Inflammation: Acute

Introductory article

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Inflammation represents the response of a vascularized tissue to injury. Inflammation and repair are essential to maintain tissue integrity.

Article Contents

Introduction

Inflammation is a defensive response that begins after cellular injury, which may be caused by microbes, physical agents (burns, radiation, trauma), chemicals (toxins, caustic substances), necrotic tissue and/or immunological reactions. The acute inflammatory reaction is characterized by a series of interrelated and overlapping events including coagulation, an increase in blood flow and vascular permeability at the afflicted site, exudation of fluid (oedema), localized pain, the migration and accumulation of inflammatory leucocytes from the blood vessels into the tissue, formation of granulation tissue and, finally, tissue repair (**Figure 1**).

Characteristics of Inflammation

Acute inflammation usually has a sudden onset, becoming obvious within minutes or at most hours after tissue trauma, and may be characterized by the classical symptoms of redness, heat, oedema and pain, as described nearly 2000 years ago by Celsus. These symptoms generally represent a complex group of vascular, neurological and cellular responses to the initiating trauma. As all inflammatory responses are intended to be transient, control of initiation and termination of inflammation is crucial. Control of inflammation is mediated to a large degree by soluble proteins (cytokines, growth factors) acting between inflammatory cells and nonhaematopoietic cells, such as fibroblasts and vascular endothelial cells, within the traumatized tissue. Under normal circumstances, these cytokines and growth factors cooperate in exquisitely coordinated networks to sequester and/or eliminate the injurious agent and then to restore and maintain homeostasis in the tissue. If an acute response cannot be resolved, it becomes chronic. Evidence of chronic nonhealing wounds is recorded in archaeological history, but only in modern times has sufficient progress been made in understanding inflammation and tissue repair to appreciate how this programmed sequence of events may be disrupted to impair or delay wound healing.

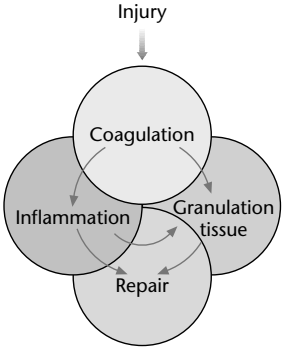

Figure 1 Intersecting components of acute inflammation. The inflammatory process begins with the coagulation (clotting) process which sets the stage for inflammation, with leucocyte recruitment and activation leading to clearance of the damaged tissue and/or infection. Granulation tissue forms as inflammatory leucocytes produce mediators, which influence new blood vessel formation and recruitment of fibroblasts. Fibroblasts make matrix to repair the damaged tissue. Illustration by Jeffrey Aarons.

Initiation of Acute Inflammation

Whether initiated by infection or trauma, the inflammatory response involves a predictable sequence of cellular, biochemical and molecular events. Damage to the blood vessels is an initial consequence of tissue trauma, and possibly during microbial invasion, necessitating blood containment and vessel repair. Thus, the blood clotting system is rapidly engaged to fabricate a temporary vascular plug or clot, not only to restore vessel integrity, but to serve as a scaffolding for platelet adhesion and leucocyte recruitment. The foundation of clot assembly is fibrinogen, which is manufactured in the liver and present in the blood, and, upon activation at a site of inflammation, these molecules stack up on one another to form a double-stranded protein known as fibrin. The fibrin strands are woven into a stable three-dimensional scaffolding that traps platelets and blood cells (**Figure 2**). Trapped and aggregating platelets release coagulation factors which are pivotal in haemostasis (**Figure 3**). First and foremost, the changes in platelet structure and function regulate fibrin and clot production to quell loss of blood. Second,

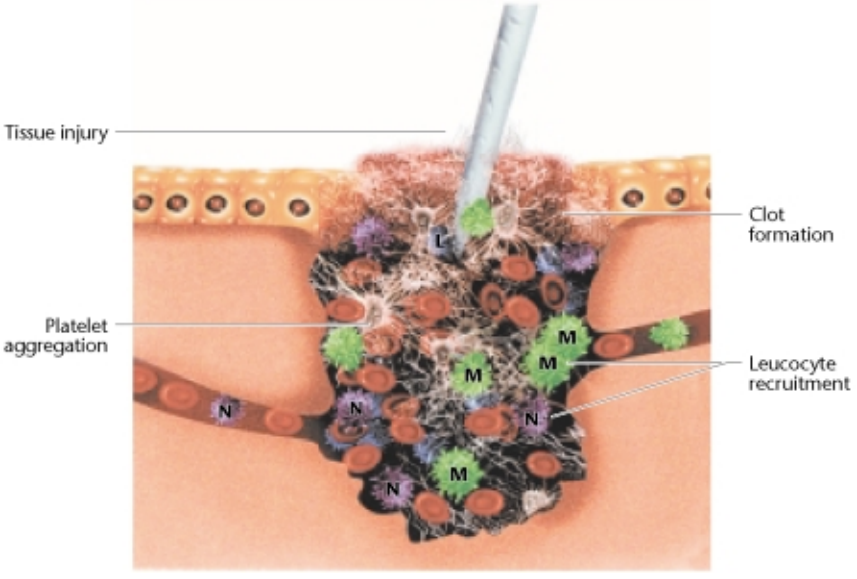

Figure 2 Clot formation. Tissue injury results in fibrin formation to form the blood clot, which stops the bleeding and provides the scaffolding upon which platelets aggregate and release mediators. The mediators influence vascular permeability and attract leucocytes from the blood. L, lymphocyte; M, macrophage; N, neutrophil.

α Granule	Dense granule
PDGF	Serotonin
TGFα	ADP
TGFβ	Calcium
FGF	
PF4	**Other**
Fibronectin	TXA_2
Fibrinogen	12-HETE
Thrombospondin	
Plasminogen	
Von Willebrand factor	
α_2-Plasmin inhibitor	
β-Lysin	
DAF	
Permeability factor	
Factors D and H	

Figure 3 Platelet inflammatory mediators. ADP, adenosine diphosphate; DAF, decay-accelerating factor; FGF, fibroblast growth factor; PDGF, platelet-derived growth factor; PF4, platelet factor 4; TGF, transforming growth factor; TX, thromboxane. Illustration by Jeffrey Aarons.

aggregated platelets within the clot release leucocyte recruitment factors which orchestrate the rapid influx of leucocytes (initially neutrophils and also monocytes) from the circulation into the wound site, and also growth factors which set the stage for the subsequent wound healing process (**Figure 3**).

Vascular Response

With the activation of the clotting system, inflammatory mediators are released which control the vascular response. The vascular response includes changes in permeability, blood flow and adhesiveness. The increased permeability triggered by inflammatory mediators includes contraction of endothelial and perivascular cells, and, as these cells contract, fluid escapes between them. The purpose of the movement of cells and fluids into the tissue is severalfold: the movement of fluids plays an important role in diluting toxic factors generated at sites of trauma and infection, and allows the influx of important serum proteins, including components of the complement system and immunoglobulins (antibodies) which promote antimicrobial activity. Moreover, changes in vessel permeability enable migration of blood leucocytes between endothelial cells to reach the tissue site of inflammation and/or infection (**Figure 4**).

The endothelial cells themselves are also active participants in the inflammatory response. In addition to coagulation and permeability factors, they release recruitment factors and the proinflammatory cytokines, tumour necrosis factor α (TNFα) and interleukin (IL) 1. As they become stimulated by factors, including TNFα and IL-1, the endothelial cells expose adhesion molecules on their lumenal surface to snare blood leucocytes as they pass by the site of injury. The movement of leucocytes, particularly neutrophils (which are the first cells to the rescue), into the inflamed tissue is necessary for destruction of microbial agents and removal of tissue debris by phagocytosis, and represents a key step in the ultimate resolution of inflammation (**Figures 4** and **5**).

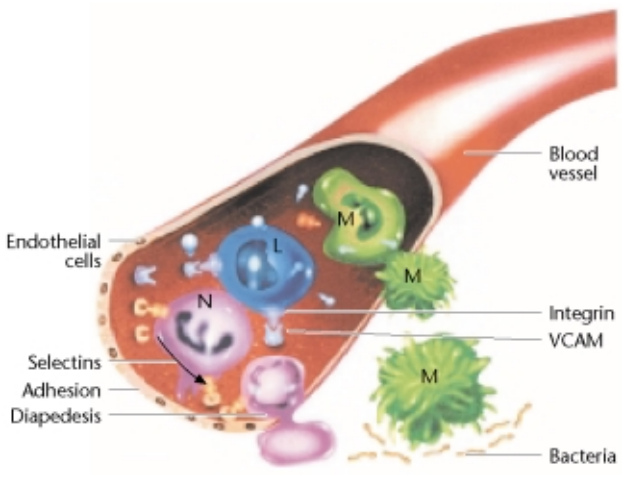

Figure 4 Leucocyte adhesion and recruitment. At a site of inflammation, activated vascular endothelial cells express adhesion receptors which bind leucocytes that bear the matching adhesion molecules. This initially slows the leucocytes down, allowing them to sense the environment and then to attach more firmly and migrate between the endothelial cells to the inflamed tissue. N, neutrophil; M, macrophage; L, lymphocyte; VCAM, vascular cell adhesion molecule. Illustration by Jeffrey Aarons.

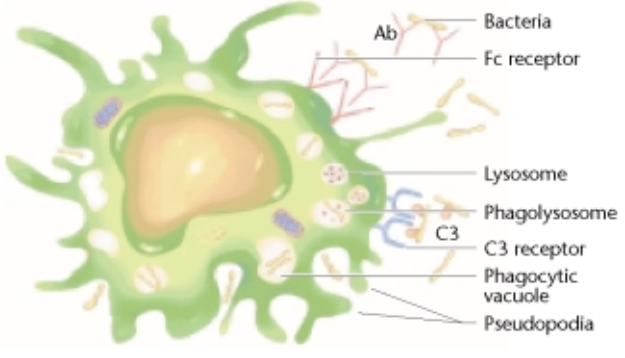

Figure 5 Phagocytosis. Once in the inflamed or infected tissue, the macrophages eat tissue debri and bacteria. Bacteria are rapidly recognized if they are opsonized (coated by antibodies or complement) by the Fc and C3 receptors. Pseudopodia wrap around the attached particle and engulf it into a phagocytic vacuole. Lysosomes, which contain many enzymes, fuse with the phagocytic vacuole to form a phagolysosome, where the particles are digested. Illustration by Jeffrey Aarons.

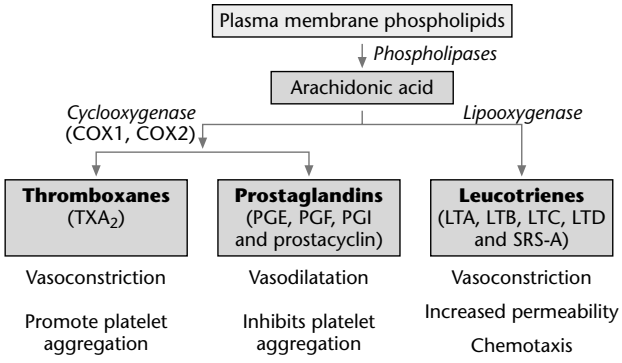

Figure 6 Arachidonic acid metabolism. SRS-A, slow-reacting substance of anaphylaxis.

Inflammatory Mediators

In addition to mediators released by the coagulation pathway and by complement activation, a multitude of serum- and cell-derived products is important in the early initiation and amplification of inflammatory reactions. Besides platelets and endothelial cells, leucocytes and their neighbouring connective tissue cells all release products if perturbed, which contribute to the inflammatory response. For example, mast cells, part of the normal cellular constituents of most tissues, are activated early in inflammation to release vasoactive amines in addition to histamine. Histamine and serotonin contribute to the characteristic redness, swelling, heat and pain, and histamine also leads to a rapid expression of endothelial adhesion molecules on the cell surface. Leucocytes produce cytokines, enzymes and lipid mediators whose function is to orchestrate the inflammatory response.

During an acute response, enzymes known as cellular phospholipases (present in leucocytes and platelets) are activated to degrade membrane phospholipids into arachidonic acid (**Figure 6**). Arachidonic acid, in turn, is metabolized via the cyclooxygenase (COX) enzyme pathway to prostaglandins, and by other enzymes – the lipoxygenases – to leucotrienes, all of which influence vascular blood flow and permeability. Prostaglandins can induce fever (are pyrogenic), increase sensitivity to pain, and stimulate numerous inflammatory cell functions. Inhibition of the cyclooxygenase pathway by aspirin and related products to reduce prostaglandin synthesis is effective in reducing fever and minor pain. However, platelet aggregation is also dependent on products of the cyclooxygenase pathway, and chronic use of these inhibitors (aspirin) may impair blood clotting. After the initial release of inflammatory mediators controlling the bleeding response, additional mediators facilitate leucocyte recruitment.

Leucocyte recruitment

It is the rapid and selective deployment of neutrophils that best typifies the early stages of an acute inflammatory response. A variety of factors collaborate to bring these leucocytes from the circulation to the inflamed site. In addition to changes in blood flow and increased vascular permeability, endothelial cells encourage leucocyte localization and retention by expression of adhesion molecules and chemoattractants (**Figure 4**). The cell surface adhesion

molecule interactions function like a lock and key to mediate adhesion, and transform the normal vessel wall into a pro-adhesive or sticky surface for the anchorage of circulating neutrophils. Based on structural similarities, four superfamilies of adhesion molecules are involved in the recruitment of circulating blood cells: (1) the integrins, (2) immunoglobulin-like proteins known as intercellular adhesion molecule (ICAM) 1 and 2, and vascular cell adhesion molecule (VCAM), (3) the selectins (L-, P- and E-selectin) and (4) the mucin-like selectin ligands. Once the leucocytes are snared, chemotactic signals, which are usually small proteins radiating from the damaged tissue, bind to leucocyte receptors and signal them to move towards the highest concentration of the chemoattractant (concentration gradient). This process of emigration of neutrophils and other inflammatory cells from the lumen of the vessel into the tissues has successive phases of leucocyte adherence (margination), 'rolling', firm attachment and, finally, transmigration between the endothelial cells (extravasation or diapedesis) (**Figure 4**).

Chemotaxis

A major function of leucocyte rolling is to slow circulating leucocytes and to allow them time to 'sense' local environments, responding only if sufficiently high concentrations of recognized chemoattractants are encountered. Chemoattractants are molecules for which leucocytes have receptors and, if they detect a concentration gradient emanating from the site, will respond by crawling in that direction. Numerous molecules have the potential to attract leucocytes, including transforming growth factor β (TGFβ), leucotriene B_4 (LTB_4) and the complement fragment C5a, which have broad specificity, attracting and promoting activation of most leucocyte types. Among the proteins stored in platelet granules (**Figure 3**) and also released by activated leucocytes is the cytokine, TGFβ which is the most potent leucocyte chemoattractant known and is capable of promoting cellular migration at femtomolar concentrations. In the event of an infection, bacteria-derived peptides such as *N*-formyl-methionyl-leucyl-phenylalanine (FMLP) also cause leucocyte chemotaxis (**Figure 4**). The recent identification and characterization of a large family of related chemoattractant proteins called 'chemokines' has helped to explain how cells are recruited to an inflammatory site in an orderly manner.

Chemokines are a large superfamily of highly homologous low-molecular weight proteins. Approximately 40 chemokines have been identified in humans representing five structurally based families of which the CC chemokines have two adjoining cysteines (C) and the CXC chemokines have two cysteines with an intervening amino acid (X). CXC chemokines (IL-8) typically recruit neutrophils, whereas the CC chemokines, monocyte chemotactic peptide (MCP) 1, RANTES (*r*egulated on *a*ctivation *n*ormal *T* cell *e*xpressed and *s*ecreted) and macrophage inflammatory peptides (MIP-1α and MIP-1β), preferentially attract mononuclear cells. However, leucocytes respond not to each chemoattractant separately, but rather to the cumulative stimuli of multiple chemotactic factors to which the cell is exposed.

Once rolling leucocytes have encountered and responded to a sufficiently high chemotactic gradient, they begin to exit the vasculature and migrate into the subvascular tissue. This transmigration involves activation of leucocyte adhesion molecules known as selectins and then of integrins, which are membrane proteins composed of one α and one β subunit. Leucocyte integrins composed of a β2 subunit (CD18), together with one of multiple possible α subunits, participate in more firm cell–cell adhesive interactions, as do members of the β1 integrin family. Inflammatory cells expressing β1 integrins recognize ICAM-1 and VCAM-1, which are upregulated on endothelial cells by TNFα and IL-1 (**Figure 4**). Certain β1 integrins interact not only with endothelial cell adhesion molecules, but also with extracellular matrix molecules such as fibronectin as the leucocytes move into the clot and tissues. Associated with leucocyte adhesion to activated endothelial cells is the disruption of endothelial cell tight junctions, facilitating the last step in leucocyte extravasation: transmigration. In this process, the cells, responding to chemoattractants, insert their pseudopodia (feet) between the endothelial cells and then migrate between the cells and the basement membrane in a process called diapedesis (**Figure 4**).

Purpose of the Response

As the key players are assembled, including the platelets, neutrophils, mast cells, monocytes, fibroblasts and endothelial cells, in an acute inflammatory response, their function is coordinately to orchestrate haemostasis (coagulation) to stop blood flow, to clear infectious agents and tissue debris, then to remove themselves from the site and to restore or replace damaged tissue. This sequence of events is mediated through a myriad of inflammatory proteins which transduce intracellular signals to define cellular responses essential to carrying out these functions. The phenomenal coordination of these multiple events is successful most of the time, and the acute inflammatory response fades as the initiating stimulus is eliminated. If the initiating stimulus cannot be resolved, or if the regulation of the response becomes impaired, chronic inflammatory diseases may result.

Phagocytosis

Once bleeding has been halted, the major role of neutrophils in host defence is the rapid recognition and

elimination of debri and bacteria that may have penetrated the epithelial barriers, normally the first level of host defence. As the migrating neutrophils accumulate at the site of inflammation, they phagocytose and destroy any foreign material present and, together with infiltrating monocytes, remove dead and dying tissues. Microbial organisms are destroyed by phagocytosis, release of proteolytic enzymes, and via metabolic pathways resulting in a respiratory burst. The latter pathway leads to the production of reactive oxygen intermediates (hydrogen peroxide, superoxide and hydroxyl, and hypochlorite-free radicals) and reactive nitrogen intermediates (nitric oxide), which are directly and nonspecifically lethal to pathogens. The release of some of these intermediates, as well as the release of products found in cytoplasmic granules (proteases, phospholipases, elastase and collagenases), has a fundamental role in bactericidal activity.

Monocytes

As the neutrophils are clearing the area, monocytes enter inflamed tissues from the blood by a similar pathway, although they typically accumulate later than neutrophils, due in part to fewer numbers of circulating monocytes and also to the temporal release of cell-specific chemokines. In addition to monocytes, nearby tissue monocyte-derived macrophages, which are distributed ubiquitously, converge on the scene. Upon their arrival in the tissue, monocytes mature into macrophages and quickly begin clearance of damaged tissues and microorganisms within the vicinity, as well as dying neutrophils (**Figure 5**). Phagocytosis is dependent on the recognition of an invader or foreign antigen through cell surface receptors for complement (C3) and the Fc component of immunoglobulin (antibody) molecules. With the activation of the complement cascade, C3 fragments are liberated and bind bacterial membranes, thereby functioning as opsonins. Opsonins can be antibodies or complement fragments that bind to antigens and enable them to be recognized by the C3 or Fc receptors to trigger phagocytosis. The binding of an opsonized particle to C3 or Fc receptors on macrophages triggers the extension of pseudopodia, like arms, that engulf the attached particle and then fuse to form a vacuole (**Figure 5**). Macrophage lysosomes, which are cytoplasmic compartments containing enzymes, fuse with and secrete their components into the phagocytic vacuoles to form phagolysosomes where the ingested particles are degraded. These processes allow the removal and destruction of the microorganisms, which is essential in host defence – and in the ultimate resolution of the inflammatory process. Macrophages are involved not only in microbicidal activity, but also in the regulation of the inflammatory/immune response through antigen presentation, cytokine production, clearance or debridement through phagocytic and enzymatic activity, and orchestration of tissue repair through the release of fibroblast recruitment, growth and matrix-inducing molecules.

Cytokines

Cytokines released within the inflammatory site coordinate the activities of the various cells involved, positively supporting the response, regulating the effector functions of inflammatory cells, and helping to signal its maturity and termination. Cytokines are secreted regulatory polypeptides or glycoproteins that serve to pass information between cells, usually at a short distance (paracrine), but can also enter the circulation to target distant cells (endocrine). They function to alter the phenotype of target cells that express the appropriate cytokine receptors, including the cells that produce the cytokine (autocrine action), to influence their patterns of gene expression and protein secretion. Phenotypically, cytokine actions can lead to an increase or decrease in the rate of cell proliferation, differentiation, activation and/or change in the expression of some differentiated functions. Cytokines are secreted by most cells, including resident tissue fibroblasts, endothelial cells and epithelial cells, but the monocyte–macrophage lineage of leucocytes represents an abundant source. As many cytokines regulate the expression or release of additional cytokines, which in turn feedback both positively and negatively to regulate the original cytokine, the concept of interacting cytokine networks is useful. Numerous cytokines are present within inflammatory foci, and two key cytokines, TNFα and IL-1, induce the expression of a wide variety of 'downstream' mediators. TNFα and IL-1, along with the bacteria-derived lipid, lipopolysaccharide (LPS), are often referred to as the 'septic triad' owing to their association with acute septic bacterial infections, a severe and potentially fatal systemic acute inflammatory response, in which excess TNFα and IL-1 exert cytotoxic effects on target tissues.

Levels of cytokines at different stages of acute inflammation are dependent on the balance of synthesis and utilization, presence of inhibitors, and rate of degradation. Increased cytokine expression usually results from alterations in gene transcription, although other modes of regulation also exist. Although all genes contain binding sites for at least several transcription factors in their promoter regions, a surprising number of genes involved in inflammation and immune surveillance share the deoxyribonucleic acid (DNA) binding motif for the transcription factor known as nuclear factor κB (NFκB). In unstimulated cells, NFκB is sequestered in the cell cytoplasm via its association with the inhibitory protein IκB (inhibitor of NFκB). Upon cell stimulation, IκB is released from the complex, and the now-active NFκB dimer is translocated to the cell nucleus where it binds to gene promoters and triggers increased transcription and production of TNFα and other cytokines, as well as the adhesion molecules,

E-selectin, ICAM-1 and VCAM-1, all of which promote an inflammatory response. Low concentrations of hydrogen peroxide activate NFκB, and antioxidants can prevent this induction, suggesting that NFκB represents an oxidative stress-responsive transcription factor, perhaps reacting to the accumulation of reactive oxygen and nitrogen intermediates produced during the neutrophil respiratory burst. NFκB is activated by multiple other inflammatory stimuli including IL-1, TNFα, viruses, double-stranded ribonucleic acid (RNA), endotoxins, phorbol esters, ultraviolet light and ionizing radiation.

Resolution of the response

Clearance of the offending microbes or other stimuli, tissue debri and recruited cells from the inflammatory site marks the beginning of the final stage of resolution and return of the tissue to homeostasis. The duration and intensity of the local inflammatory response must be carefully regulated to limit tissue damage and to facilitate tissue repair mechanisms that are necessary for wound healing. Healing represents restoration of vascular integrity, replacement of lost or damaged tissue and, at epithelial sites, resurfacing of the wound. For this to occur, the inflammatory process must be successful with resolution of the underlying trauma (e.g. clearance of microbes and debridement), cessation of new leucocyte recruitment, elimination of proinflammatory leucocytes (apoptosis) and accumulation of reparative cell populations.

Removal of inflammatory cells

Following sequestration and clearance of the offending agent, it is necessary to eliminate leucocytes that have accumulated and are no longer needed. Although neutrophils are constitutively programmed to undergo apoptosis after having fulfilled their function, they may undergo accidental death (necrosis) triggered by noxious stimuli and, as they disintegrate, they release mediators and enzymes that exacerbate inflammation. The process of apoptosis (programmed cell death or cell suicide), on the other hand, plays a major role in promoting the resolution of the acute inflammatory response. Crucially, apoptosis leads to swift clearance by phagocytosis of intact dying cells, and therefore the surrounding tissues are protected from proinflammatory cell contents and enzymes. Newly expressed molecules on the surface of apoptotic cells are recognized by phagocytic macrophages to facilitate their rapid elimination. For example, thrombospondin (TSP) 1 expressed on apoptotic neutrophils bridges them to the macrophage integrin receptors ($\alpha_v\beta_3$) and to the TSP-1 receptor (CD36) for quick phagocytosis. Other mechanisms of recognition include the phosphatidylserine receptor on macrophages which recognizes phosphatidylserine, newly exposed on the surface of apoptotic cells (normally it is localized to the inner side of the plasma cell membrane). Following clearance of neutrophils, macrophages also undergo apoptosis and their number begins to decline.

Antiinflammatory mediators

Suppression of the inflammatory response, as well as its initiation and maintenance, is supported by cytokine networks. One of these antiinflammatory cytokines is IL-4, capable of inhibiting IL-8 production by neutrophils, reducing procoagulant activity of activated endothelial cells, and blocking macrophage activation while promoting their apoptosis. In a cascading fashion, IL-4 also induces differentiation of T lymphocytes into T-cell helper type 2 (T_H2) lymphocytes, which secrete further macrophage inhibitory cytokines, primarily IL-10 and IL-13. Once cells are activated, they become susceptible to inhibition by TGFβ, a potent antagonist of TNFα and IL-1. Both IL-4 and TGFβ upregulate production of the IL-1 receptor antagonist, a protein that binds competitively to IL-1 receptors and inhibits the activities of IL-1. Inhibition of proinflammatory TNFα occurs through the release of soluble TNFα receptors, which function like a sponge to bind TNFα and prevent it from reaching cell-bound TNFα receptors. Another mechanism of reversal involves glucocorticoids, produced following a cascade of events initiated by IL-1, TNFα and IL-6, involving the neuroendocrine axis, which effectively dampens proinflammatory cytokine production. Thus, the host has a very effective check-and-balance system to inhibit inflammatory processes once they have accomplished their objective (ridding the host of the offensive antigen or pathogen).

Tissue repair

With the downsizing of the inflammatory response, macrophages continue to play a vital role in the transition to the proliferative phase of wound repair (**Figure 7**). Wound macrophages synthesize and release growth and regulatory factors including platelet-derived growth factor (PDGF), fibroblast growth factors (FGFs), insulin-like growth factor (IGF) 1 and TGFβ, which coordinate initiation and propagation of granulation tissue formation necessary for the reparative phase. The formation of new tissue involves angiogenesis, a process by which new capillaries sprout from existing vessels. Angiogenesis involves a concerted sequence of events involving enzymatic degradation of the underlying basement membrane and extracellular matrix to free the endothelial cells, directed migration, and proliferation of the endothelial cells. Then the newly grown endothelium differentiates into tube-like structures that are stabilized by mesenchymal cells (pericytes) and matrix production to prevent leakage, and fused to allow blood circulation. These processes require that endothelial cells respond to a variety of

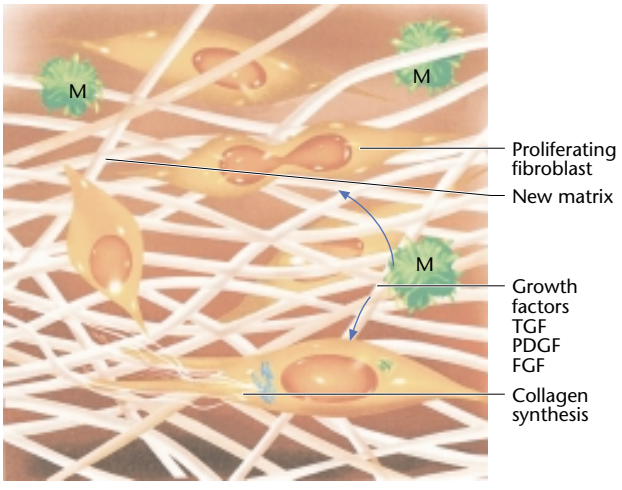

Figure 7 Healing and scar formation. As the inflammation is resolved, leucocytes, especially macrophages (M), release growth factors which stimulate fibroblasts to divide and to make new extracellular matrix (scar) to heal injured tissue. FGF, fibroblast growth factor; PDGF, platelet-derived growth factor; TGFβ, transforming growth factor β. Illustration by Jeffrey Aarons.

extracellular signals that activate the receptors responsible for growth and differentiation. Among these is vascular endothelial growth factor (VEGF) produced by macrophages and other cells which binds to VEGF-1 and VEGF-2 tyrosine kinase receptors to induce mitosis. In addition to VEGF, macrophages influence these events through the production of enzymes and growth mediators, particularly FGF, and also TNFα, which increases FGF activity, to regulate endothelial cell proliferation and migration. In an autocrine pathway, endothelial cells influence their own growth through the production of basic FGF, PDGF, IGF-1 and angiopoietin. As capillary loops appear, they are visualized as small granules, giving the tissue its name of granulation tissue.

Granulation tissue includes inflammatory cells, fibroblasts, myofibroblasts and matrix tissue, in addition to growing vessels. These cells become embedded in a loose matrix of collagens, fibrin, fibronectin and proteoglycans rich in hyaluronic acid. In the development of the granulation tissue, the neighbouring fibroblasts are influenced by inflammatory mediators to express surface integrins that recognize, among other molecules, the fibrin components of the initial clot. The deposition of fibronectin, glycosaminoglycans and other proteins in the clot provides a provisional matrix upon which the fibroblasts enter the site in response to secreted recruitment and growth-promoting signals (FGF, PDGF, TGFβ). Fibroblasts express TGFβ receptors represented by a type II ligand-binding receptor, a type I signal-transducing receptor (serine/threonine kinase) and a type III ligand-presenting receptor, which coordinate the response to this chemoattractant, growth-promoting, matrix-inducing molecule.

The expanding population of recruited and proliferating fibroblasts begins to lay down new matrix (**Figure 7**). Collagen, a triple helical structure, is the dominant component of the extracellular matrix and provides strength and form. Although there are nearly 20 different types of collagen, their distribution is generally tissue specific. The strength of collagen (scar tissue) is derived from intramolecular and intermolecular crosslinking events which occur after secretion. Although matrix repair and scar formation may not be evident for 5–7 days after cutaneous injury, the healing process was actually initiated with the first aggregating platelets that released, among other products, PDGF and TGFβ (see **Figure 3**). Eventually, matrix will fill in the damaged tissue site. In order to re-establish homeostasis, interferon and other cytokines are produced that inhibit fibroblast growth and serve to counterbalance the growth-promoting factors.

Fibroblasts acquire the capacity of contraction (myofibroblasts) and thus facilitate contraction and healing. As the wound contracts and depending on location, re-epithelialization occurs to resurface the wound. In the epidermis, keratinocytes detach, migrate, proliferate and cover the lesion site. The final step in wound healing, which may start simultaneously with granulation tissue formation, is tissue remodelling. Remodelling with collagen fibril crosslinking and scar maturation can continue for many months or even years after granulation tissue has resolved. Excess collagen and matrix are degraded by enzymes called collagenases, which cleave collagen at a specific site, leaving it vulnerable to further breakdown by other proteolytic enzymes. The rate of turnover (synthesis and degradation) of matrix is enhanced. During remodelling, the highly cellular and vascular granulation tissue is gradually replaced and reshaped to form scar tissue, which is less cellular and less vascular. The decrease in cellularity may be the consequence of cellular apoptosis and/or migration out of the wound. Unfortunately, the remodelled tissue is not generally as strong nor as functionally intact as the original, but it serves to restore tissue integrity. To this end, normal inflammation and wound healing involve a coordinated interplay amongst cells, fibrous proteins, chemokines, cytokines and growth factors as described. Dysregulation of these complex events may provide the basis for pathology exemplified by chronic nonhealing wounds, tissue destruction and/or fibrotic disruption of tissue function.

Further Reading

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