Pathogenesis of Fever

3

Core Messages

- Although infection is the most common cause of fever, fever is also a common finding in hypersensitivity reaction, autoimmune diseases and malignancy.
- Febrile response is mediated by endogenous pyrogens (cytokines) in response to exogenous pyrogens, primarily micro-organisms or their direct products (toxins).
- These endogenous pyrogens act on thermo-sensitive neurons in the hypothalamus, which ultimately upgrade the set point via prostaglandins.
- The body reacts by increasing the heat production and decreasing the heat loss until the body temperature reaches this elevated set point.
- Fever, in contrast to hyperthermia, will not climb up relentlessly because of an effective central control of the hypothalamic centre.
- Cytokines play a pivotal role in the immune response by activation of the B cells and T-lymphocytes. The production of fever simultaneously with lymphocyte activation constitutes the clearest and strongest evidence in favour of the protective role of fever.
- The protective processes of the immune response are optimal at high temperature (around 39.5 °C).
- Not all effects resulting from fever generation benefit the host; some are harmful and even lethal. This occurs mainly by overproduction of the cytokines or imbalance between cytokines and their inhibitors, such as severe and fulminate infections and septic shock.

3.1 History of Research

Research in fever has been centred on the hypothesis that fever results from physiological processes that are set in motion by an external stimulus. Egyptian scholars recognized that local inflammation was responsible for fever. In 1868,

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Billroth (1829–1894) attempted to confirm this ancient observation by injecting pus into animals, thereby producing a febrile response. In 1943, Menkin carried out similar experiments and isolated a product termed "pyrexin" [1]. Beeson in 1948 isolated a fever-inducing substance from a leukocyte, leukocyte pyrogens, which later became known as endogenous pyrogen (EP). Interleukin-1 (IL-1) was first identified as a cytokine by Gery and Waksman and proved to be identical with EP [2].

3.2 Definitions

- Fever (pyrexia) is a regulated body temperature above the normal range occurring as a result of IL-1-mediated elevation of the hypothalamic set point. Once fever is established, body temperature is regulated, as in health, by a net balance between heat production and loss.
- Hyperthermia is an unregulated elevated body temperature above the normal range due to imbalance between heat production and loss. Interleukins are not involved and therefore the hypothalamic set point is normal.
- A pyrogen is a substance (infectious organisms or their product toxins or cytokines) that provokes fever.
- Exogenous pyrogens are substances, which originate outside the body and which are capable of inducing interleukins.
- Endogenous pyrogens are substances, which originate inside the body and which are capable of inducing fever by acting on the hypothalamic thermoregulatory centre. IL-1, tumour necrosis factor (TNF) and interferon (INF) are endogenous of albumin and transferrin decreases. Characteristically there are a decreased concentration of iron and zinc and an increased copper concentration. The low iron is the result of reduced intestinal assimilation of iron and increased liver storage of iron. These changes contribute to host defence by depriving invading micro-organisms of essential nutrients, such as iron and zinc. The process is referred to as nutritional immunity.
- Cytokines are proteins produced throughout the body, mainly by activated macrophages, monocytes and T cells to regulate the immune responses within the body, control inflammatory and haematopoietic processes and may induce fever. As they enter the circulation and act on distant organs, they are considered as hormones. Pro-inflammatory cytokines (e.g. IL-1, IL-6, TNF-α, INF-γ, granulocytes-macrophages colony stimulating factor, GM-CSF) are responsible for initiating an effective defence against exogenous organisms (e.g. activating neutrophils). Their overproduction may be harmful by causing shock, multiple organ failure and death. Anti-inflammatory cytokines (e.g. IL-1 receptor antagonist, IL-4, IL-10) antagonize the pro-inflammatory cytokines and thus promoting healing and reducing inflammation.
- Monokines are cytokines that are produced by mononuclear phagocytic cells.

- Chemokines are cytokines that attract cells to the site of infection using chemical message (chemotaxis). Typical chemokine is CXCL-8 that attracts neutrophils.
- Interleukins are cytokines, acting specifically as mediators between leukocytes, hence their name. Their number known nowadays is enormous: at least 37 interleukins have been identified. If their amino acid sequence is known, they are assigned an interleukin number. If their sequence is not known, then they are named according to the biological property. IL-1 and IL-6 play a major part in the pathogenesis of fever.
- Lymphokines are cytokines that are secreted by lymphocytes to regulate the immune response. Important lymphokines are IL-2, IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, IL-14 and TNF-gamma.
- Prostaglandins are lipids that are made at sites of infection and tissue damage to produce inflammation and fever as part of the healing process.
- Acute-phase response is the term used for haematological, endocrinological and metabolic changes that follow (within hours or days) the onset of fever in response to infections or local damage to a tissue. These changes are induced by several cytokines (IL-6 being the primary inducer), which are beneficial to the host. During the response, various acute-phase proteins, notably C-reactive protein (CRP) and serum amyloid A, are synthesized by hepatocytes and released into circulation in large amounts. CRP plays a role in complement activation, opsonization and increasing platelet aggregation. Although acute-phase response is closely associated with fever, CRP levels can be normal in viral infections and high in diseases without fever (e.g. tumours). Syntheses of albumin and transferrin and the concentration of iron and zinc decrease, while copper concentration increases. The low iron is the result of reduced intestinal assimilation of iron and increased liver storage of iron. These changes contribute to host defence by depriving invading micro-organisms of essential nutrients, such as iron and zinc. The process is referred to as nutritional immunity.

3.3 Exogenous Pyrogens (ExP) (Fig. 3.1)

Exogenous pyrogens (e.g. bacteria, viruses, toxins) initiate fever, usually within 2 h of exposure, by interacting with macrophages or monocytes, leading to cytokine induction. Other mechanisms to initiate fever include:

- Some endotoxins, produced by bacteria, act directly on the hypothalamus to alter the set point. IL-1 is not involved. Radiation of the hypothalamus, DDT (dichlorodiphenyltrichloroethane), poisoning and scorpion venom may also induce fever by a direct effect on hypothalamus.
- ExP may activate lymphocytes to secrete lymphokines, particularly INF-y, which in turn stimulate macrophages and monocytes to produce IL-1.

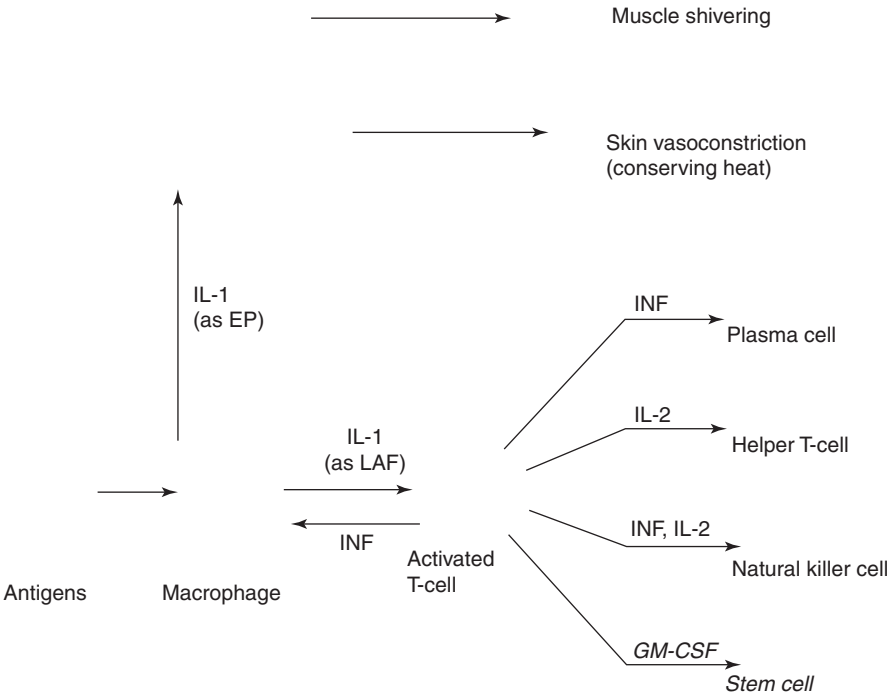

Fig. 3.1 The mechanisms of fever induction

- Some bacteria produce exotoxins, which stimulate macrophages and monocytes to release IL-1. This mechanism operates in scarlet fever and toxic shock syndrome. In toxic shock syndrome, the shock is due to the toxin. Diseases involving exotoxins produced by Gram-positive bacilli are less fever-inducing than those produced by pyrogenic Gram-positive cocci.
- Borrelia spirochetes (the cause of relapsing fever) do not contain endotoxin, and the attachment of these bacteria to the mononuclear cells induces IL-1.
- Other bacteria, such as pneumococci, have no endotoxin or other pyrogens, and the mechanisms responsible for fever are presumably immunological

3.3.1 Microbial Exogenous Pyrogens

- Gram-negative bacteria. The pyrogenicity of Gram-negative bacteria (e.g. *Escherichia coli*, *Salmonella*) is due to a heat-stable factor, endotoxin. The active components of endotoxin are lipid and carbohydrate (lipopolysaccharide, LPS), which are the major components of the outer membrane of these bacteria. Endotoxin causes a dose-related progressive increase in temperature. In severe

cases, it causes shock with vasodilatation, capillary leakage and hypotension. Septicaemia caused by Gram-negative endotoxin does not elicit fever in certain situations such as neonates, young infants or children with fulminating infection or with malnutrition. These children may present with normal temperature or even hypothermia in response to severe infection. Mortality is significantly higher in septic children [3] and adult [4] patients due to reduced capacity to release TNF-α and IL-β upon infection with LPS.

- Gram-positive bacteria. The main pyrogen of most bacteria is peptidoglycan that forms the cell wall. Penicillin works by inhibiting the biosynthesis of peptidoglycan, which results in cell lysis. This explains why penicillin is more effective against Gram-positive bacteria.
- Viruses. It is well known in clinical practice that viruses cause fever. Mechanisms by which viruses may produce fever include direct invasion of macrophages, immunological reaction to viral components involving antibody formation, induction by INF and necrosis of cells by viruses.
- Fungi. Live or killed fungal products are exogenous pyrogens that induce fever. The induction of fever mainly occurs when the fungi are in the bloodstream. Children with neoplastic diseases who develop fever associated with neutropenia are at high risk for developing invasive fungal infection.

3.3.2 Nonmicrobial Pyrogens

- Phagocytosis is largely responsible for fever in blood transfusion reactions (once an infection is excluded) and immune haemolytic anaemia.
- Antigen-antibody complexes. An exogenous antigen may react with circulating, sensitized antibodies to form a complex, which induces IL-1 production (immune fever). Examples of immunologically mediated fever include systemic lupus erythematosis and adverse drug reactions. Fever associated with penicillin hypersensitivity results from interaction of antigen-antibody complexes with leukocytes, which release IL-1.
- Most steroids are endogenous antipyretics, which suppress fever through their inhibitory effects on IL-1 and TNF-α production as well as inhibition of prostaglandin synthesis. Certain steroids, however, are pyrogenic in human such as etiocholanolone, a major metabolite of testosterone and 17-ketosteroid, which induce the release of interleukin-1. Etiocholanolone produces fever only when injected intramuscularly (not intravenously). Etiocholanolone fever is characterized by recurrent fever for few days, in association with arthralgia, abdominal pain, leukocytosis, high ESR and etiocholanolone level. Fever does not respond to antipyretics but to steroids, e.g. prednisolone. Etiocholanolone is responsible for fever in some patients with adrenogenital syndrome.
- Other nonmicrobial pyrogens include some hormones, drugs and intracranial lesions such as bleeding and thrombosis

3.4 Monocyte: Macrophage System (MMS) (Fig. 3.2)

Mononuclear cells are leukocytes (3–8% of the leukocytes) and are largely responsible for the production of IL-1 and fever induction. Polymorphonuclear granulocytes are no longer thought to be responsible for IL-1 production because fever may occur in their absence, e.g. agranulocytosis. The mononuclear cells are either circulating monocytes in the peripheral blood or tissue macrophages (histocytes) scattered in organs such as lung (alveolar macrophages), lymph nodes, placenta, peritoneal cavity and the subcutaneous tissue. The origin of both monocytes and macrophages is the granulocyte-monocyte colony-forming unit (GM-CFU) in the bone marrow. Monocytes enter the circulation either to remain there for a few days as circulating monocytes or to migrate to the tissue where they undergo functional and morphological transformation into macrophages, when their life span is several months. These cells play an important role in:

- Host defence, including engulfing and destroying the microbe (phagocytosis) recognition of antigen and presenting it to attached lymphocytes.
- Activation of T-lymphocytes and tumour cell destruction.

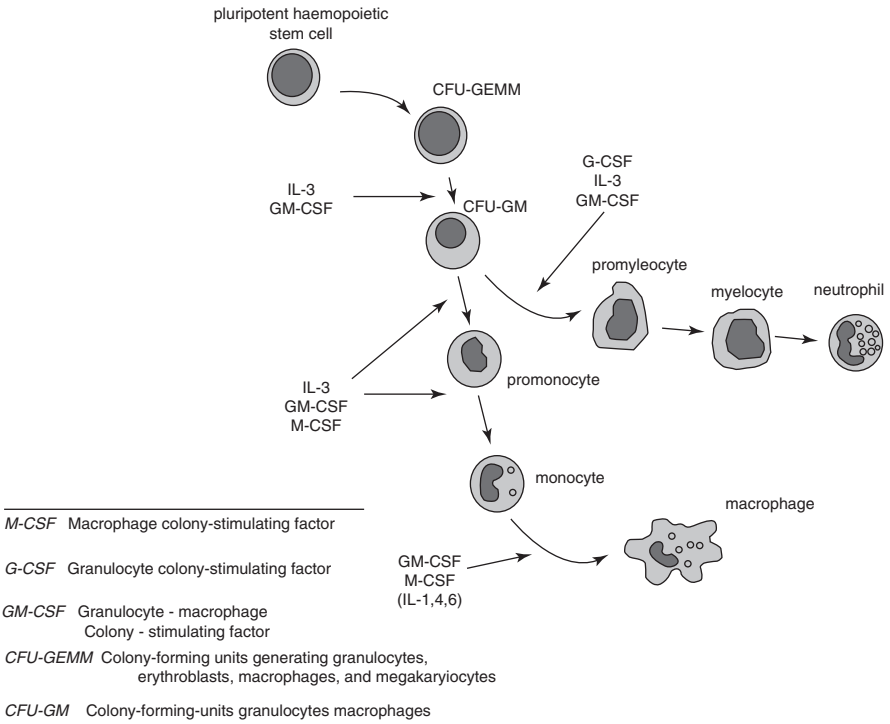

Fig. 3.2 Showing monocytes and macrophages

Situations associated with reduced function of the MMS include newborn infants, corticosteroid and other immunosuppressive therapy, systemic lupus erythematous, Wiskott-Aldrich syndrome (immune deficiency involving B and T cells, eczema and thrombocytopenia) and chronic granulomatous disease. The two major monocyte-macrophage products (cytokines) are IL-1 and TNF.

3.5 Endogenous Pyrogens (EP)

3.5.1 Interleukin-1 (IL-1)

IL-1 consists of three structurally related polypeptide, two agonists (IL-1α and IL-1β) and an antagonist (IL-1 receptor antagonist = IL-1ra), which inhibit the activities of the two powerful agonists. Anakinra is a naturally IL-1ra. IL-1α is produced in:

- Cells of healthy people including in all epithelial cells of mucosal membranes.
- Blood monocytes and tissue macrophages.
- Hepatic Kupffer cells, keratinocytes and pancreatic Langerhans cells.
- Astrocytes in the brain tissue, which may contribute to the immunological responses within the CNS and the fever secondary to CNS bleeding.
- Cells from certain malignant tumours (e.g. Hodgkin's disease, acute leukaemia and renal carcinoma). This explains the frequent association of fever in these conditions in the absence of infection.

IL-1β is not present in cells of healthy people and is mainly produced by monocytes, macrophages and dendritic cells.

Interleukin-1 has important roles in the following conditions (Fig. 3.3):

- Induction of fever by acting on the hypothalamus to raise its set point.
- Induction of hepatic acute-phase proteins (see above).
- Induction of inflammatory response and lymphocyte activation factor.
- Appetite suppression. IL-1 is a potent anorexic cytokine (more potent than the hunger inhibitor Leptin), which explains the reduction of food intake commonly

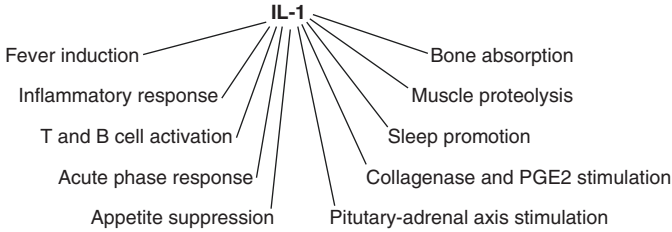

Fig. 3.3 Summary of the main functions of IL-1

seen in febrile illness. IL-1ra reverses the decrease in food intake. Circulating IL-1ra, along with IL-18, are increased in obese and type 2 diabetes [5].

- IL-1β (along with TNF-α) regulates sleep by promoting non-rapid eye movement sleep. This cytokine is produced in astrocytes of the brain. The action of IL-1β may explain the observation of increased sleep in febrile illnesses.
- Joint diseases such as rheumatoid arthritis (RA) and ankylosing spondylitis. RA is an autoimmune mediated by IL-1. Treatment with anakinra prevents the migration of inflammatory cells into the joint.
- Inflammation of the blood vessels (vasculitis).
- Stimulating the liver to produce acute-phase proteins (see above).
- Congenital deficiency of IL-1 receptor antagonist is associated with overwhelming inflammation of the skin, joints and bones and large infiltration of neutrophils. Infants with this condition die early in life unless anakinra is given that rapidly reverses the inflammation and prevents the death [6].
- Auto-inflammatory diseases are characterized by periodic fever due to recurrent episodes of systemic and local inflammation. Anakinra has been successful in treating conditions such as familial Mediterranean fever (see Chap. 6).
- IL-1-mediated inflammation is contributing to the acute ischaemic conditions such as myocardial infarction, stroke, liver and renal failure.
- HIV replication. IL-1ra has suppressive effects on the virus.
- Macrophage activation syndrome is a life-threatening disease in patients who suffer from EB-virus or cytomegalovirus. Anakinra causes rapid recovery.
- Diabetes (type 1 is an autoimmune disease mediated by T-lymphocytes; type 2 is associated with obesity and physical inactivity causing insulin resistance). Both types produce high glucose concentration that stimulates IL-1β causing destruction of the insulin-producing β-cells of the pancreas.

3.5.2 Tumour Necrosis Factor (TNF)

TNF-α, discovered in 1975, is a pro-inflammatory cytokine produced by immune cells, e.g. monocytes and macrophages (TNF-α), lymphocytes (TNF-β), natural killer cells, Kupffer cells, astrocytes and microglia of the CNS, in response to invasive or injurious insults. TNF-α is an endogenous pyrogen acting on the hypothalamus to induce fever. Unlike IL-1, TNF has no direct effect on stem cell and lymphocyte activation. TNF-α has diverse beneficial biological effects, including:

- Sharing many biological properties with IL-1, e.g. early enhancing host defence against infection, promoting normal tissue remoulding, including wound healing, enhancing chemotaxis of macrophages and neutrophils as well as increasing their phagocytic and cytotoxic activity.
- Stimulant (along with IL-6) for acute-phase response.
- Crucial physiological processes in the CNS such as learning and memory, sleep and water and food intake.

The initial enthusiasm to use TNF-α as a systemic antitumour treatment has waned because of its significant toxicity and lack of therapeutical benefit. However, TNF-α blockers (monoclonal antibodies, infliximab, adalimumab and etanercept) have altered the outcomes for children with inflammatory bowel disease, such as Crohn's disease and ulcerative colitis and rheumatoid arthritis. According to a systematic review of literature [7], the treatment has resulted in a variety of infections in the treated children including bacterial, fungal, viral and TB. Few children died.

3.6 Activated Lymphocytes

The antigen-specific cells of the immune system are lymphocytes, of which there are two main types:

- B cells are responsible for antibody production.
- T cells are the master regulators of the antigen-specific adaptive immune response. They regulate antibody synthesis and mediate cytotoxic function as well as inflammatory response of delayed-type hypersensitivity. T cells are either:
  - Th1 cells which produce INF-γ, IL-2 and TNF-β and promote cell- mediated immunity and phagocytic activity.
  - Th2 cells which produce Il-4, IL-5, IL-6, IL-9 and IL-10. These promote antibody production and play a crucial role in allergic responses (immediate-type hypersensitivity).

IL-1 has an essential role in the activation of lymphocytes. The T-lymphocyte recognizes antigen only after the antigens are processed and presented to them by macrophages; only then do T-lymphocytes become active.

3.6.1 Interferons (INF)

Interferons are known for their ability to "interfere" (hence the name) with viral replication in infected cells. In addition, these cytokines have pyrogenic effect, antitumour and immuno-regulatory functions. There are three types, type 1 (IFN-α, IFN-β), type II (IFN–γ) and type III (IFN-λ). Only type I is used as therapy. Type I and III are produced by a variety of cells (such as leukocytes, dendritic cells, fibroblasts and macrophages), whereas synthesis of type II is restricted to T-lymphocytes.

The functions of the interferons include:

- Key mediators of both innate and adaptive immune responses, stimulating B cells to increase antibody production, and increasing the efficiency of natural killer cells.
- Inhibition of viral replication including HIV-1 replication.

- Interferon-γ release assays (IGRA) serve as a useful blood test in patients with TB. The result cannot distinguish between latent and active TB, and it is not affected by BCG vaccination status.

Type I INF is used as a treatment for a variety of diseases, including:

- Various viral infections, in particular hepatitis B and C.
- Upper respiratory tract infection. INF-α in a nasal spray is capable of significantly reducing symptoms due to rhinoviruses, but not those due to influenza viruses, parainfluenza viruses or coronaviruses.
- Thrombocytosis associated with myeloproliferative disorders.
- Childhood angiomatous disease results from INF-anti-proliferative effect.
- Malignancy including non-Hodgkin's lymphoma, melanoma, multiple myeloma, basal cell carcinoma and chronic myelogenous leukaemia. Hairy cell leukaemia remains one of the most important indications for INF-α therapy, showing a response rate of more than 90%.

Toxic effects of INF preparations are numerous and include fever, chills, arthralgia, myalgia, severe headaches, somnolence and vomiting. Fever may occur in over 50% of the patients who receive INF and may reach 40.0 °C. These side-effects are responsive to paracetamol and prednisolone. Severe side-effects include hepatic and cardiac failure, neuropathy and pancytopenia. INF therapy is contraindicated in pregnancy owing to its anti-proliferative effect.

3.6.2 Interleukin-2 (IL-2)

IL-2 is probably the second most important lymphokine (after INF), which is released by activated T-lymphocytes (in particular $CD4^+$ and $CD8^+$) in response to exogenous pyrogen. It has a crucial effect on the growth and function of T cells, natural killer cells and B cells and for the development of $CD4^+$ T cells. Cases of severe congenital combined immunodeficiency due to a specific defect in the production of IL-2 have been reported. Effects of IL-2 include:

- Stimulating the release of other cytokines, including IL-1, TNF and INF-γ.
- As IL-2 is also produced by mast cells, it controls the severity of chronic allergic dermatitis.
- Antitumour cytotoxicity (e.g. melanoma, including metastatic melanoma, renal cell carcinoma, acute myelogenous leukaemia) as a result of proliferation and activation of activated cytotoxic T lymphocytes.

3.6.3 Interleukin-6 (IL-6)

IL-6 is the third most studied cytokines that has the following characteristics:

- A pro-inflammatory, multifunction cytokine, which is secreted by macrophages and T-lymphocytes to stimulate both B and T cell function and immune response against infection.
- Acting on hepatocytes to induce acute-phase proteins such as CRP, amyloid and haptoglobin.
- An early marker of infection (preceding the increase of CRP), responding within 3–4 h of bacterial infection, e.g. in early-onset neonatal bacterial infection.
- Increased in many diseases, e.g. sepsis, autoimmune diseases (e.g. systemic lupus erythematosus), Kawasaki disease, tumours (e.g. multiple myeloma, renal cell carcinoma), brain disorders (e.g. astrocytoma, glioma, psychosis), and auto-immune and chronic inflammatory diseases.

Table 3.1 Main lymphokines produced by T cells and their main effect/use

Interleukin	Effects
IL-3	Stimulatory effect on haematopoietic cells by controlling the production and function of granulocytes and macrophages. It plays an important role in myelomonocytic leukaemia
IL-4 (&IL-13, 14)	B-cell proliferation, regulating immune response
IL-5	Eosinophil differentiation factor, plays an important role in diseases associated with increased eosinophils, e.g. asthma
IL-7 (IL-27 &IL-36)	Regulates B and T cells, natural killer (NK) cells
IL-8	Pro-inflammatory cytokine, potent neutrophil activator and chemoattractant
IL-9	Stimulation of the growth of mast cells and erythroid, support growth of IL-2 and IL-4 growth of helper T cells
IL-10 (& IL-20)	Inhibition of Th1 cell production, including Th1-dependent IL-2, implicated in inflammatory process of JIA and development of haematopoietic cells. IL-20 helps proliferate keratinocytes
IL-11 (&IL-22)	Production of acute-phase proteins. IL-11 is effective for chemotherapy-induced thrombocytopenia
IL-12	Inhibition of IL-1 synthesis, plays a role in defence against mycobacteria, salmonella, toxoplasmosis, measles HIV virus
IL-13 (&IL-14, 17)	Stimulating activated B cells to proliferate and produce IgM, IgG and IgE. It plays an important role in ulcerative colitis
IL-15	Elevated and responsible for the pathogenesis in coeliac disease and may have a therapeutic value in this disease
IL-16	Chemoattracts immune cells
IL-17 (&IL-23)	Mediating the inflammatory, differentiation of T cells
IL-18	Pro-inflammatory, immuno-regulatory cytokine that induces IFN-γ from T-lymphocyte and natural killer cells; it does not induce fever. It is increased in obese and type 2 diabetes
IL-28 (& IL-29)	Playing a role in host defence against micro-organisms
IL-31 (&IL-32, 33)	Induction of cytokines (TNF, Il-8) and helper T cells

- Is markedly elevated in many rheumatic diseases including systemic juvenile rheumatoid arthritis (JRA) and ankylosing spondylitis. Anti-IL-6 receptor antibody, tocilizumab, has successfully been used to treat patients with JRA.

Other cytokines with their main effects are shown in Table 3.1.

3.6.4 Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF)

Of the four haematopoietic colony-stimulating factors (erythropoietin, granulocyte-colony-stimulating factor (G-CSF), macrophage colony-stimulating factor (M-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF)), GM-CSF appears to have the most potential clinical benefits. It is a pro-inflammatory cytokine, which is produced mainly by lymphocytes, although monocytes, macrophages and mast cells are also capable of producing it. GM-CSF's principal functions and potential therapeutic uses are:

- To stimulate haematopoietic progenitor cells to proliferate and differentiate into granulocytes and macrophages, enhancing phagocytosis and promoting leukocyte chemotaxis and adhesion.
- As a treatment in sepsis-associated immunosuppression.
- It has a central role in the pathogenesis of autoimmune inflammatory diseases such as rheumatoid arthritis, multiple sclerosis and Crohn's disease [8].
- Approved to treat chemotherapy-induced neutropenia, myelodysplasia and aplastic anaemia associated with stem cell transplantation.
- GM-CSF alone or with IL-4 have been used in cancer treatment, including melanoma, renal cell carcinoma and glioma.

The administration of GM-CSF may be associated with the development of fever, which is blocked by non-steroidal anti-inflammatory drugs such as ibuprofen.

3.7 Thermoregulation

Thermoregulation requires intact peripheral mechanisms, which balance heat production and loss, and a functioning hypothalamic thermoregulatory centre regulating these mechanisms. This centre receives thermoreceptors from the temperature of the blood as it passes through the brain (the core temperature) and thermoreceptors from the skin via the dorsal horn of the spinal cord. Both thermoreceptors have cold and warm receptors. The activation of warm receptors causes inhibition of cold receptors. The aim of the thermoregulation is to maintain a relatively constant body temperature at 37 °C.

3.7.1 Heat Production

Heat production occurs by various mechanisms:

- At rest as many organs such as the brain, muscles, viscera, liver, heart, thyroid, pancreas and adrenal glands contribute to heat production at the cellular level involving adenosine triphosphate (ATP).
- The newborn infants have no shivering due to skeletal muscle immaturity, and they rely on non-shivering thermogenesis to produce heat to protect newborns against cold exposure. Brown adipose tissue (BAT), localized mainly in the neck and scapular area, is highly vascularized and contains a large quantity of mitochondria. Fatty acid oxidation in these mitochondria can increase heat production to twofold in response to cold.
- In older children and adults, the first response to cold is behavioural (e.g. curling up, putting more clothes). If this response is insufficient, then the hypothalamic centre is stimulated to conserve heat by vasoconstriction and generate heat by shivering. The predominant stimulus for shivering is the skin rather than the core temperature. The energy produced is released as heat.
- BAT was, until recently, thought to be only functional in neonates and some animals. BAT as a non-shivering thermogenesis has now emerged as a significant component of thermoregulation in elevating body temperature. This process induces and activates mitochondria, which uncouples protein to release chemical energy as heat. The BAT-metabolic thermogenesis is regulated by norepinephrine which is secreted by BAT-sympathetic nerve terminals.

Pathological uncontrollable increase of heat production occurs in malignant hyperthermia (see Chap. 2).

3.7.2 Heat Loss

In response to a rise in body temperature above 37 °C (or ambient temperature above 30–31 °C), heat is lost from the body via the four physical modalities: evaporation, radiation, convection and conduction. When the body core temperature rises (e.g. fever), heat loss through evaporation (causing sweating) becomes the primary mechanism of heat loss. This is associated with cutaneous vasodilatation via acetylcholine-mediated relaxation of the vascular smooth muscles. The following are the mechanisms by which heat loss occurs at rest:

- About one-quarter is lost by evaporation from the skin and lungs, which occurs as water is converted from liquid to gas (58 kcal is lost for every 100 mL of water).
- In general, 60% of the total heat is lost by radiation (transfer of heat from the skin surface to the external surroundings not in contact), through electromagnetic waves.

- Convection (12% of the heat loss) is increasing blood flow to body surfaces to maximize heat loss.
- Conduction (3% of the heat loss) is the heat transfer between two objects in direct contact and at different temperatures. This is the primary mode of heat loss from the core to the surface.

In a warm environment or when core temperature is elevated, the hypothalamic thermoregulatory centre activates efferent fibres of the automatic nervous system to produce vasodilatation. The increased blood flow to the skin causes heat loss from the core through the skin surface to the surroundings in the form of sweating. The hypothalamus stimulates vasodilatation to increase insensible loss (for every 1 °C elevation of body temperature, there is a 10% insensible loss) and activates the sweat glands to increase perspiration production.

Physical factors obviously affect the ability to respond to temperature changes. The greater heat loss in the newborn infant is mainly due to a greater surface area compared to that of an older child. Failure of heat loss occurs in anhidrotic ectodermal dysplasia and during anticholinergic drug overdose.

3.7.3 Temperature Regulation at the CNS Level

In the classical model of pathogenesis, fever induction includes the following stages:

- Pyrogenic endogenous cytokines (e.g. IL-1, TNF, IL-6 and interferons) are released into the bloodstream in response to exogenous pyrogens (e.g. viruses, bacteria, toxins).
- These endogenous pyrogens act on a specific preoptic area of the anterior hypothalamus, which contains clusters of thermo-sensitive neurons localized within the rostral wall of the third ventricle. The site is called organum vasculosum of the lamina terminalis (OVLT), which has emerged as an interface between circulation and brain. The firing rate of these thermo-sensitive neurons changes according to the temperature of the area's blood supply and the input from the skin and muscular thermoreceptors. Warm-sensitive neurons have firing rates that increase with warming and decrease with cooling, whereas the firing rates of cold-sensitive neurons increase with cooling or decrease with warming.
- Endogenous pyrogens enter the perivascular space of the OVLT through the fenestrated capillary wall to stimulate cells to produce prostaglandin E2 (PGE2), which diffuses into the adjacent preoptic area to upturn the temperature set point and cause fever.
- Another structure termed circumventricular organs (CVOs), which are situated in the anterior wall of the third ventricle. These organs are characterized by extensive vasculature and lack of blood-brain barrier allowing direct exchange between blood and nervous tissue. When circulating pyrogenic cytokines are detected by the CVOS, PGE2 is induced.

- The ultimate result of these complex mechanisms is an upward shift of the thermostatic set point to a febrile level that signals efferent nerves, especially sympathetic fibres innervating peripheral blood vessels, to initiate heat conservation (vasoconstriction) and heat production (shivering). This is aided by behavioural means aimed also to increase body temperature, such as seeking a warmer environment or covering up with a blanket. The resulting temperature increase continues until body temperature approximates to the temperature of the elevated set point.
- The raised set point is reset back to normal if the concentration of the cytokines falls or if antipyretics are administered that block prostaglandin synthesis. The normalization of temperature is initiated by vasodilatation and sweating through increased skin blood flow controlled by sympathetic fibres. Prostaglandin E2 has been found to exert a negative feedback on the release of the cytokines, thus terminating the mechanisms that initially induced the fever

The peptide angiotensin 11 has been shown to lower body temperature at the final step of fever. It is involved in maintaining body temperature at the set point. In addition, arginine vasopressin (AVP) acts within the CNS to reduce pyrogens-induced fevers. A decrease in hypothalamic calcium concentration or an increase in sodium concentration elevates body temperature.

3.8 Summary of Fever Induction

The generation of fever involves the following steps:

- Numerous substances from outside the body, exogenous pyrogens, initiate the fever cycle. Endotoxin of Gram-negative bacteria, with their pyrogenic component lipopolysaccharide, is the most potent exogenous pyrogen. Fever is also a common finding in children without obvious evidence of infection, for example hypersensitivity reaction, autoimmune diseases and malignancy.
- Exogenous pyrogens initiate fever by inducing host cells (primarily macrophages) to produce and release endogenous pyrogens such as interleukin-1, which has multiple biological functions essential for the immune response.
- Endogenous pyrogens are transmitted to the hypothalamic thermoregulatory centre, specifically organum vasculosum of the lamina terminalis (OVLT), where they induce synthesis of prostaglandins, of which PGE2 is the most important. These raise the thermostatic set point to initiate the febrile response.
- The hypothalamic thermoregulatory centre accomplishes heat production by inducing shivering and heat conservation through vasoconstriction. At an established degree, fever is regulated (even at a temperature of over 41.0 °C), and heat production approximates loss, as in health, though at a higher level of the set point. Therefore fever does not climb up relentlessly.
- In addition to the function as an endogenous pyrogen, IL-1 activates T-lymphocytes to produce various factors, such as INF and IL-2, which are vital

for immune response. The production of fever simultaneously with lymphocyte activation constitutes the clearest and strongest evidence in favour of the protective role of fever.

- The induction of fever results in inhibition of bacterial growth, increased bactericidal of neutrophils, production of acute-phase protein synthesis and other physiological changes such as anorexia and somnolence. These changes suggest that fever has an adaptive role in the host's survival during infection (see Chap. 9 for detail).

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