, their effectiveness is less than that of neutrophilic granulocytes. By secreting growth factors (e.g. TGF-β, VEGF), the eosinophilic granulocytes play a role in the healing process of the inflammation. The secretion of growth factors usually implies connective tissue proliferation in the sense of fibrosis. Finally, eosinophilic granulocytes may interact with other immune cells of the innate and acquired immune system (Rothenberg and Hogan 2006; Wechsler et al. 2021).

Basophilic granulocytes are particularly rare in the blood and have a half-life of only a few hours. They then migrate into the tissue, where they remain for a few weeks. After activation by IgE, for example, degranulation occurs with the release of heparin and histamine. In this way, local blood circulation is promoted, which supports the inflammatory process or allergic reactions (Stone et al. 2010) (Figure 1.5).

Lymphocytes morphologically belong to the mononuclear cells and develop from lymphatic stem cell lineage. The majority of lymphocytes are located in the bone marrow and lymphoid organs. The life span of lymphocytes is function-dependent and ranges from a few days to several years. The lymphocytes represent the specific defence and can be divided into three main groups, depending on the respective tasks. These can be classified morphologically on the basis of specific CD-surface molecules (cluster of differentiation).

The CD3-positive T cells, like the macrophages, represent the cellular immune response in the area of inflammation.

CD4-positive T helper cells support the immune response of T- and B-lymphocytes through secretion of cytokines and via direct interaction with surface molecules of the target cells. They are stimulated by antigen-presenting cells and can be differentiated into two subtypes TH1 and TH2 cells with different functions. TH1 lymphocytes secrete, for example, IFN-γ, TNF-β and IL-2, and thereby regulate the inflammatory response by stimulating the phagocytotic activity of macrophages and cytotoxic T cells. In addition, the differentiation of B-lymphocytes into plasma cells is supported.

TH2 cells essentially secrete IL-4, 5, 9 and 13 and trigger the maturation and differentiation of B-lymphocytes. IL-4 induces isotype switching from IgM to IgG and IgE, while IL-5 increases IgA synthesis.

The CD8-positive T cells act cytotoxically against extracellular and intracellular bacteria as well as virus-infected cells. They are activated by antigenic peptides presented by the MHC I molecules present on all nucleated somatic cells. By releasing granules with cytotoxic molecules (e.g. perforin), and receptor induction of the target cells, the cytotoxic cells can induce apoptosis of the target cell.

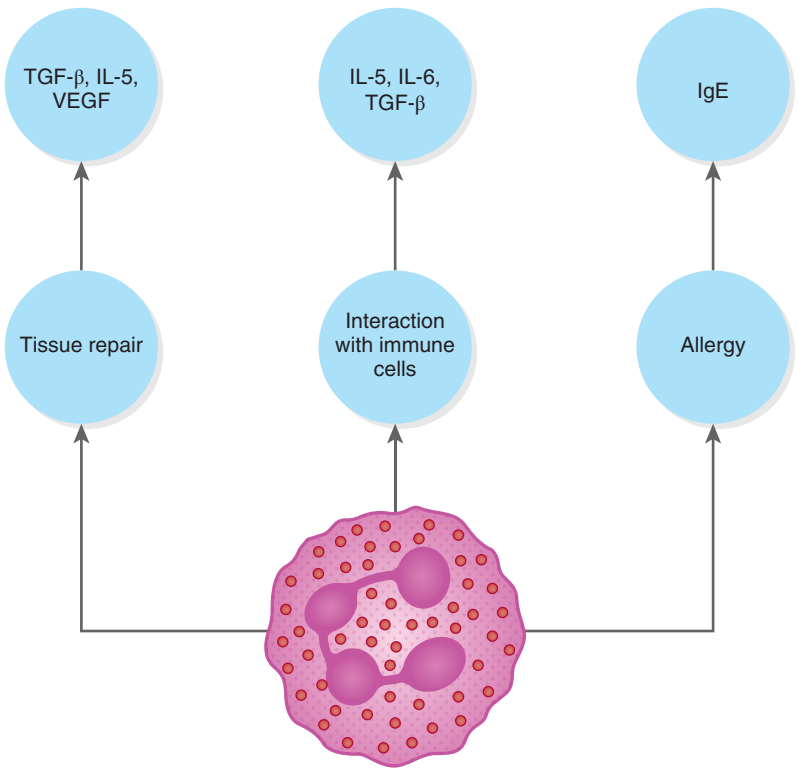

Figure 1.5 Function of the eosinophilic granulocytes.

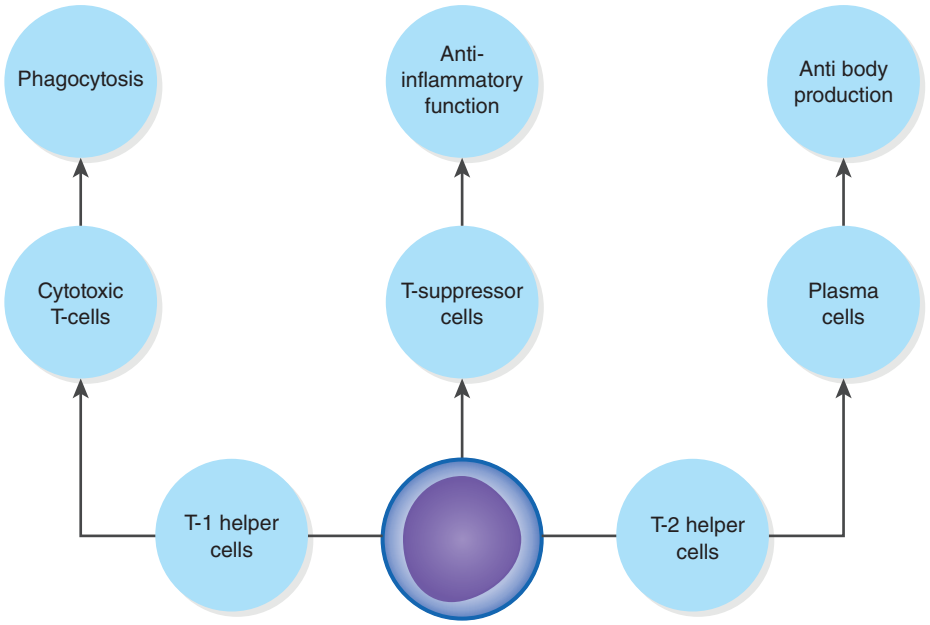

Figure 1.6 Function of the lymphocytes.

CD4-positive T-suppressor cells suppress the immune response and serve to finalise the inflammatory process.

The B cells produce and secrete specific antibodies and can also present antigen. Activation of the B-lymphocytes takes place via antigen binding to surface receptors. The complex of receptor and antigen is taken up by the cell and proteolysed, forming peptides that are bound to MHC II molecules to be presented on the B-lymphocyte surface. CD4-positive T helper cells recognise the structures and stimulate the differentiation and clonal expansion of B-lymphocytes into antibody-producing plasma cells. The antibodies, in turn, bind to the antigen and can directly inactivate it by forming insoluble complexes or neutralise it by activating the complement system. Antigen–antibody complexes are also more likely to be taken up by phagocytes.

Another lymphocyte subpopulation is the natural killer (NK) cell. Like the T cells, they belong to the cellular defence system. Their primary function is to recognise and eliminate virus-infected or neoplastic body cells. In contrast to the T and B cells, the NK cells do not recognise foreign antigens, but modified endogenous cells on the basis of the expression pattern of the MHC molecules. Active NK cells secrete cytotoxic (including perforin, granzymes and TNF-β) and various regulatory (including IFN-γ, IL-1, IL-5, IL-8, IL-10 and GM-CSF) cytokines that initiate destruction of the malignant degenerated or virus-infected target cell (Freitas and Rocha 2000; LeBien and Tedder 2008) (Figure 1.6).

Course of the Acute Inflammation

The inflammatory process is initiated by the receptor binding of molecules of the inflammatory trigger. These are called ‘pathogen-associated molecular patterns’ (PAMPs) for external triggers or danger-associated molecular patterns (DAMPs) for internal triggers. They react with so-called ‘germline-encoded pattern-recognition receptors’ (PRRs), which also include toll-like receptors (TLRs). This is followed by intracellular signal transduction via various pathways (NF-κ B, MAPK, JAK-Stat) and increased gene expression of inflammatory mediators (cytokines, chemokines) (Fioranelli et al. 2021).

The pattern of mediators and chemokines can be influenced by the type of pathogen. For example, the reaction of glycan components of the *Staphylococcus aureus* cell wall with TLR2 induces the secretion of CXCL-8 by dendritic cells; this induces the migration of neutrophilic granulocytes into the area. The reaction of lipopolysaccharides of *Escherichia coli* with TLR leads to the secretion of CXCL-10, which induces migration of T cells into the area (Luster 2002) (Table 1.3).

The time course of inflammation begins with vasodilation and an increase in the permeability of the blood vessels.

Vasodilation is caused by leucocyte mediators, such as bradykinin. This is structurally an oligopeptide and functionally a tissue hormone. It binds to endothelial cell receptors in the vessel wall and initiates a change in smooth muscle tone.

The consequence of vascular dilatation is increased intravascular hydrostatic pressure. This increases the pressure gradient to the surrounding tissue and promotes an increase in the permeability of the vessel wall.

Table 1.3 Cytokines, resource, effect.

Cytokines	Source	Effect
IL-1	Macrophages	Stimulation of macrophages and T lymphocytes, acute phase reaction
IL-2	Activated Th1 lymphocytes	Proliferation of B cells and activated T cells
IL-5	Th2 lymphocytes, mast cells	Formation of eosinophilic granulocytes
IL-6	Activated Th2 lymphocytes, macrophages, somatic cells	Acute phase reaction, B cell proliferation
IL-8	Macrophages, somatic cells, neutrophilic granulocytes	Chemoattractant for neutrophils and T cells
IL-10	Activated Th2 lymphocytes, macrophages	Inhibits cytokine production, promotes B cell proliferation and antibody production, suppresses cellular immunity
IFN-α IFN-β	Macrophages, neutrophilic granulocytes, somatic cells	Antiviral effects, induction of MHC I activation of NK cells and macrophages
IFN-γ	Activated Th1 lymphocytes, NK cells	Induces MHC I + II activates macrophages, neutrophilic granulocytes, NK cells, antiviral effects
TNF-α	Macrophages, mast cells	Inflammation induction, phagocytosis

In addition, the increase in permeability is achieved by the leukocytes penetrating the endothelial cell wall of the vessel transcellularly or mostly paracellularly, attracted by chemokines. For this purpose, the expression of transcellular endothelial cell adhesion molecules is influenced under the influence of inflammation, and leukocytes are also able to enzymatically cleave the cell-to-cell adhesion molecules, and therefore migrate into the surrounding tissue (Reglero-Real et al. 2016). In the tissue, leukocytes follow chemokine gradients and can orient themselves in different chemoattractive fields (Foxman et al. 1997).

The inflammatory reaction is essentially controlled by different mediators. In addition to cytokines, which are messenger substances that enable the interaction between the cells of the inflammatory cascade, some mediators serve as initiators of the inflammatory reaction.

These include eicosanoids that are formed by activating several enzyme systems in the arachidonic acid metabolism. Arachidonic acid is formed from phospholipids of the cell membranes under the influence of phospholipase A2. This in turn can be converted to prostaglandins, prostacyclin and thromboxanes under the catalysis of cyclooxygenases (COX). The lipoxygenases serve to synthesise leukotrienes from arachidonic acid. Eicosanoids can be formed in all cells of the body with the exception of erythrocytes. There are specific differences. In the thrombocytes, thromboxanes are formed almost exclusively. The vascular endothelial cells, on the other hand, produce mainly prostacyclins. The eicosanoids have hormone-like properties. They act as second messengers via cyclic AMP (cAMP). Unlike hormones, however, eicosanoids are formed locally and are not transported via the bloodstream to the site of their effect. Eicosanoids are not stored in the body. They have a half-life of a few minutes (Table 1.4).

In addition, inflammatory cytokines induce the secretion of acute phase proteins, which include over 40 proteins classified by function into transport proteins (e.g. ceruloplasmin), coagulation and fibrinolysis proteins (e.g. prothrombin, fibrinogen), complement system proteins (e.g. complement C3), antiproteases (e.g. α1-antitrypsin) and immune proteins (e.g. prothrombin, fibrinogen) and immunoactive proteins (e.g. CRP, SAA). The synthesis of acute phase proteins takes place in different organs, such as the liver (Ceron et al. 2005) (Table 1.5).

Table 1.4 Some eicosanoids with effect.

Eicosanoid	Effect
Prostaglandin	Pain response
Prostacyclin	Vasodilation, inhibition of platelet aggregation
Leukotriene	Leukocyte chemotaxis, adhesion of leukocytes to vascular endothelium, increase of capillary permeability
Thromboxane	Vasoconstriction, platelet aggregation

Table 1.5 Some acute phase proteins.

Name	Source	Effect
C-reactive protein (CRP)	Predominantly hepatocytes, also lymphocytes, macrophages	Opsonisation and activation of the complement system
Serum amyloid A (SAA)	Hepatocytes, adipocytes	Activation of inflammatory cells, and MMP
Haptoglobin	Hepatocytes	Binding of free haemoglobin
Ceruloplasmin		Iron oxidation

The acute phase proteins fulfil different functions in the course of the inflammation.

C-reactive protein (CRP) belongs to the opsonins that activate the complement system. It binds to phosphocholine, a component of bacterial cell membranes, among other things. The binding activates the complement system and the macrophage function.

Serum amyloid A (SAA) is involved in immune cell chemotaxis and activation of matrix metalloproteinases.

Haptoglobulin and ceruloplasmin and other metal-binding molecules serve the bacterial defence via the binding of iron by withholding iron from the bacterial metabolism (Figure 1.7).

After the initiation of the **inflammatory** process, the process follows a similar pattern. This is initially characterised by an infiltration of neutrophilic granulocytes. Due to their phagocytosis activity, these are able to eliminate the inflammatory triggers. This is followed by a phase with increased activity of lymphocytes and monocytes, which represents an essential link between innate and acquired immunity. Finally, the increase of eosinophilic granulocytes in the inflammatory area completes the response.

The termination of the inflammatory response is controlled by various mediators and cytokines, such as IL-10, and serves to protect the tissue.

The interleukin prevents the production of various cytokines, inhibits phagocytosis and weakens the microbicidal activity of neutrophilic granulocytes. In addition, their migration is reduced. IL-10 prevents the differentiation of immature dendritic cells and thus inhibits inflammatory responses. IL-10 inhibits INF-γ and TNF production by NK cells. It also induces lysis of infected cells (Mocellin et al. 2004) (Figure 1.8).

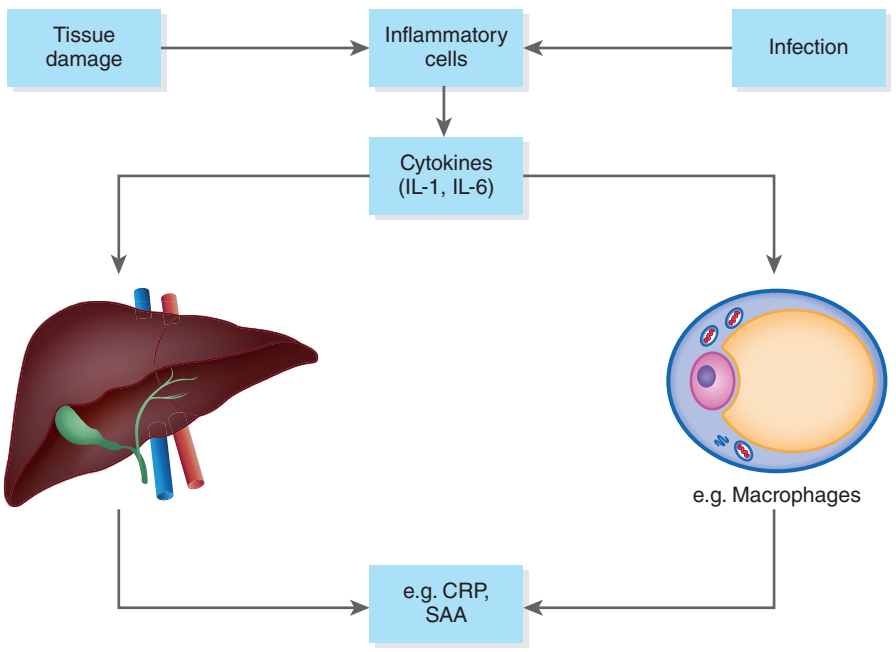

Figure 1.7 Induction of the acute phase response.

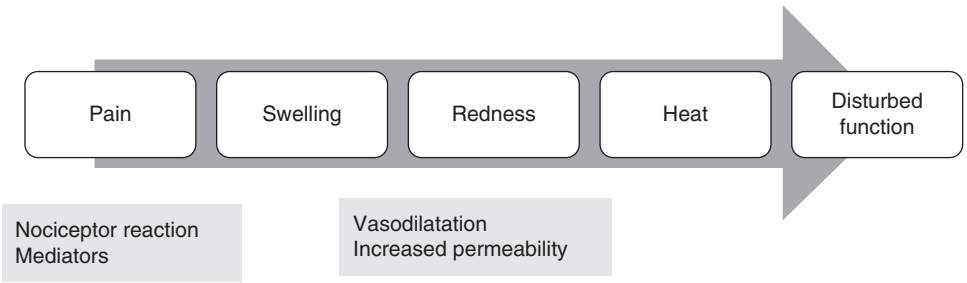

Figure 1.8 Overview of the inflammatory reaction.

Clinically, acute inflammation proceeds with the reactions described as cardinal symptoms: pain, redness, swelling and heat. These changes can be explained by the inflammatory process described, which is accompanied by increased blood flow, the formation of mediators and an increase in vascular permeability. In sum, a disturbance of tissue or organ function also develops in the inflamed area; this is called 'functio laesa'. This induces major clinical consequences of the acute inflammation and includes pain, destruction of tissue architecture and metaplasia.

An acute inflammatory event can develop into a chronic process. This results predominantly from a persistent inflammatory stimulus or an insufficient anti-inflammatory response after the elimination of the noxious agent has been completed. The process of chronic inflammation extends over several weeks or months. The result is a tissue remodelling that prevents a restitutio and thus a restoration of the initial tissue situation. In such a case, chronic inflammation leads to a fibrotic remodelling of the tissue.

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