Points of control in inflammation

Carl Nathan

Department of Microbiology and Immunology and Graduate Programs in Immunology and Molecular Biology, Weill Medical College of Cornell University, Box 62, 1300 York Avenue, New York 10021, USA (e-mail: cnathan@med.cornell.edu)

Inflammation is a complex set of interactions among soluble factors and cells that can arise in any tissue in response to traumatic, infectious, post-ischaemic, toxic or autoimmune injury. The process normally leads to recovery from infection and to healing, However, if targeted destruction and assisted repair are not properly phased, inflammation can lead to persistent tissue damage by leukocytes, lymphocytes or collagen. Inflammation may be considered in terms of its checkpoints, where binary or higher-order signals drive each commitment to escalate, go signals trigger stop signals, and molecules responsible for mediating the inflammatory response also suppress it, depending on timing and context. The non-inflammatory state does not arise passively from an absence of inflammatory stimuli; rather, maintenance of health requires the positive actions of specific gene products to suppress reactions to potentially inflammatory stimuli that do not warrant a full response.

The 'inflammatory process'[1] includes a tissue-based startle reaction to trauma; go/no-go decisions based on integration of molecular clues for tissue penetration by microbes; the beckoning, instruction and dispatch of cells; the killing of microbes and host cells they infect; liquefaction of surrounding tissue to prevent microbial metastasis; and the healing of tissues damaged by trauma or by the host's response. If at any step an order to proceed is issued but progress to the next step is blocked, the inflammatory process may detour into a holding pattern, such as infiltration of a tissue with aggregates of lymphocytes and leukocytes (granulomas) that are sometimes embedded in proliferating synovial fibroblasts (pannus), or distortion of a tissue with collagen bundles (fibrosis). Persistent inflammation can oxidize DNA badly enough to promote neoplastic transformation.

What Celsus defined around AD40 as 'rubor, calor, dolor, tumor' (redness, heat, pain and swelling) is today an intellectually engaging problem in signal transduction and systems biology, as well as a multibillion dollar market for the pharmaceutical industry. When primary pathogenetic events are unknown, control of inflammation is sometimes the next best option. The number of diseases considered 'inflammatory' in origin may decline as infectious causes continue to be discovered for some of them, such as *Helicobacter pylori*-dependent chronic gastritis with ulcer formation. However, in this and several other important infectious diseases, the inflammatory response may cause more damage than the microbe. Although the search continues for possible infectious causes of multiple sclerosis, rheumatoid arthritis and atherosclerosis, inflammation *per se* remains one of the main therapeutic targets in diverse disorders with a staggering collective impact (Table 1).

Inflammation is usually life preserving, as reflected by the increased risk of grave infections in people with genetic deficiencies in principal components of the inflammatory process. For example, inability to mobilize leukocytes to sites of inflammation in type I or II leukocyte adhesion deficiency, if untreated, often leads to death from infection[2]. Inability to produce the complement components properdin and factors D, C5, C6, C7, C8 or C9 predisposes to meningococcal infection[3]. Thus, the medical focus on inhibiting inflammation is accompanied by an effort of potentially comparable importance to learn how to induce inflammation more effectively, in at least two important settings. First, causing and prolonging inflammation are among the essential functions of adjuvants, and a better understanding of the role of inflammation in adjuvanticity may enable prophylactic immunization against a wider range of infectious diseases. Second, generation of inflammation is one of the main goals of tumour immunology, both for therapeutic immunization[4] and for nonspecific immunostimulation, such as by instilling Bacille Calmette-Guérin into the urinary bladder to prevent recurrence of tumours[5].

The accompanying articles in this issue integrate cross-sections of inflammation biology by peering inside blood vessels, joints, brain, viscera and epithelia. The papers form a backdrop against which to evaluate diverse new anti-inflammatory treatments. These include neutralizers of tumour-necrosis factor (TNF); blockers of leukotriene receptors; inhibitors of cyclooxygenase (COX)-2, leukotriene synthetase and 3-hydroxy-3-methylglutaryl coenzyme A reductase; and agonism at protease-activated receptor 1 by activated protein C (ref. 6). Many more anti-inflammatory compounds are in the pipeline.

In this article I offer a perspective on inflammation as a system of information flow in response to injury and infection. If tissue is injured, the basic challenge facing the host is to detect whether there is accompanying infection. If infection is the initial event, the challenge is to detect whether tissue is injured. When injury and infection coincide, the goal is to react as quickly as possible to terminate the spread of infection, even at the cost of further tissue damage. The need to detect two states at once before risking self-inflicted damage dictates a dependence on binary or higher-order signals. The need to accelerate at a potentially high cost brings with it the need to decelerate as soon as the goal has been met. A full stop requires repairing the tissue whose damage triggered inflammation or that inflammation damaged.

Such a complex system can be characterized by its checkpoints. I first consider checkpoints evident early and late after an inflammatory response is activated, and then present evidence that another set of checkpoints operates constitutively in the basal state to prevent the inappropriate initiation of inflammation.

Go signals in early checkpoints

Evolution did not anticipate surgery with aseptic technique. Thus, the body reacts to trauma as if the emergency is infec-

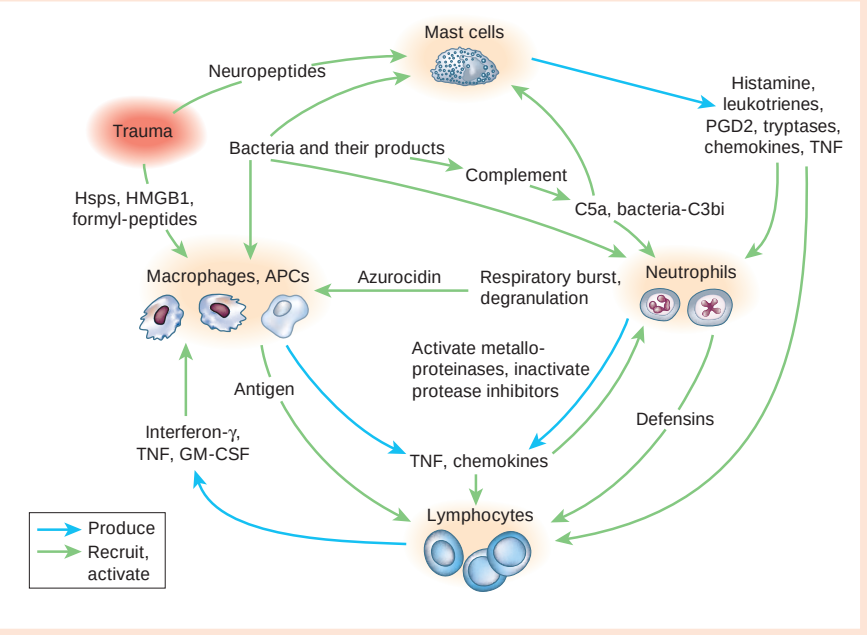

Figure 1 Information flow in the early stages following mild trauma with infection. Each cell commits to recruit and activate others based on multiple inputs, generally requiring evidence of both injury and infection, before it joins fully in amplifying the inflammatory process. Not shown are interactions among leukocytes, endothelium, platelets and coagulation factors; the generation of stop signals; and the flow of information over subsequent days, including the transition to wound healing (see text).

tion, until proven otherwise. For simplicity, the present discussion deals with mild trauma and considers only some of the go signals.

The take-home message is apparent with the following experiment. Expose one forearm with the inner surface facing up. Spread the three middle fingers on your other hand and slap them down hard on your forearm. Within about 15 seconds the skin of your forearm will display a red bas-relief of the offending digits. Over the next hour the image will fade. In contrast, if the epidermis had been broken and bacteria had entered, redness and swelling would persist, testifying to an escalating series of events that is synchronized according to bacterial replication time and metastatic potential. The episode would probably culminate in the confinement and killing of the penetrant bacteria and the destruction and repair of a small amount of tissue. Then again, if the inflammatory response were feeble and antibiotics unavailable, the outcome might be death from sepsis.

Figure 1 schematizes the flow of information following mild trauma with infection. Tissue damage unleashes up to three types of go signals. First, in response to pain, neurons release bioactive peptides[7]. Second, broken cells release constitutively expressed intracellular proteins that trigger cytokine production when found in the extracellular space. Examples include heat-shock proteins[8], the transcription factor HMGB1 (for high mobility group 1)[9] and mitochondrial peptides bearing the *N*-formyl group characteristic of prokaryotic proteins[10]. Third, microbes and their shed or secreted products are sensed through binding of their conserved molecular constituents to soluble receptors such as complement, mannose-binding protein and lipopolysaccharide-binding protein, and to cell-surface receptors such as Toll family members, peptidoglycan recognition proteins and scavenger receptors.

Much attention in inflammation research has focused on the recruitment of leukocytes from the blood[11]. However, a rapid response requires sentinel cells pre-stationed in the tissues. Mast cells and macrophages fulfil this function. The importance of mast cells as first responders (see review in this issue by Benoist and Mathis, pages 875–878), recently emphasized in experimental rheumatoid arthritis[12], is symbolized by their placement atop Fig. 1. Responding to the signals listed above, perivascular mast cells release histamine, eicosanoids, pre-formed TNF, newly synthesized cytokines, tryptases, other proteases, and chemokines. Histamine, eicosanoids and tryptases cause vasodilatation (responsible for the heat and redness) and extravasation of fluid (the cause of swelling).

Mast-cell tryptases cleave protease-activated receptors whose neo-termini then engage G-protein-coupled receptors on mast cells, sensory nerve endings[7], endothelium and neutrophils. This further activates mast cells and neurons, makes endothelium sticky for leukocytes and leaky to fluid, and prompts leukocytes to release platelet-activating factor (PAF). PAF reinforces the pro-adhesive conversion of endothelium, which results in leukocyte emigration from the vasculature. For simplicity, interactions among endothelial cells, leukocytes and extravascular signals[11] are omitted from Fig. 1. Also omitted here, but discussed in this issue by Cohen (pages 885–891), are the impacts of the coagulation and kinin cascades on interactions of endothelium and leukocytes[6,13,14] and the reciprocal influence of inflammation on the interactions of endothelium and coagulation factors (see review in this issue by Libby, pages 868–874).

Neutrophils are partially activated (primed) by the TNF and leukotrienes produced by mast cells and by other neutrophils,

Table 1 Examples of inflammatory disorders

Disorders in which an important pathogenetic role is assigned to inflammation	
Alzheimer's disease	Osteoarthritis
Anaphylaxis	Pemphigus
Ankylosing spondylitis	Periodic fever syndromes
Asthma	Psoriasis
Atherosclerosis	Rheumatoid arthritis
Atopic dermatitis	Sarcoidosis
Chronic obstructive pulmonary disease	Systemic lupus erythematosus
Crohn's disease (regional enteritis)	Type I diabetes mellitus
Gout	Ulcerative colitis
Hashimoto's thyroiditis	Vasculitides (Wegener's syndrome, Goodpasture's syndrome, giant cell arteritis, polyarteritis nodosa)
Ischaemia-reperfusion injury (occlusive and embolic stroke and myocardial infarction)	Xenograft rejection
Multiple sclerosis	
Diseases of infectious origin in which inflammation may contribute as much to pathology as does microbial toxicity	
Bacterial dysentery	Influenza virus pneumonia
Chagas disease (*Trypanosoma cruzi*)	Leprosy (tuberculoid form)
Cystic fibrosis pneumonitis	Neisserial or pneumococcal meningitis
Filariasis	Post-streptococcal glomerulonephritis
Helicobacter pylori gastritis	Sepsis syndrome
Hepatitis C	Tuberculosis
Diseases of diverse origin in which post-inflammatory fibrosis is a principal cause of pathology	
Bleomycin-induced pulmonary fibrosis	Hepatic cirrhosis (post-viral or alcoholic)
Chronic allograft rejection	Radiation-induced pulmonary fibrosis
Idiopathic pulmonary fibrosis	Schistosomiasis

Table 2 Products encoded by genes whose disruption or mutation leads to spontaneous inflammation*

Gene product(s)	Human (H) or mouse (M)	Inflammatory phenotype	Predominant sites	Reference
Factors directly involved in regulation of apoptosis				
Fas (CD95)	H	Urticarial rash, glomerulonephritis, oral ulceration, lymphocyte infiltration	Skin, kidney, mouth, liver	50–52
Fas (CD95) (lpr)	M	Glomerulonephritis, necrotizing vasculitis, erosive synovitis, interstitial pneumonitis, dermatitis	Kidney, mesentery, joints, lung, skin, vessels	53
Factors thought to be involved in clearance of immune complexes and material from apoptotic cells				
C1q (*A*, *B* and *C* genes)	H	Rash, glomerulonephritis, oral ulceration	Skin, kidney, mouth	42
C1q (*a* gene)	M	Glomerulonephritis	Kidney	54
C2	H	Rash, vasculitis, arthritis, glomerulonephritis, asthma	Skin, joints, lung	42, 55
C4	H	Rash	Skin	43
C4	M	Glomerulonephritis	Kidney	56
C3	H	Glomerulonephritis	Kidney	43
C4-binding protein	H	Ulcerations	Mouth	57
Factor H	H	Glomerulonephritis, rash	Kidney, skin	57
Crry	M	Neutrophil infiltration	Placenta	58
Serum amyloid P component	M	Glomerulonephritis	Kidney	59
DNAse I	M	Glomerulonephritis	Kidney	60
FcγRIIB	M	Glomerulonephritis	Kidney	61
WASP (Wiskott–Aldrich syndrome protein)	H	Eczema, vasculitis, renal disease, arthritis, inflammatory bowel disease	Skin, kidney, joints, bowels	62, 63
WASP	M	Lymphocyte and neutrophil infiltration	Colon	64
Cytokines, cytokine receptors and other cell surface receptors				
TNF-R1 (tumour-necrosis factor receptor 1)	H	Familial Hibernian fever (periodic fever, conjunctivitis, periorbital edema, arthralgia)	Systemic, eyes, joints	65
TGF-β1 (transforming growth factor-β1)	M	Macrophage, lymphocyte and neutrophil infiltration in blood vessels and parenchyma; gastric ulceratiion	Lung, heart, stomach, liver spleen, lymph nodes, pancreas, colon, salivary glands, striated muscle	66, 67
IL-2Rα (interleukin-2 receptor-α)	M	Lymphocyte and neutrophil infiltration; ulceration	Colon	68
IL-2	M	Granulocyte, lymphocyte and plasma cell infiltration; ulceration	Colon	69
IL-10	M	Lymphocyte and neutrophil infiltration	Duodenum, jejunum, ileum, colon	70
GM-CSF (granulocyte–macrophage colony-stimulating factor)	M	Lymphocyte infiltration around airways and veins	Lung	71
IL-1Ra (IL-1 receptor antagonist)	M	Neutrophil, macrophage and $CD4^+$ lymphocyte infiltration	Aorta, coronaries, iliac and popliteal arteries	72
IL-1Ra	M	Erosive arthritis	Joints	73
T-cell receptor-α	M	γδ T-cell, B-cell, plasma cell and neutrophil infiltration	Colon	74
T-cell receptor-β	M	γδ T-cell, B-cell, plasma cell and neutrophil infiltration	Colon	74
Major histocompatibility complex class II	M	Lymphocyte and neutrophil infiltration	Colon	74
CTLA4 (cytotoxic T-lymphocyte antigen 4)	M	Lymphocyte, macrophage and granulocyte infiltration	Heart, pancreas, lung, bone marrow, liver, salivary glands, joints, blood vessels	75, 76
PD-1 (immunoreceptor tyrosine-based inhibitory motif (ITIM)-bearing Ig superfamily member; orphan receptor)	M	Arthritis, glomerulonephritis, carditis	Joints, kidneys, heart	77
Intracellular factors in lymphocytes, leukocytes and epithelial cells affecting their activation				
LAT (linker for activation of T cells)	M	$CD4^+$ T-cell, eosinophil, B-cell and macrophage infiltration	Multiple organs	78
SOCS1 (suppressor of cytokine signalling)	M	Macrophage infiltration	Liver, lungs, pancreas, heart, skin	79
Phosphatidylinositol 3-phosphate kinase p110δ	M	Leukocyte infiltration	Caecum, rectum	80

leading to release of small amounts of elastase. This cleaves the anti-adhesive coat of CD43 (leukosialin) from neutrophils, allowing their integrins to engage extracellular matrix proteins[15]. The binary signal of integrin engagement plus stimulation by TNF, chemokines or C5a triggers degranulation and a massive respiratory burst[16], resulting in release of proteinases (such as the serprocidins elastase, cathepsin G and protease 3), other hydrolases, antibiotic proteins (such as bacterial permeability increasing factor, four α-defensins, the three serprocidins and their proteolytically inactive homologue, azurocidin) and oxidants (such as hydrogen peroxide, hypohalites and chloramines). The oxidants activate matrix metalloproteinases (MMPs) and inactivate protease inhibitors[17].

The foregoing actions promote tissue breakdown. Metalloproteinases cleave TNF from tissue macrophages as well as from monocytes that are chemotactically attracted from the bloodstream into the tissue by azurocidin[18]. Macrophage- and monocyte-derived TNF and chemokines attract and activate more neutrophils. TNF and chemokines combine with mast cell-derived prostaglandin E2 (PGE2) and neutrophil-derived defensins to recruit lymphocytes[19], while leukotrienes help attract antigen-presenting dendritic cells[20]. Lymphocytes, in conjunction with microbial products, activate macrophages to secrete proteases, eicosanoids, cytokines and reactive oxygen and nitrogen intermediates (ROIs and RNIs, respectively).

In summary, the inflammatory system is geared for lag-free acceleration, but requires ongoing verification of emergency to avoid defaulting to the resting state. Each newly recruited cell generally commits to release pro-inflammatory signals only after integrating inputs of both host and microbial origin.

It is a canon of immunology that for cellular activation, B cells generally need antigen-receptor engagement plus signals from T cells; T cells need antigen-receptor engagement plus signals from antigen-presenting cells (APCs); and APCs, including macrophages, need cytokines plus microbial products, or cytokines plus CD40 ligation, or microbial products plus products of necrotic host cells. The

Table 2 Products encoded by genes whose disruption or mutation leads to spontaneous inflammation* (Continued)

Gene product(s)	Human (H) or mouse (M)	Inflammatory phenotype	Predominant sites	Reference
Pten (phosphatase active on PtdIns(3,4,5)P_3)	M	Inflammatory interstitial infiltration	Lung	81
Lyn	M	Glomerulonephritis, renal capillary vasculitis	Kidney	82, 83
Cbl	M	Activated B- and T-cell infiltration	Salivary glands, pancreas, liver, intestine, lung, kidney, heart, skeletal muscle, urinary bladder	84
$G\alpha_{i2}$	M	Lymphocyte, plasma cell and neutrophil infiltration; ulceration	Colon	85
SHP-1 (protein tyrosine phosphatase)	M	Neutrophil abscesses, interstitial pneumonitis	Skin, lung	86, 87
SHIP (inositol-5-phosphatase)	M	Macrophage infiltration	Lungs	88
p21	M	Leukocyte infiltration, glomerulonephritis	Kidney	89
Tristetraproline	M	Neutrophil, macrophage and lymphocyte infiltration; pannus formation; bone erosion; glomerulonephritis	Skin, conjunctivae, joints, kidney	90
NFAT (nuclear factor of activated T cells)-p and NFAT4 (double deletion)	M	Lymphocyte, macrophage, plasma cell, neutrophil, and mast cell infiltration	Eyelids, lungs	91
IKK (IκB kinase)-2 (deficiency restricted to keratinocytes)	M	Macrophage, neutrophil and $CD4^+$ T-cell infiltration	Skin	92
IKKγ (NEMO: NF-κB essential modulator)	H	Rash; eosinophil and neutrophil infiltration	Skin	93
IKKγ (NEMO: NF-κB essential modulator)	M	Neutrophil and eosinophil infiltration; iNOS expression	Skin	94, 95
IκBα (inhibitor of NF-κB)	M	Neutrophil abscesses and macrophage infiltration	Skin	96
E3 ubiquitin ligase	M	Macrophage and plasma cell infiltration; fibrosis; alveolar proteinosis	Lung	97
RelB	M	T-cell, eosinophil, neutrophil, macrophage and mast cell infiltration; collagen deposition; hyperplasia of mucus-secreting cells	Skin, lungs, liver, salivary glands, skeletal muscles, stomach, epididymis, ovaries, uterus	98–100
NF-κB1 (p105) (retaining p50)	M	Lymphocyte infiltration around vessels, portal tracts and airways	Lungs, liver	101
T-bet	M	Peribronchial and perivenular eosinophil and lymphocyte infiltration; collagen deposition	Lungs	102
Gadd45a (growth arrest and DNA damage-inducible gene)	M	Glomerulonephritis, perivascular mononuclear infiltration	Kidney	103
Mdr (multiple drug resistance)-1a	M	$CD4^+$ T-cell, B-cell and granulocyte infiltration; mucosal thickening and ulceration	Colon	104
NOD2/CARD15	H	Crohn's disease (granulomas, fibrosis)	Ileum	105, 106
NOD2/CARD15	H	Blau syndrome (granulomatous arthritis, uveitis, rash)	Joints, eyes, skin	107
Pyrin	H	Familial Mediterranean fever (fever, neutrophil infiltration)	Systemic, joints, peritoneum, pleural space	108, 109
Cryopyrin or CIAS (cold-induced autoinflammatory syndrome)-1	H	Cold-induced periodic fever, rash, arthralgia, conjunctivitis; or without cold induction (Muckle–Wells syndrome)	Systemic, skin, joints, conjunctivae	110
Mevalonate kinase	H	Periodic fever, athralgia, abdominal pain, rash	Systemic, joints, peritoneum (?), skin	111, 112
Factors affecting oxidative stress				
Haem oxygenase 1	M	Lymphocyte, neutrophil and macrophage infiltration; fibrosis; glomerulonephritis	Liver, lung, kidney	113
Surfactant protein D	M	Monocyte peribronchiolar and perivascular infiltration; emphysema	Lung	44

*'Spontaneous' indicates substantially more frequent occurrence than in wild-type hosts, despite lack of known infection or experimental intervention, in subjects living under normal conditions, presumably with normal gastrointestinal flora. People with Wiskott-Aldrich syndrome experience frequent infections but the disorder is included for comparison with the mutant mouse, in which infections have not been described. Only inflammatory aspects of the phenotype are listed, even when these are not the major manifestations of the disorder. Abnormal accumulation of lymphocytes in lymphoid organs and the development of autoantibodies are not considered signs of inflammation. Entries are omitted for disorders in which the mutated gene has not been identified; the mutation is thought to confer a gain of function; the phenotype requires that two known genes both be mutated; or only a single case has been reported. For mice, the phenotype is described in the strain background in which it is most pronounced, provided that the background does not furnish another known mutation with a related phenotype.

discussion above stresses that a requirement for binary or higher-order go signals begins with the activation of mast cells and neutrophils, and that sustained activation of mast cells and neutrophils usually precedes and conditions the activation of APCs, T cells and B cells as the inflammatory response evolves into the immune response. That a combination of tissue injury plus infection sustains inflammation helps clarify what provokes an immune response[21,22].

Massive trauma, post-ischaemic or toxic necrosis, and haemorrhage and resuscitation can each trigger an inflammatory response that appears to be independent of infection. This may reflect the ability of some host cell products that are altered (for example, fragmented matrix proteins or oxidized lipoproteins), abnormally released (for example, heat-shock proteins) or released in abnormally large amounts to interact with receptors (for example, Toll-like receptor 4) that otherwise detect microbial signals[23]. Alternatively, cryptic microbial signals may be involved, because such stresses may be associated with the translocation of bacteria or diffusion of their products across the intestinal wall[24].

Stop signals in early checkpoints

Superimposed on the feed-forward cycles illustrated above are sets of brakes. Brakes involving lipid autacoids illustrate one mechanism: to progressively raise the threshold for continuing the inflammatory reaction[25]. Neutrophil-derived arachidonate serves as substrate for neutrophil 5-lipoxygenase to generate the inflammatory leukotriene B4. However, as neutrophils infiltrate tissues, they also pass arachidonate to tissue cells expressing 15-lipoxygenase, which produces lipoxins. Lipoxins are a class of oxidized eicosanoids that bind cellular receptors and block neutrophil influx[25]. Neutrophils also pass to other cells a 5-lipoxygenase intermediate, leukotriene A4; 15-lipoxygenase converts this to a lipoxin as well[25]. In this manner, cell–cell interactions favour a transition in the profile of arachidonate products from pro-inflammatory leukotrienes to anti-inflammatory lipoxins. At the

same time, COX2 is induced in macrophages by microbial products and cytokines. COX2 converts arachidonate to PGE2, which contributes to fluid leak from blood vessels. However, as PGE2 levels rise, PGE2 feeds back to inhibit COX2 as well as 5-lipoxygenase, while transcriptionally inducing 15-lipoxygenase in neutrophils. These delayed effects shift arachidonate metabolism towards lipoxin formation in neutrophils themselves[25]. In this way, over several hours, PGE2, at first a go signal, becomes a stop signal. The anti-inflammatory drug aspirin recapitulates this phenomenon by acetylating COX2; the acetylated enzyme switches from making PGE2 to making lipoxins[25].

Studies with gene-disrupted mice highlight additional stop signals. Mice lacking the ectonucleotidase CD39 over-react to chemical irritation of the skin[26]. Mice deprived of purinergic A2a receptors succumb to normally sublethal doses of microbial and chemical toxins[27]. These observations suggest that CD39 breaks down extracellular ATP and ADP secreted by activated cells or leaking from broken cells, generating adenosine. Adenosine then acts to suppress inflammatory responses by neighbouring cells.

In another set of examples, mice lacking the cell-surface immunoglobulin superfamily molecule CD200 suffer more macrophage influx and worse experimental autoimmune encephalomyelitis and collagen-induced arthritis than do wild-type mice[28]. Similarly, mast cells lacking the integrin-binding receptor gp49B1 degranulate excessively in response to immunoglobulin E–antigen complexes[29]. These studies hint at a wide array of protein–protein interactions among cells, and between cells and their matrix, that temper inflammation in its early phase.

A fourth type of stop signal is issued by the autonomic nervous system. As reviewed by Tracey in this issue (pages 853–859), cholinergic discharge blocks the release of TNF from macrophages in the viscera.

Signals for switching from killing to healing

A crucial commitment made late in inflammation is to convert the response from the antibacterial, tissue-damaging mode to a mode that promotes tissue repair and epithelial closure. The timing is critical — to close a wound before it is disinfected invites disaster. Some of the signals involved are revealed by the failure of mice to resolve late-phase inflammation when they are deficient in the CD44 hyaluronan receptor[30], secretory leukocyte protease inhibitor (SLPI)[31] or TNF[32,33]. The scenario below integrates findings from these reports; space limitation precludes citing additional examples.

Continuing from the point reached in the description of Fig. 1, as long as microbial and host pro-inflammatory stimuli predominate, macrophage-derived chemokines continue to attract neutrophils. ROI and hyaluronidase from macrophages and neutrophils break down hyaluronic acid in the extracellular matrix to low molecular weight fragments. Like the heat-shock proteins, HMGB1 protein and *N*-formyl peptides described earlier, hyaluronan fragments act as signals of injury, working via CD44 on macrophages to induce the further release of chemokines and perhaps MMPs. Neutrophils with engaged integrins are activated by macrophage-derived TNF to release abundant elastase. Elastase and ROI activate MMPs. MMPs activate macrophage-derived latent transforming growth factor-β (TGF-β), the most potent known chemoattractant for neutrophils. MMPs also degrade collagen, proteoglycans and fibronectin. Elastase degrades latent TGF-β-binding protein, contributing to the activation of TGF-β.

The transformation from tissue damage to tissue repair begins as complement, neutrophils and macrophages kill microbes, and macrophages secrete more SLPI, a serine protease inhibitor expressed late after exposure to microbial products or cytokines. SLPI has anti-inflammatory[34] and wound-healing effects[31] that include suppressing the release of elastase and ROI by TNF-stimulated neutrophils[35], inhibiting elastase that has already been released and preventing the breakdown of TGF-β[31]. Furthermore, SLPI binds and synergizes with proepithelin, a cytokine that promotes epithelial growth and suppresses neutrophil activation, protecting it from proteolytic conversion into pro-inflammatory epithelins[36]. CD44-positive macrophages clear the hyaluronan fragments. Fresh neutrophils no longer enter the site, and those present undergo apoptosis. Macrophages ingest apoptotic neutrophils and degrade their residual stores of elastase. TNF induces macrophages to release interleukin-12, which induces lymphocytes to release interferon-γ (IFN-γ). IFN-γ acts early on to induce macrophage chemokine production, but now suppresses it[33]. Ingestion of apoptotic neutrophils elicits more TGF-β from macrophages, and the predominant action of TGF-β is no longer the recruitment of neutrophils, but instead the promotion of tissue repair. Thus, TNF, IFN-γ and TGF-β join PGE2 as examples of molecules whose actions switch from pro-inflammatory to anti-inflammatory, depending on timing and context.

ROIs and RNIs are two additional sets of molecules that can either promote or suppress inflammation. Chronic granulomatous disease (CGD), a genetic disorder predisposing to life-threatening bacterial and fungal infections, results from a deficiency in the ROI-producing enzyme phagocyte oxidase (phox). In CGD, chronic inflammation sometimes seems to precede infection or long outlast it[37]. The clinical impression of an exaggerated granulomatous response in CGD has been confirmed in phox-deficient mice, which form abnormally large granulomas when injected with sterile fungal cell walls[38]. These observations demonstrate that phox has an important anti-inflammatory role, such as oxidatively inactivating chemotactic factors[39], even though phox can be profoundly pro-inflammatory by virtue of oxidizing tissue constituents, oxidatively activating metalloproteinases and oxidatively inactivating protease inhibitors[17]. Similarly, mice deficient in inducible nitric oxidase synthase (iNOS) display a triple phenotype — increased susceptibility to infection, reduced inflammation or excessive inflammation — depending on the experimental setting[40,41]. Without infection or other experimental intervention, however, mice lacking phox or iNOS appear normal, in contrast to the situation discussed next.

Genes whose disruption predisposes to inflammation

Another level of control is revealed by the fact that there are numerous genes whose disruption predisposes to inflammation in people or mice living under conventional conditions without evident provocations that are known to elicit inflammation in wild-type hosts (Table 2).

That loss-of-function mutations can lead to spontaneous inflammation was probably shown first and most clearly by human C1q deficiency[42]. This disorder confers a >90% incidence of systemic lupus erythematosus[43]. That Table 2, although incomplete, includes over 50 genes implies that health does not arise passively from a lack of pro-inflammatory stimuli. On the contrary, potentially inflammatory stimuli seem to be ubiquitous, and it takes an active process to avoid over-reacting to those that pose a minimal threat.

The diverse genes necessary to suppress spontaneous inflammation can be classified into functional sets. Although such groupings are subjective, it is difficult to posit less than three key elements of the tonic anti-inflammatory state. First is the solubilization and clearance of immune complexes and cellular debris. The second element is the balanced progression of leukocytes and lymphocytes through programmes of activation, proliferation and apoptosis. Third is the avoidance of oxidative injury, such as by disposal of haem and by constitutive restraint on the respiratory burst activity of macrophages that are continually exposed to particulate stimuli[44].

Gene products are included in Table 2 because of their demonstrated importance for avoiding inflammation. In a paradox that is now familiar, most of these proteins, such as TNF-R1 and NF-κB, are better known for their essential contributions to promoting inflammation. Again it emerges that pro-inflammatory gene products are often essential effectors of anti-inflammatory homeostasis.

Many of the phenotypes listed in Table 2 are strongly dependent on genetic background, age, sex and environmental conditions (such as intestinal flora). The profound influence of epistatic or nongenetic

factors is apparent when considering the following contrasts. First, mice of one strain contrasted with mice of another, such as those whose deficiency in interleukin-1 receptor antagonist (IL-1Ra) leads either to arthritis or arteritis. Second, one person contrasted with another, such as those with NOD2 mutations who develop either enterocolitis or arthritis (NOD2 is an intracellular lipopolysaccharide- and kinase-binding protein with a caspase-recruitment domain (CARD), a nucleotide-binding domain and leucine-rich repeats (LRRs)[45]). Third, people contrasted with mice, such as those whose disrupted C4 gene predisposes to rash or glomerulonephritis, respectively.

It is a puzzle that disrupting a given gene has tissue-specific consequences when expression of the gene in question is not restricted to, or in some cases even manifest by, the tissue that is inflamed. This is not fully explained by the ability of leukocytes and lymphocytes to enter any tissue. Overall, the sites most frequently affected by inflammation in association with the listed mutations (skin~lung > kidney > joints > colon~liver > heart > pancreas ~ eyes > other organs) are those that are anatomically large (skin, lung, colon and liver), continually exposed to microbes (skin, lung, colon and conjunctivae), or prone to trapping immune complexes (kidney, joints and skin).

Finally, Table 2 can be viewed as a collection of mechanistic mysteries that invite investigation. Among the most intriguing are the genes whose mutation predisposes to periodic fever syndromes. Cryopyrin resembles NOD2, Toll-like receptors and CD14 in carrying an LRR. Pyrin and cryopyrin contain pyrin domains, which are predicted to share structural features with CARDs, such as those present in NOD2[46]. What is the mechanism of the anti-inflammatory actions of these proteins? Do they have pro-inflammatory actions as well? What are the contributions of their LRR, pyrin and CARD domains? Why do the phenotypes of their mutations mimic those associated with mutations in genes encoding two additional and very different proteins, TNF-R1 and mevalonate kinase? Mevalonate kinase is essential for synthesis of isoprenoids and cholesterol. Perhaps this sheds light on the unexplained anti-inflammatory effects of statins, drugs that block cholesterol synthesis at a later step[47]. Administration of statins might lead to accumulation of a cholesterol precursor whose formation depends on mevalonate kinase. Perhaps this intermediate has potent anti-inflammatory actions on its own, or confers such actions on a protein to which it becomes attached.

Perspective

Our bodies sustain the replication of hundreds of different genomes. Only the largest is heritable in the germ line. To preserve its opportunity to be transmitted, the germ line genome must encode hair-trigger vigilance against take-over of the soma by genomes that replicate far faster. The rapid mobilization of microbicidal defences evolved at the cost of potentially suicidal autotoxicity (see review in this issue by Cohen, pages 885–891). Thus, for host survival, two sets of mechanisms must be matched: the ability to mount a rapid inflammatory response to injurious microbial invasion, and the ability to refrain from doing so otherwise.

For those seeking the origins of inflammatory or autoimmune diseases, this analysis encourages two lines of inquiry: First, what might predispose to the formation, modification or relocalization of endogenous molecules such that they activate detection systems that normally report injury and infection? Second, are there dysfunctions in pathways whose integrity is required to prevent inflammation from arising spontaneously?

For those trying to promote inflammation, the analysis offered above commends combinations of signals that mimic both injury of the host and the presence of infectious agents, without resorting to either.

For those developing anti-inflammatory therapies, the need for each of several go signals suggests that it should be relatively straightforward to interrupt inflammation. Unfortunately, the redundancy of many signals (over-determination) complicates this goal. The recognition of stop signals offers additional opportunities to abort inflammation[48]. However, predictability is complicated by the tendency of signals to shift sense, as illustrated for PGE2, TNF, IFN-γ, TGF-β, ROIs and RNIs. Finally, there remains the dilemma that the more broadly an agent suppresses inflammation, the more likely it will exacerbate infections. Corticosteroids taught this lesson, and TNF-neutralizing agents reinforced it[49]. Nonetheless, many of those working in anti-inflammatory research are optimistic. Experimental biology is uncovering an unprecedented wealth of molecular detail at a time when systems biology seems poised to put into perspective the complexity and dynamics of the inflammatory process. An alliance between experimental and systems biology should be a powerful force to identify points of control amenable to relatively safe and effective intervention. □

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