Literature Review
Inflammation is an adaptive response that is triggered by noxious stimuli and conditions such as infection and tissue injury. Considerable progress has been made in understanding the cellular and molecular events that are involved in the acute inflammatory response to infection and, to a lesser extent, to tissue injury. Inflammation may be defined as the response of living tissue to injury. It involves a well-organized cascade of fluidic and cellular changes (Barton, 2008), is recognizable grossly and histologically, and has both beneficial and detrimental effects locally and systemically (Pober and Sessa, 2007).

**Signs and symptoms of inflammation**

**Redness** (rubor): An acutely inflamed tissue appears red, due to dilation of small blood vessels within the damaged area (hyperemia).

**Swelling** (tumor): Swelling results from edema, the accumulation of fluid in the extravascular space as part of the inflammatory fluid exudate, and, to a much lesser extent, from the physical mass of the inflammatory cells migrating into the area.

**Heat** (calor): Increase in temperature is readily detected in the skin. It is due to increased blood flow (hyperemia) through the region, resulting in vascular dilation and the delivery of warm blood to the area.

**Pain** (dolor): Pain results partly from the stretching and distortion of tissues due to inflammatory edema and, in part, from some of the chemical mediators of acute inflammation, especially bradykinin and some of the prostaglandins.
Loss of function (functio laesa): Loss of function, a well-known consequence of inflammation, was added by Virchow (1821-1902) to the list of features described in Celsus’ written work. Movement of an inflamed area is inhibited by pain, either consciously or by reflexes, while severe swelling may physically immobilize the affected area.

Causes of Inflammation (Nathan, 2002)

1. Microbial infections
One of the most common causes of inflammation is microbial infection. Microbes include viruses, bacteria, protozoa, fungi and various parasites. Viruses lead to death of individual cells by intracellular multiplication, and either cause the cell to stop functioning and die, or cause explosion of the cell (cytolytic), in which case also it dies. Bacteria release specific toxins – either exotoxins or endotoxins. Exotoxins are produced specifically for export (like anthrax toxins or tetanus toxins), whereas endotoxins are just part of the cell walls of Gram negative bacteria and also do terrible things to the body, but they aren’t as specific in their actions as the exotoxins (van der Poll and Opal, 2008)

2. Hypersensitivity reactions
A hypersensitivity reaction occurs when an altered state of immunologic responsiveness causes an inappropriate or excessive immune reaction that damages the tissues. Hypersensitivity reactions require a pre-sensitized (immune) state of the host. Hypersensitivity reactions can be divided into four types: type I, type II, type III and type IV, based on the mechanisms involved and time taken for the reaction. Frequently, a particular clinical condition (disease) may involve more than one type of reaction.

3. Physical agents, irritant and corrosive chemicals
   Tissue damage leading to inflammation may occur through physical trauma, ultraviolet or other ionizing radiation, burns or excessive cooling ('frostbite'). Corrosive chemicals (acids, alkalis, oxidizing agents) provoke inflammation through direct tissue damage. These chemical irritants cause tissue damage that leads directly to inflammation.
4. Tissue necrosis

Death of tissues from lack of oxygen or nutrients resulting from inadequate blood flow (infarction) is a potent inflammatory stimulus. The edge of a recent infarct often shows an acute inflammatory response.

**Early stages of acute inflammation**

In the early stages, oedema, fibrin and neutrophil polymorphs accumulate in the extracellular spaces of the damaged tissue. The presence of the cellular component neutrophil is essential for a histological diagnosis of acute inflammation. These cells begin to appear in the wound rapidly after damage has occurred, usually achieving their maximum population within 48 hours, phagocytosing bacteria. Neutrophils have a very short life span; their numbers begin to decline after around 72 hours, particularly if there is no infection (Serhan and Savill, 2005).

The acute inflammatory response involves three processes:
1. Changes in vessel diameter and, consequently, flow.
2. Increased vascular permeability and formation of the fluid exudates.
3. Formation of the cellular exudate - emigration of the neutrophil polymorphs into the extravascular space.

**Changes in vessel diameter**

The microcirculation consists of the network of small capillaries lying between arterioles, which have a thick muscular wall, and thin-walled venules. Capillaries have no smooth muscle in their walls to control their diameter, and are so narrow that red blood cells must pass through them in single file. The smooth muscle of arteriolar walls forms pre-capillary sphincters which regulate blood flow through the capillary bed. Flow through the capillaries is intermittent, and some form preferential channels for flow while others are usually shut down. In blood vessels larger than capillaries, blood cells flow mainly in the centre of the lumen (axial flow), while the area near the vessel wall carries only plasma (plasmatic zone). This feature of normal blood flow keeps blood cells away from the vessel wall. Changes in the microcirculation occur as a physiological
response; for example, there is hyperaemia in exercising muscle and active endocrine glands. The changes following injury which make up the vascular component of the acute inflammatory reaction were described by Lewis in 1927 as 'the triple response to injury': a flush, a flare and a wheal.

For example, if a blunt instrument is drawn firmly across the skin, the following sequential changes take place. A momentary white line follows the stroke; this is due to arteriolar vasoconstriction, the smooth muscle of arterioles contracting as a direct response to injury (Jussila and Alitalo, 2002). This is followed by:

1. The flush: a dull red line follows due to capillary dilatation.
2. The flare: a red, irregular, surrounding zone then develops, due to arteriolar dilatation. Both nervous and chemical factors are involved in these vascular changes.
3. The wheal: a zone of edema develops due to exudation into the extra-vascular space.

The initial phase of arteriolar constriction is transient, and probably of little importance in inflammation. The subsequent phase of vasodilation (active hyperaemia) may last from 15 minutes to several hours, depending upon the severity of the injury. As blood flow begins to slow down, blood cells begin to flow nearer to the vessel wall, in the plasmatic zone rather than the axial stream. This allows 'pavementing' of leukocytes (their adhesion to the vascular epithelium) to occur, which is the first step in leukocyte emigration into the extravascular space. The slowing of blood flow which follows the phase of hyperaemia is due to increased vascular permeability,
allowing plasma to escape into the tissues while blood cells are retained within the vessels. The blood viscosity is therefore increased.

**Increased vascular permeability**

Small blood vessels are lined by a single layer of endothelial cells. In some tissues, these form a complete layer of uniform thickness around the vessel wall, while in other tissues there are areas of endothelial cell thinning, known as fenestrations. The walls of small blood vessels act as a microfilter, allowing the passage of water and solutes but blocking that of large molecules and cells. Oxygen, carbon dioxide and some nutrients transfer across the wall by diffusion, but the main transfer of fluid and solutes is by ultra filtration. The high colloid osmotic pressure inside the vessel, due to the presence of plasma proteins, encourages fluid return to the vascular compartment. Under normal circumstances, high hydrostatic pressure at the arteriolar end of capillaries forces fluid out into the extra vascular space, but this fluid returns into the capillaries at their venous end, where hydrostatic pressure is low. In acute inflammation, however, not only is capillary hydrostatic pressure increased, but there is also escape of plasma proteins into the extra vascular space, increasing the osmotic pressure there. Consequently, much more fluid leaves the vessels than is returned to them. The net escape of protein-rich fluid is called exudation; hence, the fluid is called the fluid exudates (Byzova et al., 2002; Jussila and Alitalo, 2002; Karkkainen et al., 2004).

![Changes in vascular permeability during inflammation](image)
Formation of cellular exudates

The accumulation of neutrophil polymorphs (neutrophils) within the extracellular space is the diagnostic histological feature of acute inflammation. There are a number of steps to this process:

1. Margination of neutrophils - In the normal circulation, cells are confined to the central (axial) stream in blood vessels and do not flow in the peripheral (plasmatic) zone near to the endothelium. However, loss of intravascular fluid and increase in plasma viscosity with slowing of flow at the site of acute inflammation allow neutrophils to flow in this plasmatic zone.

2. Adhesion of neutrophils - The adhesion of neutrophils to the vascular endothelium which occurs at sites of acute inflammation is termed 'pavementing' of neutrophils. Neutrophils randomly contact the endothelium in normal tissues, but do not adhere to it. However, at sites of injury, pavementing occurs early in the acute inflammatory response and appears to be a specific process occurring independently of the eventual slowing of blood flow. Increased leukocyte adhesion results from interaction between adhesion molecules on leukocyte and endothelial surfaces (Matsushima et al., 1988). Leukocyte surface adhesion molecule expression is increased by complement factors, leukotrienes, and tumour necrosis factor (TNF).
Neutrophil and endothelial cell interactions in inflammation

As the neutrophil rolls along the blood-vessel wall, the L-selectin on its surface binds to carbohydrate structures such as Sialyl Lewis X on the adhesion molecules on the vascular endothelium, and its progress is eventually halted. As the neutrophil becomes activated, it replaces L-selectin with other cell-surface adhesion molecules such as integrins. These molecules bind E-selectin, which is present on the blood-vessel wall as a result of the influence of inflammatory mediators such as bacterial lipopolysaccharides and the cytokines interleukin-1 and TNF-alpha. The activated neutrophil then enters the tissues, where it is attracted to the infection site by a number of chemoattractants. The neutrophil can then phagocytose and destroy the C3b-coated bacteria.

3. Neutrophil emigration - Leukocytes migrate by active amoeboid movement through the walls of venules and small veins, but do not commonly exit from capillaries. Electron microscopy shows that neutrophil and eosinophil polymorphs and macrophages can insert pseudopodia between endothelial cells, migrate through the gap so created between the endothelial cells, and then on through the basal lamina into the vessel wall. This process is
known as diapedesis. The defect appears to be self-sealing, and the endothelial cells are not damaged by this process.

Transendothelial migration of neutrophils during inflammation

4. Escape of red cells – Red cells may also escape from vessels, but in this case the process is passive and depends on hydrostatic pressure forcing the red cells out. The presence of large numbers of red cells in the extravascular space implies severe vascular injury, such as a tear in the vessel wall (Sokol et al., 2008).

The following are the next consequences of acute inflammation:

Beneficial effects: Both the fluid and cellular exudates may have useful effects. Beneficial effects of the fluid exudates are:

• Dilution of toxins, such as those produced by bacteria, allows them to be carried away in lymphatics.

• Entry of antibodies, due to increased vascular permeability into the extravascular space, may lead either to lysis of micro-organisms, through the participation of complement, or to their phagocytosis by opsonisation. Antibodies are also important in neutralisation of toxins.

• Transport of drugs such as antibiotics may occur to the site where bacteria are multiplying.
• Fibrin formation from exuded fibrinogen may impede the movement of microorganisms, trapping them and so facilitating phagocytosis.

• Delivery of nutrients and oxygen, essential for cells such as neutrophils which have high metabolic activity, is aided by increased fluid flow through the area.

• Stimulation of immune response by drainage of this fluid exudate into the lymphatics allows particulate and soluble antigens to reach the local lymph nodes where they may stimulate the immune response.

The role of neutrophils in the cellular exudate has already been mentioned. They have a life-span of only 1-3 days and must be constantly replaced. Most die locally, but some leave the site via the lymphatics. Blood monocytes also arrive at the site and, on leaving the blood vessels, transform into macrophages, becoming more metabolically active, motile and phagocytic. Phagocytosis of micro-organisms is enhanced by opsonisation by antibodies or by complement. In most acute inflammatory reactions, macrophages play a lesser role in phagocytosis compared with that of neutrophils. They appear late in the response and are usually responsible for clearing away tissue debris and damaged cells (Goerdt and Orfanos, 1999).
Harmful effects:

The release of lysosomal enzymes by inflammatory cells may also have harmful effects.

- **Digestion of normal tissues**: Enzymes such as collagenases and proteases may digest normal tissues, resulting in their destruction. This may particularly result in vascular damage.
- **Swelling**: The swelling of acutely inflamed tissues may be harmful by increasing pressure on surrounding tissues, or resulting in a blockage of a vessel or duct.
- **Inappropriate inflammatory response**: Sometimes acute inflammatory responses appear inappropriate, such as those which occur in type I hypersensitivity reactions (e.g. hay fever) where the provoking environmental antigen (e.g. pollen) otherwise poses no threat to the individual. Such allergic inflammatory responses may be life-threatening, e.g., asthma.

**Chronic inflammation**

Chronic inflammation, like its acute counterpart, is a host response to an inciting stimulus. There are, however, some distinct differences. First and foremost is the time factor. Chronic inflammation is considered to be an inflammation of prolonged duration - weeks to months. Second, rather than being just exudative, chronic inflammation usually is productive or proliferative. It is rarely gooey. Cells in the chronic inflammatory process tend to produce substances that add new tissues, such as collagen and new blood vessels. Many of these changes also represent the repair process and there is a blurry continuum between chronic inflammation and the whole repair process. In general, chronic inflammation is characterized by inflammation, tissue destruction, and attempts at repair all happening at once (Gutcher and Becher, 2007; Romagnani, 1996).

Grossly, chronic inflammation does not have as much *rubor* (redness) or *calor* (heat) as in the acute reaction. Also, exudates are not as grossly apparent as they are in acute inflammation. Because of the fibroplasia and neovascularization, areas affected by chronic inflammation tend to be slightly swollen and firm. If fibrosis is extensive, the lesions can be large and disfiguring. Fibrosis (granulation tissue) is the best indicator that the inflammatory response is chronic.
The commonest appearances of chronic inflammation are:

- Chronic ulcer, such as a chronic peptic ulcer of the stomach with breach of the mucosa, a base lined by granulation tissue and with fibrous tissue extending through the muscle layers of the wall
- Chronic abscess cavity, for example osteomyelitis.
- Thickening of the wall of a hollow structure by fibrous tissue in the presence of a chronic inflammatory cell infiltrate.
- Granulomatous inflammation, perhaps with caseous necrosis as in chronic fibrocaseous tuberculosis of the lung.
- Fibrosis, which may become the most prominent feature of the chronic inflammatory reaction when most of the chronic inflammatory cell infiltrate has subsided.

**Progression to chronic inflammation**

If the causative agent is not removed, acute inflammation may progress to the chronic stage. In addition to organisation of the tissue as just described, the character of the cellular exudate changes, with lymphocytes, plasma cells and macrophages (sometimes including multinucleate giant cells) replacing the neutrophil polymorphs. Sometimes chronic inflammation occurs as a primary event, there being no preceding period of acute inflammation (Firlik, 1992).
The inflammatory ‘pathway’

The inflammatory response is coordinated by a large range of mediators that form complex regulatory networks. To dissect these complex networks, it is helpful to place these signals into functional categories and to distinguish between inducers and mediators of inflammation. Inducers are the signals that initiate the inflammatory response (Fujiwara and Kobayashi, 2005; Mogensen, 2009; Petaja). They activate specialized sensors, which then elicit the production of specific sets of mediators.
Example of a common inflammatory signaling process

The mediators, in turn, alter the functional states of tissues and organs (which are the effectors of inflammation) in a way that allows them to adapt to the conditions indicated by the particular inducer of inflammation. Thus, a generic inflammatory pathway consists of inducers, sensors, mediators and effectors, with each component determining the type of inflammatory response.
The four pathway components are discussed below.

Exogenous inducers can be classified into two groups: microbial and non-microbial. There are, in turn, two classes of microbial inducers: pathogen-associated molecular patterns (PAMPs) and virulence factors. The first class of microbial inducer, PAMPs, is a limited and defined set of conserved molecular patterns that is carried by all microorganisms of a given class (whether pathogenic or commensal) (Medzhitov and Janeway, 1997).

PAMPs are defined in the sense that the host has evolved a corresponding set of receptors (known as pattern-recognition receptors) that detect their presence. The second class of microbial inducers comprises a variety of virulence factors and is therefore restricted to pathogens. In contrast to PAMPs, they are not sensed directly by dedicated receptors. Instead, the effects of their activity, particularly their adverse effects on host tissues, are responsible for triggering the inflammatory response.

Typical activities of virulence factors can be detected by specialized sensors. For example, the pore-forming exotoxins produced by Gram-positive bacteria are detected by the NALP3 (NACHT-, leucine-rich-repeat- and pyrin-domain-containing protein) inflammasome, which is sensitive to the efflux of K+ ions that results from pore formation (Mariathasan et al., 2006). Similarly, the proteolytic activity of proteases produced by helminthes is sensed by basophils through an unknown sensor (Sokol et al., 2008). Notably, this sensing mechanism can be inadvertently activated by functional mimics, so allergens that are proteases can trigger the pathway that is usually induced by helminthes. An alternative way of sensing virulence activity...
is non-specific and even more indirect, through detecting the effects on cell death and tissue damage. In this case, the actual inducers of the inflammatory response are endogenous products of damaged cells and tissues. Importantly, the inflammatory responses that are induced by these two sensing mechanisms of virulence activity differ in their specificity, because the former is characteristic of pathogens (and in some cases, pathogen classes), but the latter is not. These inflammatory responses are likely to have different characteristics, and it will be interesting to investigate whether they result in distinct physiological and pathological outcomes.

It should be emphasized that microbial inducers of inflammation are not necessarily derived from pathogens. Commensal bacteria provide an important source of inflammation inducers that are detected by TLR (Rakoff-Nahoum et al., 2004). The activation of TLRs by these bacteria is actively suppressed by multiple mechanisms. An example of this is the lethal TLR-dependent inflammation that develops in mice that lack A20, one of the crucial negative regulators of TLR signaling (Turer et al., 2008).

Exogenous inducers of inflammation that are of non-microbial origin include allergens, irritants, foreign bodies and toxic compounds. Certain allergens are detected because they mimic the virulence activity of parasites (as mentioned earlier); others can act as irritants on the mucosal epithelia. The inflammatory response induced by both types of allergen is largely similar because defence against parasites and environmental irritants relies on expulsion and clearance mediated by the mucosal epithelia. The sensors for allergens are largely unknown. Foreign bodies are indigestible particles that either are too large to be phagocytosed or cause phagosomal membrane damage in macrophages. Silica and asbestos particles are notorious examples of foreign bodies that elicit an inflammatory response. Their large size and resistance to removal, as well as a lack of self markers (such as CD47) that are normally present on autologous cells and prevent their phagocytosis (by engaging inhibitory receptors), point to an abnormal occurrence in the tissues. The ‘missing self’ recognition presumably triggers a ‘phagocytic reflex’ in macrophages, but the large size or the shape of foreign particles results in ‘frustrated phagocytosis’, that is, a phagocytic cup is formed but cannot close to form a phagosome. If a foreign body is too large for a phagocytic cup to be formed, the macrophage forms a granuloma around this body instead. The sensor that triggers this reaction in macrophages is unknown. In some cases, macrophages can fuse with each other to form ‘giant cells’ that encapsulate the foreign body. The encapsulation of
foreign objects is an ancient defensive strategy, which is also found in *Drosophila melanogaster*, in which lamellocytes (macrophage-like cells) encapsulate parasitoid wasp eggs to protect the host (Rizki and Rizki, 1992). Regardless of whether a foreign body is too large to be phagocytosed or disrupts the phagosomal membrane, the NALP3 inflammasome (a sensor) is activated when a macrophage encounters foreign bodies (Dostert et al., 2008).

**Mediators and effectors of inflammation**

Inducers of inflammation trigger the production of numerous inflammatory mediators, which in turn alter the functionality of many tissues and organs — the downstream effectors of the inflammatory pathway. Many of these inflammatory mediators have effects in common on the vasculature and on the recruitment of leukocytes. These mediators can be derived from plasma proteins or secreted by cells (Barton, 2008). The cellular mediators can be produced by specialized leukocytes (particularly tissue-resident macrophages and mast cells) or by cells present in local tissues. Some mediators (such as histamine and serotonin) are preformed and stored in the granules of mast cells, basophils and platelets. Others are preformed and circulate as inactive precursors in the plasma. The plasma concentration of these mediators can increase markedly as a result of increased secretion of the precursors by hepatocytes during the acute-phase response. Other mediators are produced directly in response to appropriate stimulation by inducers of inflammation. Inflammatory mediators can be classified into seven groups according to their biochemical properties (Barton, 2008): vasoactive amines, vasoactive peptides, fragments of complement components, lipid mediators, cytokines, chemokines and proteolytic enzymes.

**First**, vasoactive amines (histamine and serotonin) are produced in an all-or-none manner when mast cells and platelets degranulate. They have complex effects on the vasculature, causing increased vascular permeability and vasodilation, or vasoconstriction, depending on the context. The immediate consequences of their release by mast cells can be highly detrimental in sensitized organisms, resulting in vascular and respiratory collapse during anaphylactic shock.
Second, vasoactive peptides can be stored in an active form in secretory vesicles (for example, substance P) or generated by proteolytic processing of inactive precursors in the extracellular fluid (for example, kinins, fibrinopeptide A, fibrinopeptide B and fibrin degradation products). Substance P is released by sensory neurons and can itself cause mast-cell degranulation. Other vasoactive peptides are generated through proteolysis by the Hageman factor, thrombin or plasmin, and cause vasodilation and increased vascular permeability (either directly or by inducing the release of histamine from mast cells). The Hageman factor has a key role in coordinating these responses and functions as both a sensor of vascular damage and an inducer of inflammation. It activates the kallikrein–kinin cascade; the main product of this cascade, bradykinin, affects the vasculature, as well as exerts a potent pro-algesic (pain-stimulating) effect. Pain sensation has an important physiological role in inflammation by alerting the organism to the abnormal state of the damaged tissue.

Third, the complement fragments C3a, C4a and C5a (also known as anaphylatoxins) are produced by several pathways of complement activation. C5a (and to a lesser extent C3a and C4a) promote granulocyte and monocyte recruitment and induce mast-cell degranulation, thereby affecting the vasculature.

Fourth, lipid mediators (eicosanoids and platelet-activating factors) are derived from phospholipids, such as phosphatidylcholine, that are present in the inner leaflet of cellular membranes. After activation by intracellular Ca\(^{2+}\) ions, cytosolic phospholipase A2 generates arachidonic acid and lysophosphatidic acid, the precursors of the two classes of lipid mediators, from phosphatidylcholine. Arachidonic acid is metabolized to form eicosanoids either by cyclooxygenases (COX1 and COX2), which generate prostaglandins and thromboxanes, or by lipoxygenases, which generate leukotrienes and lipoxin (Barton, 2008). The prostaglandins PGE2 and PG12, in turn, cause vasodilation; PGE2 is also hyperalgesic and a potent inducer of fever (Boughton-Smith et al., 1988). Lipoxins (and dietary ω3-fatty-acid-derived resolvins and protectins) inhibit inflammation and promote resolution of inflammation and tissue repair (Jussila and Alitalo, 2002). The second class of lipid mediators, platelet-activating factors, are generated by the acetylation of lysophosphatidic acid and activate several processes that occur
during the inflammatory response, including recruitment of leukocytes, vasodilation and vasoconstriction, increased vascular permeability and platelet activation (Barton, 2008).

**Fifth**, inflammatory cytokines [tumour-necrosis factor-α (TNF-α), IL-1, IL-6 and many others] are produced by many cell types, most importantly by macrophages and mast cells. They have several roles in the inflammatory response, including activation of the endothelium and leukocytes and induction of the acute-phase response.

**Sixth**, chemokines are produced by many cell types in response to inducers of inflammation. They control leukocyte extravasation and chemotaxis towards the affected tissues.

**Seventh**, several proteolytic enzymes (including elastin, cathepsins and matrix metalloproteinases) have diverse roles in inflammation, in part through degrading ECM and basement-membrane proteins.

These proteases have important roles in many processes, including host defence, tissue remodeling and leukocyte migration. It is unclear to what extent the nature of an inflammatory trigger dictates the type of mediator induced. In addition, many (but not all) mediators not only have direct effects on target tissues but also themselves induce the production of additional mediators. It will be important to understand the logic underlying this hierarchy of mediators. The effectors of an inflammatory response are the tissues and cells, the functional states of which are specifically affected by the inflammatory mediators. Responsiveness to certain inflammatory mediators (such as TNF-α and IL-1) is almost ubiquitous, although these mediators have distinct effects in different tissue and cell types. Although the most obvious effect of inflammatory mediators is to induce the formation of exudates (through their effects on the vasculature and on leukocyte migration), many inflammatory mediators have other, equally important, effects on neuroendocrine and metabolic functions and on the maintenance of tissue homeostasis in general (Turnbull and Rivier, 1999). These functions of inflammatory mediators reflect a more general role for inflammation in the control of tissue homeostasis and in adaptation to noxious conditions.
The inflammatory process is usually tightly regulated, involving both signals that initiate and maintain inflammation and those that shut the process down. An imbalance between the two signals leaves inflammation unchecked, resulting in cellular and tissue damage. Macrophages are a major component of the mononuclear phagocyte system that consist of closely related cells of bone marrow origin, including blood monocytes and tissue macrophages. From the blood, monocytes migrate into various tissues and transform into macrophages. In inflammation, macrophages have three major functions: antigen presentation, phagocytosis, and immunomodulation through production of various cytokines and growth factors. Macrophages play a critical role in the initiation, maintenance, and resolution of inflammation. They are activated and deactivated in the inflammatory process. Activation signals include cytokines (interferon γ, granulocyte-monocyte colony stimulating factor, and tumor necrosis factor α), bacterial lipopolysaccharides, extracellular matrix proteins, and other chemical mediators. Inhibition of inflammation by removal or deactivation of mediators and inflammatory effector cells permits the host to repair damaged tissues. Activated macrophages are deactivated by anti-inflammatory cytokines (interleukin 10 and transforming growth factor β) and cytokine antagonists that are mainly produced by macrophages. Macrophages participate in the autoregulatory loop in the inflammatory process. Because these produce a wide range of biologically active molecules participating in both beneficial and detrimental outcomes in inflammation, therapeutic interventions targeting macrophages and their products may open new avenues for controlling inflammatory diseases.

**Systemic inflammatory response**

- Systemic insult leads to systemic inflammatory response.
- Systemic inflammatory response may not be necessarily autoaggressive.
- Inflammatory processes are delocalized; if dysregulation is than added, autoaggressive inflammation starts.
The systemic inflammatory response from sepsis and major trauma is associated with immunosuppression, in both cell-mediated and humoral systems (Barton, 2008; Jussila and Alitalo, 2002; Nathan, 2002; Pober and Sessa, 2007; Serhan and Savill, 2005; van der Poll and Opal, 2008). Interestingly, the extent of the individual’s inflammatory response is variable and unpredictable; this variability may be due to genetic differences. Although the full picture is yet to emerge, much advancement has been made in the last decade to understand the treatment process better and target it towards this complex process.

In 1991, a new concept – systemic inflammatory response syndrome (SIRS) – was postulated to define the state of patients who exhibit a systemic response to inflammatory episodes. SIRS is diagnosed by a combination of available clinical signs and symptoms. Nowadays, sepsis is generally defined as SIRS induced by infection. No worldwide statistics on the occurrence of sepsis are available. In the USA alone, however, it is estimated that there are 300,000–500,000 septic episodes each year, with mortality rates ranging from 20% to 40%. Refractory hypotension (septic shock) is the main cause of death within a few days of the onset of sepsis. Later, MOF/MODS become(s) the primary clinical problem and main cause of mortality. Patient develops septic shock or sequential MOF/MODS, the mortality rate about increases to 60–70% aprox. Gram-negative bacteria are responsible for 45–60% of sepsis caused by bacterial infection when mixed-organism infections are included (Berg et al., 2003; Brealey et al., 2002). Septic shock has been reported to be a complication in 20–50% of patients with sepsis. The initial
The cardiovascular response to sepsis is generally characterized by high cardiac output and low systemic vascular resistance. Even though the cardiac output might be maintained above normal levels, impaired myocardial contractility, inadequate distribution of blood flow, and disturbance of tissue oxygen use are common and contribute to the development of MOF/MODS which is defined as a syndrome that consists of the sequential failure of two or more organ systems. The mortality of patients who have three or more types of organ failure is particularly high. The cardiovascular system, central nervous system, coagulation system, liver, lungs, and kidneys are commonly involved in septic MOF/MODS. If specific conditions are met, the lung dysfunction is termed acute lung injury or acute respiratory distress syndrome (ARDS), and the coagulatory disorder is diagnosed as disseminated intravascular coagulation (DIC). The clinical features of the dysfunction of each organ in sepsis are summarized in below.

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<th>Type</th>
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| Moderate sepsis             | Body temperature >38°C or <36°C  
Aka, systemic inflammatory response syndrome (SIRS)  
Heart rate >90 beats/min  
Respiratory rate >20 breaths/min or partial pressure of arterial CO₂ <32 mm Hg  
White cell count >12,000/mm³, or >10 percent immature band forms  
Evidence of infection |
| Severe sepsis               | Sepsis-associated lactic acidosis, oliguria, or acute alteration of mental status |
| Septic shock                | Sepsis-induced hypotension (i.e., systolic blood pressure <90 mm Hg) despite adequate fluid resuscitation. Patients treated with vasopressors or inotropic medications may not be hypotensive at the time of measurement. |

*Types and characteristics of sepsis*

- **The LPS-induced signaling pathway**

LPS is a constituent of the cell wall of Gram-negative bacteria. The major biological activities of LPS are mainly attributed to a lipid component, termed lipid A. LPS interacts with CD14, a
receptor on macrophages/monocytes and neutrophils. CD14 is a glycerophosphatidylinositol (GPI)-anchored glycoprotein that lacks a cytoplasmic portion. LPS-binding protein (LBP) might facilitate the interaction of LPS with CD14 or effect the clearance of LPS from the circulation by transferring LPS from CD14.

Involvement of protein kinases in the transduction of LPS-induced responses has also been found in different signaling cascades. Such kinases include protein kinase C, and mitogen-activated protein kinases (MAPK) such as p42 (ERK2), p44 (ERK1) and p38. LPS-induced cytokine production requires activation of several transcription factors. Nuclear factor kB (NFkB) and nuclear factor-interleukin 6 (NF-IL-6) are involved in the gene transcription of numerous proinflammatory cytokines, tissue factors, adhesion molecules and inducible NO synthase. LPS activates nuclear translocation of NFkB by modifying its inhibitory subunit, IkB. NFkB activation requires sequential phosphorylation, ubiquitination and degradation of IkB. Recently, IkB kinases that phosphorylate N-terminal serine residues have been identified, but activation of the IkB kinases by the stimulation of monocytes or neutrophils with LPS has not been reported.

- **The pathogenesis of endotoxic shock and multiple organ failure**

A variety of pathophysiologic responses in various tissues and organ systems occur during endotoxemia. In particular, circulatory failure, leukocyte-induced tissue injury and activation of
coagulation systems appear to be critical determinants in the development of sequential organ failure. A number of mediators derived from host cells are responsible for most of the manifestations of endotoxemia. The proinflammatory cytokines, including tumor necrosis factor α (TNF-α), interleukin (IL) 1β, IL-6, IL-8, IL-12, and interferon γ (IFN-γ), play a critical role in the inflammatory responses. NO is now known to induce a variety of responses in addition to hypotension. Some chemokines have recently been found to be involved in the development of LPS induced tissue injury. Lipid mediators, such as platelet activating factor (PAF), prostaglandins, thromboxanes and leukotrienes, also exert a variety of effects in endotoxemia, and the role of the inducible cyclooxygenase 2 (COX-2), which converts arachidonic acid to prostaglandins (PGs) PGE, PGF and PGI2 and thromboxanes, has been extensively investigated. Furthermore, anti-inflammatory mediators such as IL-10 and IL-1 receptor antagonist (IL-1Ra) also contribute to the modulation of inflammatory responses in endotoxemia. A complete discussion on these mediators is outside the scope of this short review, which is focused on recent discoveries that relate to the role of NO, leukocyte-induced tissue injury, the mechanisms of the development of DIC, and immunomodulation by anti-inflammatory mediators in endotoxemia (Hack et al., 1997; Szabo, 1995).

- **Role of increased cellular apoptosis in multiple organ dysfunction and mortality in sepsis**

   Extensive apoptosis of lymphoid cells is a prominent feature of sepsis in both human patients and mice. Moreover, limiting lymphoid-cell apoptosis improves survival in mice with bacterial peritonitis, suggesting that increased programmed cell death of lymphocytes contributes to sepsis-induced lethality. Intestinal epithelial apoptosis also occurs in both patients and animals with sepsis, although most cells in the epithelial sheet are not affected. Despite these observations, neither apoptosis nor necrosis are prominent features in other organs (notably the lungs, liver, or kidneys) that are commonly involved in cases of MODS (Coopersmith et al., 2002; Hotchkiss et al., 2000; Hotchkiss et al., 1999). Thus, it is highly improbable that loss of cell mass per se can account for the development of lung, liver, gut, or kidney dysfunction in patients with MODS.
Sepsis-induced liver dysfunction

Hyperbilirubinemia and liver dysfunction frequently complicate severe sepsis. A recent large, multicenter trial showed that about 45% of patients with severe sepsis have either hepatic failure or dysfunction. Hepatocytes form a specialized epithelial barrier that separates the portal circulation (basolateral) from the biliary system (apical). The production of bile is a highly regulated and coordinated event that depends on the function of various basolateral and apical membrane transport proteins. The initial step in the formation of bile is the uptake of bile acids and bilirubin from the portal blood, which is mediated by various sodium-dependent and sodium-independent transport proteins at the sinusoidal plasma membrane. The rate-limiting step in the formation of bile is the secretion of bile acids at the canalicular plasma membrane. This ATP-dependent process is also mediated by several key transport systems.

Lipopolysaccharide (LPS) and various proinflammatory cytokines involved in the pathogenesis of sepsis (eg, TNF and IL-1β) are known to decrease the expression and activity of the sodium-taurocholate cotransporting polypeptide, the key membrane protein required for the uptake of bile salts from the portal circulation in various in vivo and hepatocyte cell culture studies. The organic anion transporting polypeptide (OATP) family is another group of key basolateral transport proteins responsible for the sodium-independent uptake of both conjugated and unconjugated bilirubin as well as other lipophilic albumin bound compounds. Decreased expression of various OATP transporters has been demonstrated in liver tissue samples from endotoxemic mice (Cui et al., 2001; Green et al., 1996; Hartmann et al., 2002; Trauner et al., 1998). These findings suggest that sepsis-induced cholestasis may be caused in part by impaired uptake of bilirubin and bile salts from the portal blood. Hepatic TJ function can be assessed by measuring serum concentrations of bile acids and conjugated bilirubin. It is noteworthy, therefore, that circulating levels of both of these bile components are increased in mice injected 12 hours earlier with LPS. Furthermore, plasma-to-bile leakage of a macromolecular tracer, another method to measure the integrity of hepatobiliary TJs, is also increased in endotoxemic rodents, further suggesting that TJ function is impaired. Finally, decreased expression of TJ proteins by immunoblotting analysis and altered subcellular localization of these proteins by
immunofluorescence staining have been demonstrated in the liver tissue from these mice, implicating altered epithelial permeability as a key event in the pathogenesis of sepsis induced liver dysfunction.

**Inflammation and neoplastic progression**

Rous was the first to recognize that cancers develop from “subthreshold neoplastic states” caused by viral or chemical carcinogens that induce somatic changes (Mackenzie and Rous, 1941; Rous and Kidd, 1941). These states, now known as “initiation”, involve DNA alterations, are irreversible, and can persist in otherwise normal tissue indefinitely until the occurrence of a second type of stimulation (now referred to as “promotion”). Promotion can result from exposure of initiated cells to chemical irritants, such as phorbol esters, factors released at the site of wounds, partial organ resection, or chronic irritation and inflammation. Functionally, many promoters, whether directly or indirectly, induce cell proliferation, recruit inflammatory cells, increase production of reactive oxygen species leading to oxidative DNA damage, and reduce DNA repair. Subversion of cell death and/or repair programmes occurs in chronically inflamed tissues, thus resulting in DNA replication and proliferation of cells that have lost normal growth control. Normal inflammation is self-limiting, because the production of anti-inflammatory cytokines follows the pro-inflammatory cytokines closely. However, chronic inflammation seems to be due to persistence of the initiating factors or a failure of mechanisms required for resolving the inflammatory response.
Wound healing versus invasive tumour growth. (a) Normal tissues and (b) Invasive carcinomas

- **Normal and cancer tissues architecture**

In normal tissue, epithelial cells sit atop a basement membrane separated from the vascularized stromal (dermis) compartment. Upon wounding or tissue assault, platelets are activated and form a haemostatic plug where they release vasoactive mediators that regulate vascular permeability, influx of serum fibrinogen, and formation of the fibrin clot. Chemotactic factors such as transforming growth factor-β and platelet-derived growth factor, derived from activated platelets, initiate granulation tissue formation, activation of fibroblasts, and induction and activation of proteolytic enzymes necessary for remodelling of the extracellular matrix (for example, matrix metalloproteinases and urokinase-type plasminogen activator). In combination, granulocytes, monocytes and fibroblasts are recruited, the venous network restored, and re-epithelialization across the wound occurs. Epithelial and stromal cell types engage in a reciprocal signalling dialogue to facilitate healing. Once the wound is healed, the reciprocal signalling subsides. Where as, neoplasia-associated angiogenesis and lymphangiogenesis produces a chaotic vascular organization of blood vessels and lymphatics where neoplastic cells interact with other cell types (mesenchymal, haematopoietic and lymphoid) and a remodelled extracellular matrix in caeeous condition. Although the vascular network is not disrupted in the same way during neoplastic progression as it is during wounding, many reciprocal interactions occur in parallel. Neoplastic
cells produce an array of cytokines and chemokines that are mitogenic and/or chemoattractants for granulocytes, mast cells, monocytes/macrophages, fibroblasts and endothelial cells. In addition, activated fibroblasts and infiltrating inflammatory cells secrete proteolytic enzymes, cytokines and chemokines, which are mitogenic for neoplastic cells, as well as endothelial cells involved in neoangiogenesis and lymphangiogenesis. These factors potentiate tumour growth, stimulate angiogenesis, induce fibroblast migration and maturation, and enable metastatic spread via engagement with either the venous or lymphatic networks.

**Inflammatory cell components of tumors**

- Tumour cells produce various cytokines and chemokines that attract leukocytes. The inflammatory component of a developing neoplasm may include a diverse leukocyte population — for example, neutrophils, dendritic cells, macrophages, eosinophils and mast cells, as well as lymphocytes — all of which are capable of producing an assorted array of cytokines, cytotoxic mediators including reactive oxygen species, serine and cysteine proteases, MMPs and membrane-perforating agents, and soluble mediators of cell killing, such as TNF-α, interleukins and interferons or IFNs (Kuper et al., 2000; Wahl and Kleinman, 1998).

- Monocytes, in the presence of granulocyte–macrophage colony-stimulating factor (GM-CSF) and interleukin (IL)-4, differentiate into immature dendritic cells. These migrate into inflamed peripheral tissues where they capture antigens and, after maturation, migrate to lymph nodes to stimulate T-lymphocyte activation. Soluble factors such as IL-6 and CSF-1, derived from neoplastic cells, push myeloid precursors towards a macrophage-like phenotype. Interestingly, dendritic cells found in neoplastic infiltrates are frequently immature and defective in T-cell stimulatory capacity.

- Tumour-associated macrophages (TAMs), derived from monocytes that are recruited largely by monocyte chemotactic protein (MCP) chemokines, are a significant component of inflammatory infiltrates in neoplastic tissues. TAMs have a dual role in neoplasms; although they may kill neoplastic cells following activation by IL-2, interferon and IL-12, they produce a number of potent angiogenic and lymphangiogenic growth factors, cytokines and proteases, all of which are mediators that potentiate neoplastic progression (Brigati et al., 2002; Schoppmann
et al., 2002; Tsung et al., 2002). TAMs and tumour cells also produce IL-10, which effectively blunts the anti-tumour response by cytotoxic T cells. During development of melanoma, activated macrophages produce TGF-β, TNF-α, IL-1α, arachidonate metabolites and extracellular proteases. In response, melanocytes express IL-8 and vascular endothelial growth factor (VEGF)-A, thereby inducing vascular angiogenesis under paracrine control. Indeed, macrophage infiltration is closely associated with the depth of invasion of primary melanoma due, in part, to macrophage regulated tumour-associated angiogenesis.

In addition to altering the local balance of pro-angiogenic factors during melanoma development, during human cervical carcinogenesis TAMs express VEGF-C and VEGF-D as well as the VEGF receptor-3 (VEGFR-3), all of which are implicated in formation of lymphatic vessels and lymphatic metastases (Tsung et al., 2002). By placing TAMs at the centre of the recruitment and response to angiogenic and lymphangiogenic stimuli, they may foster the spread of tumours. TAMs also induce VCAM-1 expression on mesothelial cells, a step also believed to be key for tumour cell dissemination into the peritoneum.

Macrophages are not unique among inflammatory cells in potentiation of neoplastic processes. Genetic and functional experiments indicate that neutrophils, mast cells, eosinophils and activated T lymphocytes also contribute to malignancies by releasing extracellular proteases, pro-angiogenic factors and chemokines (Kuper et al., 2000).

Cancers associated with chronic inflammation

Hypothesis says that many malignancies arise from areas of infection and inflammation, simply as part of the normal host response. Indeed, there is a growing body of evidence that many malignancies are initiated by infections, and upwards of 15% of malignancies worldwide can be attributed to infections, a global total of 1.2 million cases per year. Persistent infections within the host induce chronic inflammation. Leukocytes and other phagocytic cells induce DNA damage in proliferating cells, through their generation of reactive oxygen and nitrogen species that are produced normally by these cells to fight infection (Maeda and Akaike, 1998; Shacter and Weitzman, 2002). These species react to form peroxynitrite, a mutagenic agent. Hence, repeated tissue damage and regeneration of tissue, in the presence of highly reactive nitrogen and
oxygen species released from inflammatory cells, interacts with DNA in proliferating epithelium resulting in permanent genomic alterations such as point mutations, deletions, or rearrangements in damage tissue. Indeed, p53 mutations are seen at frequencies similar to those in tumours in chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease.

- **Role of chemokines tumor and angiogenesis**

Chemokines were initially defined functionally as soluble factors regulating directional migration of leukocytes during states of inflammation; however, chemokine biology extends to all cell types, including most human neoplastic cells. Attention first focused on the role of chemokines during malignancy when it was reported that experimental animals without T or natural killer (NK) cell functions, when challenged with a tumour, showed a typical inflammatory infiltrate; this suggested that neoplastic cells either produce chemotactic factors or induce their expression in nearby ‘host’ cells. It is now appreciated that the chemokine receptor system can be altered dramatically in neoplastic tissue, particularly at the invasive edges. Moreover, chemokines induce direct effects on stromal and neoplastic cells in addition to their roles in regulating leukocyte recruitment (Mantovani et al., 2001).

- **Regulation of tumour growth**

Some tumour cells not only regulate their chemokine expression to help recruit inflammatory cells, but also use these factors to further tumour growth and progression. Melanoma is perhaps the best exemplar in which chemokines (for example, GROα/CXCL1, GROβ/CXCL2, GROγ/CXCL3 and IL-8/CXCL8) have been shown to exert autocrine control over neoplastic cell proliferation. Blocking GROα or the CXCR2 receptor attenuates melanoma cell proliferation *in vitro*, whereas over expression of GROα, GROβ or GROγ in a variety of tumour-derived cell lines enhances their colony-forming activity and tumorigenicity in nude mice. Other CXCR2 ligands have been identified as having autocrine roles in the growth of pancreatic, head and neck, and non-small-cell lung carcinoma (Balentien et al., 1991; Owen et al., 1997; Vicari and Caux, 2002), whereas in mouse models ENA-78/CXCL5 variably affects tumour growth, vascularity and apoptosis. Macrophage pro-inflammatory chemokine-3α (MIP-3α/CCL20), a CC
chemokine, is over expressed in pancreatic carcinoma cells and infiltrating macrophages adjacent to tumours; MIP-3α/CCL20 stimulates growth of neoplastic cells while simultaneously enhancing migration of TAMs.

- **Regulation of angiogenesis**

Activation of angiogenic programmes represents a shift in the balance between pro- and anti-angiogenic factors. Although angiogenesis is strictly controlled, it is associated with chronic inflammatory diseases such as psoriasis, rheumatoid arthritis and fibrosis, as well as with tumour growth and metastasis. It is well established that CXC chemokines with the three amino acids (Glu-Leu-Arg/ELR) immediately amino-terminal to the CXC motif (ELR+) are pro-angiogenic and stimulate endothelial cell chemotaxis, whereas ELR− CXC chemokines (for example, PF-4/CXCL4, MIG/CXCL9 and IP-10/CXCL10) possess angiostatic activities (Strieter et al., 1995). ELR+ CXC ligands bind to CXCR2 and to a lesser degree to CXCR1, whereas ELR− CXC ligands bind to CXCR3, CXCR4 and CXCR5. Compared to VEGF-A, murine MCP-5/CCL12 exhibits only modest mitogenic properties towards endothelial cells; however, it is a potent chemoattractant. In contrast, stromal-cell-derived factor 1 (SDF-1/CXCL12) induces endothelial expression of VEGF-A; VEGF-A in turn upregulates CXCR4 on endothelial cells. Although it is not always clear if the angiostatic and angiogenic effects of chemokines are direct or indirect, it is accepted that the balance between the two regulates neoplastic cell physiology.
Cytokine and chemokine balance regulates neoplastic growth

- Involvement of cytokine and chemokine in angiogenesis

The balance of cytokines in any given tumour is critical for regulating the type and extent of inflammatory infiltrate that forms. Tumours that produce little or no cytokines or an overabundance of anti-inflammatory cytokines induce limited inflammatory and vascular responses, resulting in constrained tumour growth. In contrast, production of an abundance of pro-inflammatory cytokines can lead to a level of inflammation that potentiates angiogenesis, thus favouring neoplastic growth. Alternatively, high levels of monocytes and/or neutrophil infiltration, in response to an altered balance of pro- versus anti-inflammatory cytokines, can be associated with cytotoxicity, angiostasis and tumour regression. In tumours, interleukin-10 is generally a product of tumour cells and tumour-associated macrophages.
Inflammation as an anti-cancer therapeutic opportunity

Perhaps the best evidence for the significance of inflammation during neoplastic progression comes from a study of cancer risk among long-term users of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs). Much data indicates that use of these drugs reduces colon cancer risk by 40–50%, and may be preventative for lung, oesophagus and stomach cancer. The ability of NSAIDs to inhibit cyclo-oxygenases (COX-1 and -2) underlies their mechanism(s) of chemoprevention. COX-2 converts arachidonic acid to prostaglandins, which in turn induces inflammatory reactions in damaged tissues (Baron and Sandler, 2000; Garcia-Rodriguez and Huerta-Alvarez, 2001; Williams et al., 1999). Aspirin is non-selective in its inhibition of platelet function by acetylating and irreversibly inactivating both COX-1 and COX-2. Inactivation prevents platelet synthesis of prostaglandins, endoperoxides and thromboxane A2. Other NSAIDs, for example, flurbiprofen, may have strong anti-metastatic effects because of their inhibition of platelet aggregation. But NSAIDs may act through mechanisms other than inhibition of COX enzyme activity alone, as some NSAIDs lacking COX-inhibitory function show efficacy in inhibiting colon carcinogenesis. Other mechanisms have been proposed, including induction of apoptosis through release of cytochrome C from mitochondria and subsequent activation of caspase-9 and -3, and/or interference with cell-cycle progression, reduction of carcinogen activation and stimulation of immune surveillance.

The pro-inflammatory cytokine TNF-α is also a key downstream mediator in inflammation. Despite the name, TNF-α is important in early events in tumours, regulating a cascade of cytokines, chemokines, adhesions, MMPs and pro-angiogenic activities (Balkwill, 2002). Thus, TNF-α may be one of the ways in which inflammation acts as a tumour promoter. Blocking antibodies that have significant therapeutic efficacy in other inflammatory diseases may have applications in therapy in cancer. Tumours are also rich in mucins and other ligands that may include the sialyl Lewis X epitope recognized by selectins. Because selectins may have a role in metastasis, targeting selectin interaction with heparin or antagonists of the receptor may decrease metastasis. MMPs are produced by inflammatory cells and by stromal cells responding to chemokines and cytokines produced by inflammatory cells in tumour microenvironments. Like inflammatory cells, MMPs may both promote tumour progression and attenuate it. Indeed, MMPs may mediate many of the actions of inflammatory cells in neoplasms. MMPs can recruit
inflammatory cells by releasing chemoattractants and motogens; they also generate growth promoting and cytostatic signals. MMPs activate angiogenesis, but also produce fragments of basement-membrane collagens and plasminogen that are angiogenesis inhibitors. They have both apoptotic and anti-apoptotic actions. Thus, the efficacy of MMP inhibitors may be mediated, at least in part, through anti-inflammatory actions (Coussens et al., 2002; Egeblad and Werb, 2002; Overall and Lopez-Otin, 2002). Given their diverse actions, it is also not surprising that trials with MMP inhibitors have had mixed results, with efficacy reported mostly during early tumour progression.

Possible application of these new insights for targeting metastases

It is clear that anti-inflammatory therapy is efficacious towards early neoplastic progression and malignant conversion. In a fully developed malignancy, there are ‘excess’ inflammatory cells in the tumour microenvironment. Does the tumour need inflammation to help foster angiogenesis? We must think globally and act locally. One approach is to evaluate whether functional polymorphisms in genes that regulate inflammatory processes (for example, genes encoding MMPs, cytokines, chemokines or selectins) harbour altered risk for developing cancer or are indicators of prognosis. Yet for all the local inflammation in tumours, in many cases the overall innate immunity of the host is blunted. The challenge for the future is to normalize the inflammatory network to regain a normal host response overall: decreasing the high levels of tumour-promoting properties of the infiltrating cells, such as pro-inflammatory cytokines, while increasing their tumour-suppressing properties, such as anti-inflammatory cytokines. In this way, later in tumour progression, we can harness the activities that are anti-tumour while suppressing those that are pro-tumour.

Inflammatory cells and cancer: good or bad?

It is now evident that inflammatory cells have powerful effects on tumour development. Early in the neoplastic process, these cells are powerful tumour promoters, producing an attractive environment for tumour growth, facilitating genomic instability and promoting angiogenesis. The inflammatory cells, and the chemokines and cytokines that they produce, influence the
whole tumour organ, regulating the growth, migration and differentiation of all cell types in the tumour microenvironment, including neoplastic cells, fibroblasts and endothelial cells. Later in the tumorigenic process, neoplastic cells also divert inflammatory mechanisms such as selectin–ligand interactions, MMP production and chemokine functions to favour neoplastic spread and metastasis. This may be part of an attempt by the tumour to subvert immune cell functions, so favouring tumour development. Yet, the recruitment of inflammatory cells may also be counterproductive for tumour development, and represent an attempt by the host to suppress tumour growth.

The pro-tumour actions of inflammatory cells include releasing growth and survival factors, promoting angiogenesis and lymphangiogenesis, stimulating DNA damage, remodelling the ECM to facilitate invasion, coating tumour cells to make available receptors for disseminating cells via lymphatics and capillaries, and evading host defence mechanisms. Although inflammatory responses should also be anti-tumour, cancer patients are often defective in their inflammatory responses. This may arise by two distinct tumour-mediated mechanisms: failure to up-regulate the anti-inflammatory cytokines, or subversion of the host response resulting from desensitization of receptors owing to high chemokine and cytokine concentrations that then blunt systemic responses.

*Lipids from microbial sources and their bio-activity*

Microorganisms and their cellular component(s) may possess some degree of bioactivity, either against other microorganism(s) or against certain physiological states of a diseased body. Studies have proposed lipid-therapy approaches in several pathologies from cancer, cardiovascular diseases, neurodegenerative processes, obesity, inflammation and infectious diseases. Both the type and relative amount of lipids in the membrane control numerous functions, such as the regulation of the activity and location of membrane proteins. The existence of specific lipid regions and domains in the cell membrane supports the possibility to design therapies that act on the lipid composition of the cell membrane. The following is a list of few lipid(s) isolated from different microbial sources and their bioactivity.
Bio-active lipid from *Isaria sinclairii*

Myriocin (ISP-I) is an immunosuppressive natural product isolated from the culture broth a type of entomopathogenic fungus (*Isaria sinclairii*) that was an eternal youth nostrum in traditional Chinese medicine. Showing positive results in both *in vitro* (mixed lymphocyte reaction) and *in vivo* screening (prolonging rat skin graft survival time), myriocin was modified through chemical modification to yield fingolimod, code named at the time FTY720 and trade name Gilenya, which is marketed by Novartis. It is a structural analogue of sphingosine and is phosphorylated by sphingosine kinases in the cell (most importantly sphingosine kinase 2). The molecular biology of phosphofingolimod is thought to lie in its activity at one of the five sphingosine-1-phosphate receptors, S1PR1. It can sequester lymphocytes in lymph nodes, preventing them from moving to the central nervous system for autoimmune responses in multiple sclerosis, and was originally proposed as an antirejection medication indicated after transplantation. It has been reported to stimulate the repair process of glial cells and precursor cells after injury. Recently, fingolimod was reported to induce apoptosis in several types of cancer cells such as bladder, breast and glioma cancer cells. In addition, two recent in vivo studies showed that fingolimod prevented tumor growth and metastasis of breast and bladder xenografts in nude mice without causing detectable toxicity in vital organs. These results raised a hypothesis that fingolimod may be a potential anticancer drug (Azuma et al., 2002).

Glycolipid biosurfactants

Sophorolipids (SLs) are glycolipid biosurfactants produced by yeasts and composed of a sophorose moiety (hydrophilic part) linked by a glycosidic bond to a long chain hydroxyl fatty acid (lipophilic part). They are mixtures of many sophorolipid molecules differing in acetylation degree of sophorose, acetyl group position in the sophorose moiety, chain length and unsaturation degree of hydroxyl fatty acid, and hydroxyl group position in the fatty acid moiety. Furthermore, they can be produced in a number of different species including *Candida apicola*, *C. bogoriensis*, *C. bombicola* and *Yarrowia lipolytica* through fermentation of many different substrates, allowing for greater yield of material for modification and potential therapeutic application. Due to the properties of low toxicity, high biodegradability, biocompatibility, and
largest availability among all the biosurfactants, and also because they are easily chemoenzymatically modifiable (Bluth et al., 2006), sophorolipids have great application prospects in cosmetics, food, detergent industries such as emulsifiers, in environmental industry as bioremediation agent, and in petroleum industry as enhanced oil recovery agent. Recently, sophorolipids have attracted more attention since they were found to have good antimicrobial, anticancer, anti-inflammatory, and even anti-HIV activities. Glycolipids and their derivatives are of great interest in malignancy and other disorders because of their varied biological activities and potential for therapeutic uses. These anticancer effects have been reported for lung, cervical, breast, and brain cancers and have been shown to use mechanisms including regulation of angiogenesis and apoptosis, among others.

- **Mannosylerythritol lipid (MEL)**

The microbial extracellular glycolipid known as MEL is a biosurfactant composed of both lipophilic and hydrophilic moieties. MEL is produced in large amounts by the yeast *Candida antarctica* T-34 when this microorganism is grown on myristic acid as a source of carbon. The hydrophilic moiety of MEL was identified as 4-O-(di-O-acetyl-di-O-alkanoyl-β-D-mannopyranosyl)-erythritol. Recently, it has been reported that MEL induces differentiation in granulocytes of HL-60 promyelocytic leukemia cells. Also, it was found to be a potent inducer of both apoptosis and differentiation in B16 cells, inducing significant tyrosinase activity and enhanced production of melanin. These findings might provide the groundwork for the use of microbial extracellular glycolipids as novel therapeutic reagents in the treatment of melanoma. MEL is a glycolipid-type biosurfactant; however, the mechanistic links between the formation of micelles of MEL on cell membranes and the observed biological effects have yet to be clarified. One possible mode of action of MEL might involve qualitative and/or quantitative changes of membrane associated compounds, because it has been shown previously that the MEL-induced differentiation of carcinoma cells is accompanied by changes in the composition of cell-surface glycosphingolipids (Matsubara et al., 2005).
Lipid from Leishmania donovani

Leishmania sp. is protozoan parasites that are responsible for substantial public health problems, especially in tropical and subtropical regions. The parasite is the causative agent for the disease leishmaniasis, which is transmitted by the bite of the infected female sand fly (Phlebotomus spp.) when taking a blood meal from a host. The lifecycle of Leishmania has two distinct forms: an extracellular promastigote flagellar form found in the midgut of sand flies and an intracellular amastigote form that resides in phagolysosomes of mammalian (host) macrophages. Once in the bloodstream, promastigotes are internalized by dendritic cells and macrophages and are subsequently transformed into amastigotes by losing their flagella. Entry of promastigotes into host macrophages involves multiple parasite–host interactions such as recognition of specific ligands on the parasite cell surface by receptors on the macrophage cell surface to show the symptom of the disease.

The bio-activity of lipid from a strain of Leishmania donovani promastigote (MHO/IN/1978/UR6), developed by long-term in vitro culture, suppresses several inflammatory mediators by inducing apoptosis in adherent synovial fluid mononuclear cells (SFMCs) isolated from rheumatoid arthritis patients (Majumdar et al., 2008). These findings encouraged us to evaluate the anti-inflammatory role of pathogenic leishmanial lipid with the regulation of cancer cell growth.
References


