Inflammation

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INTRODUCTION

Definition: Inflammation is a local response (reaction) of living vasculaized tissues to endogenous and exogenous stimuli. The term is derived from the Latin "inflammare" meaning to burn. Inflammation is fundamentally destined to localize and eliminate the causative agent and to limit tissue injury.

Acute inflammation is the early (almost immediate) response of a tissue to injury. It is nonspecific and may be evoked by any injury short of one that is immediately lethal. Acute inflammation may be regarded as the first line of defense against injury and is characterized by changes in the microcirculation: exudation of fluid and emigration of leukocytes from blood vessels to the area of injury. Acute inflammation is typically of short duration, occurring before the immune response becomes established, and it is aimed primarily at removing the injurious agent.

Thus, inflammation is a physiologic (protective) response to injury, an observation made by Sir John Hunter in 1794 concluded: “inflammation is itself not to be considered as a disease but as a salutary operation consequent either to some violence or to some diseases”.

Nomenclature:

The nomenclatures of inflammatory lesion are usually indicated by the suffix 'itis'. Thus, inflammation of the appendix is called appendicitis and that of meninges as meningitis, etc.... However, like any rule, it has its own exceptions examples pneumonia, typhoid fever, etc....

Causes:

Causes of inflammation are apparently causes of diseases such as

physical agents - mechanical injuries, alteration in temperatures and pressure, radiation injuries.

chemical agents- including the ever increasing lists of drugs and toxins.

biologic agents (infectious)- bacteria,viruses,fungi, parasites

immunologic disorders- hypersensitivity reactions, autoimmunity, immunodeficiency states etc

genetic/metabolic disorders- examples gout, diabetes mellitus etc...

Classification:

Inflammation is classified crudely based on duration of the lesion and histologic appearances into acute and chronic inflammation.

ACUTE INFLAMMATION

Acute inflammation is an immediate and early response to an injurious agent and it is relatively of short duration, lasting for minutes, several hours or few days.

It is characterized by exudation of fluids and plasma proteins and the emigration of predominantly neutrophilic leucocytes to the site of injury.

The five cardinal signs of acute inflammation are

Redness (rubor) which is due to dilation of small blood vessels within damaged tissue as it occurs in cellulitis.

Heat (calor) which results from increased blood flow (hyperemia) due to regional vascular dilation

Swelling (tumor) which is due to accumulation of fluid in the

extravascular space which, in turn, is due to increased vascular permeability.

Pain (dolor), which partly results from the stretching & destruction of tissues due to inflammatory edema and in part from pus under pressure in as abscess cavity. Some chemicals of acute inflammation, including bradykinins, prostaglandins and serotonin are also known to induce pain.

Loss of function: The inflammed area is inhibited by pain while severe swelling may also physically immobilize the tissue.

Events of acute inflammation:

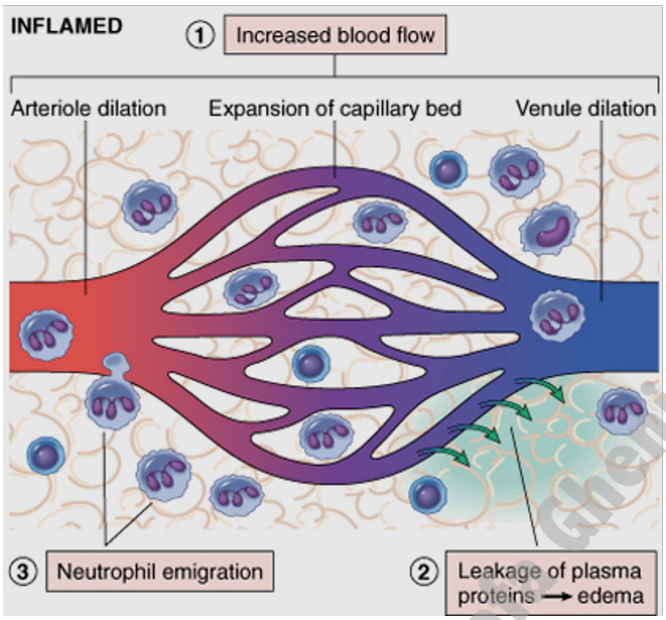
Acute inflammation is categorized into an early vascular and a late cellular response.

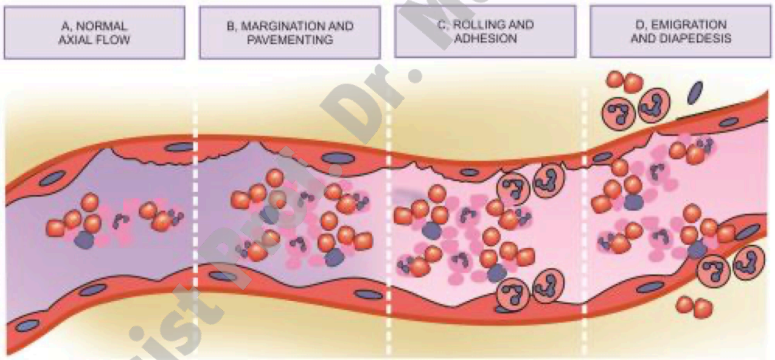
1) The **Vascular response** has the following steps:

a) Immediate (momentary) vasoconstriction in seconds due to neurogenic or chemical stimuli.

b) Vasodilatation of arterioles and venules resulting in increased blood flow.

c) After the phase of increased blood flow there is a slowing of blood flow & stasis due to increased vascular permeability that is most remarkably seen in the post-capillary venules. The increased vascular permeability oozes protein-rich fluid into extra- vascular tissues. Due to this, the already dilated blood vessels are now packed with red blood cells resulting in stasis. The protein-rich fluid which is now found in the extravascular space is called exudate. The presence of the exudates clinically appears as swelling. Chemical mediators mediate the vascular events of acute inflammation.





2) **Cellular response**

The cellular response has the following stages:

A. Migration, rolling, pavementing, & adhesion of leukocytes
B. Transmigration of leukocytes
C. Chemotaxis
D. Phagocytosis

Normally blood cells particularly erythrocytes in venules are confined to the central (axial) zone and plasma assumes the peripheral zone. As a result of increased vascular permeability (See vascular events above), more and more neutrophils accumulate along the endothelial surfaces (peripheral zone).

A) **Migration, rolling, pavementing, and adhesion of leukocytes**

- Margination is a peripheral positioning of white cells along the endothelial cells.
- Subsequently, rows of leukocytes tumble slowly along the endothelium in a process known as rolling
- In time, the endothelium can be virtually lined by white cells. This appearance is called pavementing
- Thereafter, the binding of leukocytes with endothelial cells is facilitated by cell adhesion molecules such as selectins, immunoglobulins, integrins, etc which result in adhesion of leukocytes with the endothelium.

B). **Transmigration of leukocytes**

- Leukocytes escape from venules and small veins but only occasionally from capillaries. The movement of leukocytes by extending pseudopodia through the vascular wall occurs by a process called diapedesis.
- The most important mechanism of leukocyte emigration is via widening of inter- endothelial junctions after endothelial cells contractions. The basement membrane is disrupted and resealed thereafter immediately.

C). **Chemotaxis:**

- A unidirectional attraction of leukocytes from vascular channels towards the site of inflammation within the tissue space guided by chemical gradients (including bacteria and cellular debris) is called chemotaxis.
- The most important chemotactic factors for neutrophils are components of the complement system (C5a), bacterial and mitochondrial products of arachidonic acid metabolism such as leukotriene B4 and cytokines (IL-8). All granulocytes, monocytes and to lesser extent lymphocytes respond to chemotactic stimuli.
- How do leukocytes "see" or "smell" the chemotactic agent?

This is because receptors on cell membrane of the leukocytes react with the chemoattractants resulting in the activation of phospholipase C that ultimately leads to release of cytocolic calcium ions and these ions trigger cell movement towards the stimulus.

D) **Phagocytosis**

- Phagocytosis is the process of engulfment and internalization by specialized cells of particulate material, which includes invading microorganisms, damaged cells, and tissue debris.
- These phagocytic cells include polymorphonuclear leukocytes (particularly neutrophiles), monocytes and tissue macrophages.

Phagocytosis involves three distinct but interrelated steps.

1). **Recognition and attachment** of the particle to be ingested by the leukocytes: Phagocytosis is enhanced if the material to be phagocytosed is coated with certain plasma proteins called **opsonins**. These opsonins promote the adhesion between the particulate material and the phagocyte's cell membrane. The three major opsonins are: the Fc fragment of the immunoglobulin, components of the complement system C3b and C3bi, and the carbohydrate-binding proteins – lectins.

Thus, IgG binds to receptors for the Fc piece of the immunoglobulin (FcR) whereas 3cb and 3bi are ligands for complement receptors CR1 and CR2 respectively.

2). **Engulfment:** During engulfment, extension of the cytoplasm (pseudopods) flow around the object to be engulfed, eventually resulting in complete enclosure of the particle within the phagosome created by the cytoplasmic membrane of the phagocytic cell.

As a result of fusion between the phagosome and lysosome, a phagolysosome is formed and the engulfed particle is exposed to the degradative lysosomal enzymes.

3) **Killing or degradation** The ultimate step in phagocytosis of bacteria is killing and degradation. There are two forms of bacterial

killing

a). **Oxygen-independent mechanism:**

- This is mediate by some of the constituents of the primary and secondary granules of polymorphonuclear leukocytes. These include:

Bactericidal permeability increasing protein (BPI)

Lysozymes

Lactoferrin

Major basic protein

Defenses

- It is probable that bacterial killing by lysosomal enzymes is inefficient and relatively unimportant compared with the oxygen dependent mechanisms. The lysosomal enzymes are, however, essential for the degradation of dead organisms within phagosomes.

b) **Oxygen-dependent mechanism**:

There are two types of oxygen- dependent killing mechanisms

i) **Non-myeloperoxidase dependent**

- The oxygen - dependent killing of microorganisms is due to formation of reactive oxygen species such as hydrogen peroxide (H2O2), super oxide (**O2)** and hydroxyl ion (HO-) and possibly single oxygen (1O2). These species have single unpaired electrons in their outer orbits that react with molecules in cell membrane or nucleus to cause damages. The destructive effects of **H2O2** in the body are gauged by the action of the glutathione peroxidase and catalase.

ii) **Myloperoxidase–dependent**

- The bactericidal activity of **H2O2** involves the lysosomal

enzyme myeloperoxidase, which in the presence of halide ions converts H2O2 to hypochlorous acid (HOCl). This **H2O2** – halide - myecloperoxidease system is the most efficient bactericidal system in neutrophils. A similar mechanism is also effective against fungi, viruses, protozoa and helminths.

Like the vascular events, the cellular events (i.e. the adhesion, the transmigration, the chemotaxis, & the phagocytosis) are initiated or activated by chemical mediators. Next, we will focus on the sources of these mediators.

IV. Chemical mediators of inflammation

Chemical mediators account for the events of inflammation. Inflammation has the following sequence:

Cell injury –> Chemical mediators –> Acute inflammation (i.e. the vascular & cellular events).

Sources of mediators:

The chemical mediators of inflammation can be derived from plasma or cells.

a) Plasma-derived mediators:

i) Complement activation

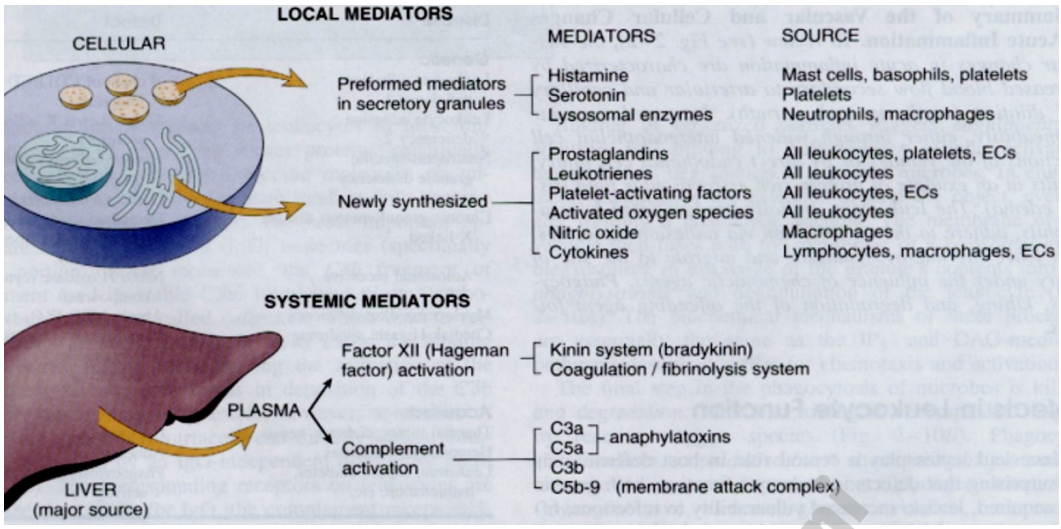
- increases vascular permeability (C3a,C5a)
- activates chemotaxis (C5a)
- opsoninization (C3b,C3bi)

ii) Factor XII (Hegman factor) activation

Its activation results in recruitment of four systems: the kinin, the clotting, the fibrinolytic and the compliment systems.

b) Cell-derived chemical mediatos:

Cell-derived chemical mediators include:



Cellular mediators	Cells of origin	Functions
Histamine	Mast cells, basophiles,	Vascular leakage & platelets
Serotonine	Platelets	Vascular leakage
Lysosomal enzymes	Neutrophiles,	Bacterial & tissue destruction
		macrophages
Prostaglandines	All leukocytes	Vasodilatation, pain, fever
Leukotriens	All leukocytes	LB4
	Chemoattractant LC4, LCD4, & LE4	Broncho and vasoconstriction
Platlete activating factor	All leukocytes	Bronchoconstriction and WBC priming
Activated oxygen species	All leukocytes	Endothelial and tissue damage
Nitric oxide	Macrophages	Leukocyte activation
Cytokines	Lymphocytes, macrophages	Leukocyte activation

- Most mediators perform their biologic activities by initially binding to specific receptors on target cells. Once activated and released from the cells, most of these mediators are short lived. Most mediators have the potential to cause harmful effects.

V. Morphology of acute inflammation

- Characteristically, the acute inflammatory response involves production of exudates. An exudate is an edema fluid with high protein concentration, which frequently contains inflammatory cells.
- A transudate is simply a non-inflammatory edema caused by cardiac, renal, undernutritional, & other disorder

The differences between an exudate and a transudate are

	EXUDATE	TRANSUDATE
Cause:	Acute inflammation	Non-inflammatory disorders
Appearance	Colored, turbid, hemorrhagic	Clear, translucent or pale yellow
Specific gravity:	Greater than or equal to 1.020	Much less
Spontaneous coagulability:	Yes	No
Protein content:	>3gm %	
Cells:	Abundant WBC, RBC, & Cell debris usually present	Only few mesothelial cells
Bacteria:	Present	Absent.

There are different morphologic types of acute inflammation:

1) Serous inflammation

- This is characterized by an outpouring of a thin fluid that is derived from either the blood serum or secretion of mesothelial cells lining the peritoneal, pleural, and pericardial cavities.
- It resolves without reactions

2) Fibrinous inflammation

- More severe injuries result in greater vascular permeability that ultimately leads to exudation of larger molecules such as fibrinogens through the vascular barrier.
- Fibrinous exudate is characteristic of inflammation in serous body cavities such as the pericardium (butter and bread appearance) and pleura.

Course of fibrinous inflammation include:

- Resolution by fibrinolysis
- Scar formation between perietal and visceral surfaces i.e. the exudates get organized
- Fibrous strand formation that bridges the pericardial space

3) Suppurative (Purulent) inflammation

This type of inflammation is characterized by the production of a large amount of pus. Pus is a thick creamy liquid, yellowish or blood stained in colour and composed of

- A large number of living or dead leukocytes (pus cells)
- Necrotic tissue debris
- Living and dead bacteria
- Edema fluid

There are two types of suppurative inflammation:

A) **Abscess formation**: An abscess is a circumscribed accumulation of pus in a living tissue. It is

encapsulated by a so-called pyogenic membrane, which consists of layers of fibrin, inflammatory cells and granulation tissue.

B) **Acute diffuse (phlegmonous) inflammation**

- This is characterized by diffuse spread of the exudate through tissue spaces. It is caused by virulent bacteria (eg. streptococci) without either localization or marked pus formation. Example: Cellulitis (in palmar spaces).
- **4) Catarrhal inflammation**
- This is a mild and superficial inflammation of the mucous membrane. It is commonly seen in the upper respiratory tract following viral infections where mucous secreting glands are present in large numbers, eg. Rhinitis.

5) Pseudomembranous inflammation

- The basic elements of pseudomembranous inflammation are extensive confluent necrosis of the surface epithelium of an inflamed mucosa and severe acute inflammation of the underlying tissues. The fibrinogens in the inflamed tissue coagulate within the necrotic epithelium. And the fibrinogen, the necrotic epithelium, the neutrophilic polymorphs, red blood cells, bacteria and tissue debris form a false (pseudo) membrane which forms a white or colored layer over the

surface of inflamed mucosa.

- Pseudomembranous inflammation is exemplified by Dipthetric infection of the pharynx or larynx and Clostridium difficille infection in the large bowel following certain antibiotic use.

VI. Effects of acute inflammation:

A. Beneficial effects

- **Dilution of toxins**: The concentration of chemical and bacterial toxins at the site of inflammation is reduced by dilution in the exudate and its removal from the site by the flow of exudates from the venules through the tissue to the lymphatics.
- **Protective antibodies**: Exudation results in the presence of plasma proteins including antibodies at the site of inflammation. Thus, antibodies directed against the causative organisms will react and promote microbial destruction by phagocytosis or complement-mediated cell lysis.
- **Fibrin formation**: This prevents bacterial spread and enhances phagocytosis by leukocytes.
- **Plasma mediator systems provisions**: The complement, coagulation, fibrinolytic, & kinin systems are provided to the area of injury by the process of inflammation.
- **Cell nutrition**: The flow of inflammatory exudates brings with it glucose, oxygen and other nutrients to meet the metabolic requirements of the greatly increased number of cells. It also removes their solute waste products via lymphatic channels.
- **Promotion of immunity**: Micro-organisms and their toxins are carried by the exudates, either free or in phagocytes, along the lymphaics to local lymph nodes where they stimulate an immune response with the generation of antibodies and cellular immune mechanisms of defense.

B. Harmful effects

- **Tissue destruction** Inflammation may result in tissue necrosis and the tissue necrosis may, in turn, incite inflammation.
- **Swelling:** The swelling caused by inflammation may have serious mechanical effects at certain locations. Examples include acute epiglottitis with interference in breathing; Acute

meningitis and encephalitis with effects of increased intracranial pressure.

- **Inappropriate response:** The inflammatory seen in hypersensitivity reactions is inappropriate (i.e. exaggerated).

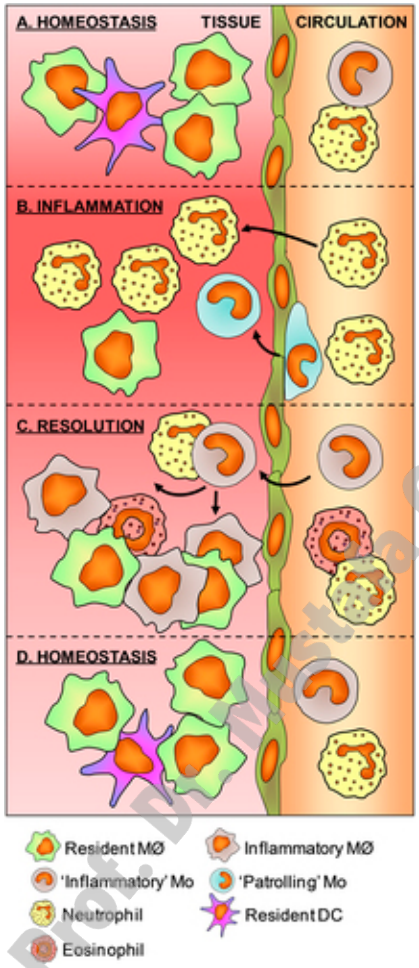
VII. Course of acute inflammation

Acute inflammation may end up in:

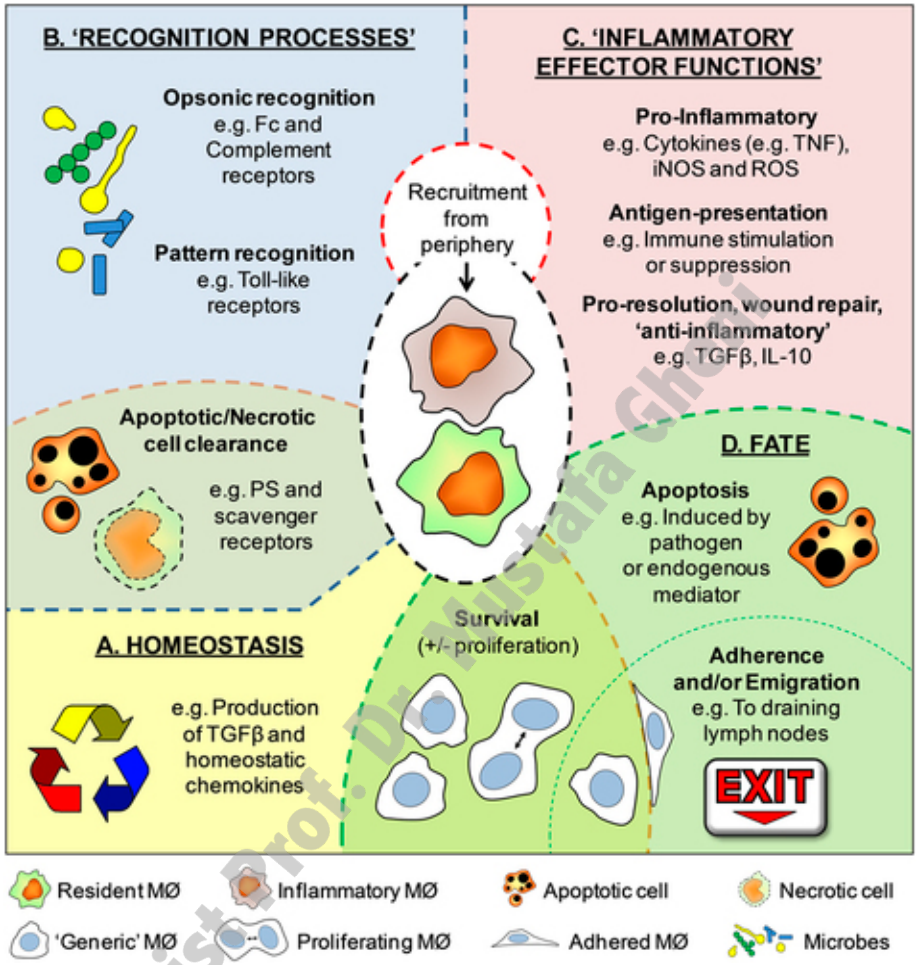
- Resolution: i.e. complete restitution of normal structure and function of the tissue, eg. lobar pneumonia.
- Healing by fibrosis (scar formation).
- Abscess formation {Surgical law states -Thou shallt (you shold) drain all abscesses.} However, if it is left untouched, it may result in

- **Sinus formation** - when an abscess cavity makes contact with only one epithelial lining.

- **Fistula formation**: when an abscess tract connects two epithelial surfaces. Or very rarely to septicemia or Pyemia with subsequent metastatic abscess in heart, kidney, brain etc.



Summary of the dynamics of monocytes and macrophages during an acute inflammatory response. (A) Under homeostatic conditions, a population of tissue-resident macrophages and DCs exists within tissues. (B) At the outset of inflammation, after injury or infection, inflammatory cells are rapidly recruited to the inflammatory lesion. The most rapidly recruited cells being neutrophils and a subset of 'patrolling' monocytes although 'conventional' monocytes enter with slower kinetics. Tissue-resident macrophage numbers drop (the 'macrophage disappearance reaction') and the mechanism for this is thought to include increased tissue adherence and emigration to draining lymph nodes, although cell death may also play a role. (C) During the resolution phase, which is often taken as the period after the drop in the predominant granulocyte population, macrophages increase in number. These macrophages are either inflammatory monocyte-derived cells or re-emerging tissue-resident macrophages of often ill-defined origins. The restoration of tissue-resident macrophages occurs by (i) either differentiation of recruited monocytes or conversion of inflammatory macrophages; (ii) existence of dedicated precursors; (ii) local proliferation of mature macrophages (as has been observed in the skin, brain and peritoneal cavity). (D) Homeostasis returns and the resident macrophage and DC populations return to normal, although this is likely to be a very protracted process.



Summary of macrophage activities during acute inflammation. During an acute inflammatory response, macrophages have been attributed to many roles from immune-surveillance to regulation of pro/anti-inflammatory responses and the restoration of homeostasis. (A) In normal tissues, macrophages play homeostatic roles integral to the tissue, both maintaining and responding to their environment. (B) Many of these processes are mediated through recognition systems, e.g. the recognition of dead or dying cells during homeostasis or disease (e.g. by scavenger and phosphatidylserine receptors); or the recognition of infecting microbes/viruses by opsonic (e.g. complement and Fc receptors) or non-opsonic receptors (e.g. lectins, scavenger receptors, Toll-like

receptors, etc.). (C) These recognition events determine the effector functions of the cells, which range from pro-inflammatory antigen-presenting roles to anti-inflammatory homeostatic roles. (D) The fate of macrophages during an acute inflammatory response can involve cell death (e.g. pathogen-induced apoptosis) or increased adherence and emigration to draining lymph nodes. Additionally, macrophage proliferation has been observed during inflammation and it is unclear in many situations what role this plays in the restoration of homeostasis. In most of these cases, it is not clear whether specific subsets of macrophages, such as inflammatory monocyte-derived macrophages and tissue-resident macrophages, favour specific activities during an acute inflammatory response.