Molecular Medicine

An Expanding Role for Interleukin-1 Blockade from Gout to Cancer

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There is an expanding role for interleukin (IL)-1 in diseases from gout to cancer. More than any other cytokine family, the IL-1 family is closely linked to innate inflammatory and immune responses. This linkage is because the cytoplasmic segment of all members of the IL-1 family of receptors contains a domain, which is highly homologous to the cytoplasmic domains of all toll-like receptors (TLRs). This domain, termed "toll IL-1 receptor (TIR) domain," signals as does the IL-1 receptors; therefore, inflammation due to the TLR and the IL-1 families is nearly the same. Fundamental responses such as the induction of cyclo-oxygenase type 2, increased surface expression of cellular adhesion molecules and increased gene expression of a broad number of inflammatory molecules characterizes IL-1 signal transduction as it does for TLR agonists. IL-1β is the most studied member of the IL-1 family because of its role in mediating autoinflammatory disease. However, a role for IL-1α in disease is being validated because of the availability of a neutralizing monoclonal antibody to human IL-1α. There are presently three approved therapies for blocking IL-1 activity. Anakinra is a recombinant form of the naturally occurring IL-1 receptor antagonist, which binds to the IL-1 receptor and prevents the binding of IL-1β as well as IL-1α. Rilonacept is a soluble decoy receptor that neutralizes primarily IL-1β but also IL-1α. Canakinumab is a human monoclonal antibody that neutralizes only IL-1β. Thus, a causal or significant contributing role can be established for IL-1β and IL-1α in human disease.

ARE IL-1 AND CACHETIN THE SAME MOLECULE?

With this question, I first met Anthony (Tony) Cerami. This first interaction resulted in an enduring scientific and personal friendship for over 30 years. We first met at a meeting at the National Institutes of Health. We had both been studying soluble mediators of inflammation released into the supernatants of mononuclear phagocytes. We had both worked to purify our respective molecules. But neither Tony nor my group with Shelly Wolff had N-terminal amino acid sequences to compare. This was the early 1980s and cDNAs were in their infancy. Researchers studying small (<20,000 Da) biologically active proteins were limited by the fact that these biologically very active proteins were present in small amounts of the supernatants, making purification difficult. The name of the molecule that I was studying was called leukocytic pyrogen, the endogenous fever-producing protein, and Tony named the molecule that he was studying "cachectin." Were these the same molecule?

IL-1: More than the "Fever Molecule"

During the late 1970s, what is now called IL-1 had been studied under different names such as leukocytic pyrogen, leukocyte endogenous mediator, mononuclear cell factor, catabolin and others. Each was characterized on the basis of a biological assay but a highly relevant bioassay. For example, the bioassay for leukocytic pyrogen was fever, and the bioassay for leukocyte endogenous mediator was a fall in serum zinc levels.

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The bioassay for the mononuclear cell factor was increased prostaglandin E_2 (PGE_2) and for catabolin was the degradation of cartilage. In each case, however, the source of the activity was found in the supernatants of mononuclear cells that had been stimulated *in vitro*. Others working with mononuclear supernatants described an activity of augmentation of T-cell proliferation to antigen challenge. They called the activity "lymphocyte activating factor." In 1979, it was decided to group all the activities from macrophage supernatants and called these IL-1, whereas activities from lymphocyte supernatants were called IL-2. At the time, biochemical characterization of these activities from cell supernatants was limited—mostly gel filtration with similar molecular weights between 15,000 and 20,000 Da. In the case of leukocytic pyrogen, considerable progress had been made on the purification of supernatants from human monocytes (1) and rabbit peritoneal granulocytes (2).

Tumor Necrosis Factor as a Mediator of Inflammation

Although many were studying the tumor-killing activities of macrophage supernatants, starting in the early 1980s, a new activity in these supernatants was reported from Tony's laboratory. The activity was the suppression lipoprotein lipase (LPL) (3). The discovery of LPL suppression was related to an observation that during infection, as well as during noninfectious inflammatory diseases, loss of lean body mass (LBM) takes place. This and other astute clinical observations are outlined in a review on the discovery of tumor necrosis factor (TNF) as an inflammatory mediator. The increase in serum lipids associated with infection and inflammatory diseases was known, but Tony's papers linked suppression of LPL to an activity that was present in the supernatants of LPS-stimulated cells. Tony had clearly made a link between chronic inflammatory diseases, the loss of LBM and the LPL-suppressive activities of endotoxin-stimulated macrophages. In addition, he made a further link between the anemia that accompanies chronic diseases such as rheumatoid arthritis and LPL suppression. This loss in LBM takes place in cancer and is called "cancer cachexia." Tony had named the LPL-suppressive activity in stimulated macrophage supernatants "cachectin" (3).

TNF Induces IL-1

Of the many collaborations in my career, the studies on the ability of cachectin's (TNFα's) inducing IL-1 stands out (4). It brought me to work with Tony and to benefit from his unique insights into science. Our collaborative studies on TNFα's inducing IL-1 has had far-reaching clinical impacts on cytokine-based therapeutics. However, exactly how this collaboration started is worth reviewing. Motivated by the ability of TNFα to killed tumor cells *in vitro*, Genentech scientists isolated the cDNA for TNFα and soon thereafter, Tony and his postdoctoral student, Bruce Beutler, published that cachetin and TNFα were the same molecule. In an instant, the biology of TNFα was transformed from a cytokine that caused tumor cell death to a major mediator of inflammation. Few saw or appreciated this transformation, but for Tony, this came as no surprise. Genentech certainly did not understand that TNFα was a highly active inflammatory molecule.

When Genentech injected recombinant TNFα into humans suffering with cancer, they observed high fevers and a fall in blood pressure. This result was unexpected, and using TNFα to treat human cancer patients would reveal the true nature of TNFα (that is, it is a highly inflammatory molecule).

In the early 1980s when the first recombinant proteins for human use were produced in *E. coli*, Genentech had injected healthy subjects with recombinant human growth hormone. Despite negative *Limulus* testing, the subjects experienced high fevers and shaking chills. The fevers were due to endotoxin contamination and the company failed to detect endotoxin in the preparations of recombinant human growth factor prepared for human use (5). But in the case of recombinant TNFα causing fever, it was an intrinsic property of TNFα to cause fever directly as well as to induce IL-1 (4).

How Much of the Benefit of Anti-TNFα Therapy Is due to Reducing IL-1?

In 1989, when Marc Feldmann and Fiona Brennan added a neutralizing monoclonal antibody to TNFα to cultured synovial tissue explants from rheumatoid arthritis patients, the readout was spontaneous IL-1 production (6). Indeed, anti-TNFα reduced the spontaneous production of IL-1, but it was a reduction in IL-1α. One year previously in 1988, Feldmann and Maini published their first paper on TNFα in rheumatoid arthritis; they measured mRNA of TNFα levels in synovial explants but also measured IL-1α, not IL-1β (7). In many ways, the Brennan-Feldmann study confirmed the observation that in a clinical setting TNFα induced IL-1 (4). Looking back, the Brennan-Feldmann study helped provide the rationale for testing anti-TNFα in patients with rheumatoid arthritis. But the concept that TNFα had a role in the pathogenesis of rheumatoid arthritis was already known well before 1988. Tony and Jean-Michel Dayer had provided a basis for using anti-TNFα in rheumatoid arthritis by showing that TNFα induced PGE_2 and collagenase in synovial fibroblasts (8). Jeremy Saklatvala (9) also provided a rationale for a role of TNFα in rheumatoid arthritis. But in the early 1980s, Tony had already proposed that anti-cachectin monoclonal antibodies should be used to treat rheumatoid arthritis (10). Although blocking TNFα in rheumatoid arthritis is a highly effective treatment for rheumatoid arthritis, other "biologicals" are also effective. Antibodies to the IL-6 receptor, the CTLA4-IgG fusion protein, blocking the IL-1 receptor with the IL-1 receptor antagonist (IL-1Ra, anakinra), are approved for treating the signs and symptoms of rheumatoid arthritis, and antibodies to IL-1β (canakinumab) are also effective (11).

A Broadening Role for IL-1–Blocking Therapies

With the availability of specific IL-1–targeting therapies, a broadening list of diseases has revealed the pathologic role of IL-1–mediated inflammation. Monotherapy blocking IL-1 activity results in a rapid and sustained reduction in disease severity. In common conditions such as heart failure (12,13) and acute gouty arthritis (14–17), IL-1 blockade can be highly effective therapy compared to standards of therapy. Three IL-1 blockers have been approved: anakinra, rilonacept and canakinumab. The IL-1 receptor antagonist, anakinra, blocks the IL-1 receptor and therefore reduces the activity of IL-1α and IL-1β. Rilonacept is a soluble decoy receptor, and canakinumab is a neutralizing monoclonal anti–interleukin-1β antibody. A monoclonal antibody directed against the IL-1 receptor and a neutralizing anti–IL-1α are in clinical trials. The antibody to IL-1α has been administered to patients with cancer cachexia and resulted in a reduction in the wasting syndrome, decreased IL-6 levels and a nonsignificant prolongation of life (18). By specifically blocking IL-1, we have learned a great deal about the role of this cytokine in inflammation, but equally important, reducing IL-1 activity has lifted the burden of disease for many patients.

Autoimmune Versus Autoinflammatory Diseases

All autoimmune diseases have a significant inflammatory component that is due to the production of IL-1β as well as IL-1α from myeloid cells, particularly macrophages. Membrane IL-1α from mesenchymal cells may also contribute to the inflammatory component in autoimmune disorders. Therefore, antiinflammatory strategies that target IL-1 will show efficacy when used to treat classic autoimmune diseases. However, what distinguishes autoimmune diseases from autoinflammatory diseases? In autoimmune diseases, the immunological dysfunction is due to autoreactive T cells that produce IL-12, TNFα, IL-17 and

other cytokines, but there are few examples that T cells, particularly CD4^{+} T cells from the peripheral blood IL-1β. B cells produce IL-1β and there is IL-1α from T cells. Biologicals that target T-cell cytokines are highly effective in treating autoimmune diseases. CTLA4-Ig is also effective for autoimmune diseases. However, during the past 10 years, a concept has emerged that several chronic inflammatory diseases are due to monocyte/macrophage dysregulated IL-1β and have been termed "autoinflammatory" diseases. These diseases are uniquely responsive to blocking IL-1β but far less response to blocking TNFα. In fact, in some diseases, such as heart failure, blocking TNFα may worsen heart failure. The primary sources of IL-1β are the myeloid cells, primarily monocytes, macrophages and neutrophils. Unlike autoimmune diseases, autoinflammatory diseases are not due to autoreactive T cells. Autoimmune diseases exhibit distinct major histocompatibility complex (MHC)-associated haplotype susceptibilities, are progressive rather than periodic and are not strongly associated with environmental stress triggers. Moreover, many autoinflammatory diseases include illnesses due to specific mutations in proteins that regulate IL-1β activity and not TNFα activity. As autoimmune diseases respond to therapies such as TNFα neutralization, CTLA4-Ig, anti–IL-6 receptor, depletion of CD20 B cells and anti–IL-12/IL-23 and IL-17 neutralizing antibodies, these agents show no benefit in patients with autoinflammatory diseases.

Mechanisms in the Pathogenesis of Autoinflammatory Diseases

In general, there is considerable evidence that the caspase-1 inflammasome and the release of IL-1β are major players in the pathogenesis of autoinflammatory diseases. In circulating human blood monocytes, caspase-1 is present in an active state (19); as soon as the monocyte is stimulated, cleavage of the precursor takes place and mature IL-1β is secreted. Caspase-1 is also constitutively active in

highly metastatic human melanoma cells (20). However, the release of active IL-1β from blood monocytes is tightly controlled; <20% of the total synthetic IL-1β precursor is processed and released (21). In contrast, monocytes from patients with autoinflammatory syndromes release more processed IL-1β, but the increase is modest (that is, <10-fold greater than that of monocytes from healthy subjects) (22,23). Only fivefold more IL-1β is produced each day in patients with cryopyrin-associated periodic syndrome (CAPS) compared with healthy controls (24).

Although it is possible to demonstrate that blood monocytes from patients with autoinflammatory diseases process and release significantly more IL-1β than monocytes from healthy controls, the basis for the increase varies. Several autoinflammatory diseases have a mutation in NACHT, LRR and PYD domains-containing protein 3 (NALP3) resulting in an active inflammasome (25–30), but many do not have mutations in genes known to regulate caspase-1 or the secretion of IL-1β. For example, the secretion of IL-1β requires triggering of the P2X7 purinergic receptor by adenosine triphosphate (ATP) (31) and active phospholipases C and A2b for secretion via secretory lysosomes (32). Although viral infections and environmental factors are thought to trigger a bout of inflammation in patients with autoinflammatory diseases, continued production of IL-1 seems to drive chronic autoinflammation. For example, steady-state mRNA levels of IL-1β, caspase-1, IL-1α, IL-6 and TNFα are elevated in blood monocytes from patients with neonatal-onset multisystem inflammatory disease (NOMID) compared with cells from healthy subjects but decrease with treatment with anakinra (23). The likely mechanism is therefore IL-1 induction of caspase-1, which results in IL-1 induction of itself. With increased levels of IL-1, IL-1 then induces other cytokines. Regardless of the mechanism of increased IL-1β release, what characterizes these diseases as autoinflammatory is the rapid and sustained response to a therapeutic reduction in IL-1β activity.

Table 1. Anakinra for hereditary systemic inflammatory diseases.

Disease	References
FMF	138–151
FCAS	115,152,153
MWS	30,104,154–161
NLRP12 autoinflammatory syndrome	162
NOMID	23,30,102,105,106,163–166
TRAPS	167–173
Hyperimmunoglobulin D syndrome (HIDS)	174–179
PAPA syndrome	180–186
Pseudoangiomatous stromal hyperplasia (PASH)	180,187
Deficiency of the IL-1 receptor antagonist (DIRA)	188–190
Blau syndrome (granulomatous arthritis)	191,192
Mevalonate kinase deficiency	193
Majeed syndrome	194

CLASSES OF AUTOINFLAMMATORY DISEASES

Autoinflammatory diseases fall into different classes. But as stated above, what characterizes these diseases as autoinflammatory is the rapid and sustained response to a therapeutic reduction in IL-1β activity. As shown in Table 1, the classic autoinflammatory diseases are hereditary. These include NOMID, the Muckle-Wells syndrome (MWS), familial cold-induced autoinflammatory syndrome (FCAS), hyperimmunoglobulin D syndrome (HIDS), TNF receptor–associated periodic syndrome (TRAPS) and familial Mediterranean fever (FMF). Although these diseases are rare, the clinical manifestations are common to nearly all inflammatory diseases as well as infectious diseases. As shown in Table 2, there are several diseases for which there is no known genetic basis. Nevertheless, each responds to anakinra or anti–IL-1β. For example, systemic-onset juvenile idiopathic arthritis (SJIA) responds to anakinra (1,2), and canakinumab (3,4) is highly effective. Adult-onset Still disease is also highly responsive to anakinra and is standard of therapy clinically (5–8). Table 2 also indicates several other chronic inflammatory diseases and the responses to IL-1 blockade by anakinra. Many are also responsive to canakinumab or rilonacept. Of these, Schnitzler syndrome is highly responsive to canakinumab and identifies IL-1β as causal in the disease (9–13). Schnitzler syndrome is similar to multiple myeloma as well as pre–multiple myeloma syndromes. Pre–multiple myeloma syndromes are also known as smoldering myeloma or also indolent myeloma. They respond to anakinra (45).An acute disease, which responds to anakinra, is macrophage activation syndrome (46–55). This life-threatening syndrome is likely under diagnosed. In a reassessment of the original anakinra trial in septic shock (56), 5% of the patients enrolled exhibited evidence of macrophage activation syndrome. The 28-day all-cause mortality was reduced by 62% ($p < 0.006$) in patients treated with anakinra compared with placebo-treated patients.

GOUT AND TYPE 2 DIABETES

Gouty Arthritis

Gout and Type 2 diabetes mellitus are also autoinflammatory diseases but hardly rare conditions. As stated above, important criteria for characterizing a disease as autoinflammatory is that on blocking IL-1, patients experience a rapid and sustained cessation of symptoms as well as reductions in biochemical, hematological and functional markers of their disease. In addition, the disease is not due to any T- or B-cell dysfunction. Gout is a perfect example. Acute as well as recurrent attacks of refractory gouty arthritis respond rapidly to anakinra (15,57–59) as well as to rilonacept (17,60) and canakinumab (14,16,61). As shown in Table 3, anakinra is effective in several joint and muscular diseases. Anakinra is used off-label but canakinumab is approved in Europe for gout. The mecha-

Table 2. Anakinra for systemic and local inflammatory diseases.

Disease	References
Schnitzler syndrome	43,195–208
Behçet disease	147,209,210
Secondary amyloidosis	43,107,143,146,147,157,211–214
Henoch-Schönlein purpura	215
Idiopathic recurrent pericarditis	157,171,216–220
Systemic-onset juvenile idiopathic arthritis	22,33,102,106,107,221–224
Adult-onset Still disease	36–39,225–243
Macrophage activation syndrome	46–50,55,244–247
Sweet syndrome (neutrophilic dermatoses)	186,248–250
Neutrophilic panniculitis	244,245,251
Erdheim-Chester (histiocytoses)	252–254
SAPHO syndrome	255–257
Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA)	258,259
Multicentric Castleman disease	260
Jessner-Kanof disease	261
Primary Sjögren syndrome fatigue	85
Kawasaki disease	262
Colitis in chronic granulomatous disease	263,264
Hidradenitis suppurativa	265
Autoimmune inner ear disease	100
Severe traumatic brain injury	266

Table 3. Anakinra for joint, bone and muscle diseases.

Disease	References
Rheumatoid arthritis	267–288
Psoriatic arthritis	289,290
Osteoarthritis	72,73
Erosive osteoarthritis of the hand	71
Arthrofibrosis (traumatic knee injury)	291,292
Anterior cruciate knee ligament tear	293
Relapsing polychondritis	294–297
Chronic recurrent multifocal osteomyelitis	256,298
Ankylosing spondylitis	299–301
Gout and pseudogout	15,57–59,61,65,66,68,302
Calcium pyrophosphate arthritis	303–305
Gout of the lumbar spine	306
Antisynthetase syndrome	209
Idiopathic inflammatory myopathies	307
Hemochromatosis-related arthritis of the hands	308

nism by which uric acid crystals induce IL-1β secretion has been studied. Uric acid crystals alone do not stimulate human blood monocytes to release IL-1β (62,63). Rather, triggering of a toll-like receptor (TLR) such as TLR2 or TLR4 (62–64) is required. Fatty acids also function to provide a priming signal (63).

Patients with recurrent attacks of gouty arthritis unable to use colchicine and other standards of therapy often require steroids to control disease flares. When treated with anakinra, canakinumab or rilonacept, a rapid, sustained and remarkable reduction in pain as well as objective signs of reduced inflammation have been observed (14–17,57,58,65–69). The effect of IL-1 blockade appears to be superior to that of steroids and results in prolonged periods without flares. The likely mechanism for urate crystal-induced inflammation in the joint is the release of active IL-1β (63). Given the characteristic neutrophilic infiltration in gouty joints, it is also likely that the IL-1β precursor is processed extracellularly by neutrophilic enzymes (70). Pyrophosphate crystal arthritis is highly responsive to anakinra (66,68). Pyrophosphate crystal arthritis is highly responsive to anakinra (66,68).

Osteoarthritis

In humans, subcutaneous anakinra improved pain and swelling in an aggressive form of erosive osteoarthritis (71).

Anakinra has also been injected intraarticularly in patients with knee osteoarthritis (72,73), but the benefit did not extend beyond 1 month (73), which may be because of the brief duration in the joint space. Systemic treatment of osteoarthritis with an antibody to the IL-1 receptor was carried out and a modest improvement was reported, particularly in those patients with high pain levels at enrollment (74).

Type 2 Diabetes

Studies of the role of IL-1β in the pathogenesis of Type 2 diabetes reported that high concentrations of glucose-stimulated IL-1β production from the β cell itself (75), thus implicating a self-destructive role of IL-1β autoinflammation by the β cell (76). Moreover, IL-1β increases the deposition of amyloid, which contributes further to β-cell loss (77). Indeed, gene expression for IL-1β is 100-fold higher in β cells from Type 2 diabetes patients (76) compared with nondiabetic patients. Thus, in Type 2 diabetes, there is progressive loss of the β cells because of IL-1–mediated inflammation, which may also underlie the mechanism of insulin resistance (78).

Clinical proof of a role for IL-1 in the pathogenesis of Type 2 diabetes can be found in the randomized, placebo-controlled study of anakinra for 13 wks, in which there was improved insulin production and glycemic control associated with decreased C-reactive protein (CRP) and IL-6 levels (79). Unexpectedly, in the 39 wks after the treatment, anakinra responders used 66% less insulin to obtain the same glycemic control compared with baseline requirements (80). This observation suggests that blocking IL-1β, even for a short period, restores the function of β cells or possibly allows for partial regeneration. These findings of anakinra treatment in Type 2 diabetes patients have been confirmed using anti–IL-1β monoclonal antibodies: Xoma gevokizumab (81), Novartis canakinumab (82) and Lilly LY2189102 (83). Gevokizumab treatment also reduced the fatigue in Type 2 diabetes patients (84), as did anakinra in the Sjögren syndrome (85). Anakinra has also been tested in obese nondiabetic patients with metabolic syndrome (78). There was a decrease in CRP and circulating leukocytes; the disposition index increased significantly after anakinra treatment, reflecting improved β-cell function (78).

Thus, Type 2 diabetes emerges as a chronic inflammatory disease, in which IL-1 progressively destroys the insulin-producing β cells or renders the β cell nonfunctional (76). The IL-1β can come from the β cell itself, but also from blood monocytes that infiltrate the islet. Obese individuals are at high risk for Type 2 diabetes, and caspase-1–dependent IL-1β production has been demonstrated in macrophages isolated from human fat (86). IL-1α and IL-1β exert the same toxic effect on the insulin-producing β cells.

A large body of preclinical data reveals that IL-1 plays a role in the progression of atherosclerosis (87–89). Because Type 2 diabetes increases the risk of cardiovascular events, blocking IL-1β activity in these patients may also reduce the incidence in myocardial infarction and stroke. The largest trial of an anticytokine is CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study), which tested whether canakinumab reduces cardiovascular events in Type 2 diabetes patients with high CRP levels despite optimal statin therapy (90). The rationale for CANTOS is based on the consistent

decrease in CRP levels observed with anakinra (79), canakinumab (91) or gevokizumab (81).

ROLE OF IL-1 HEART DISEASE

With several reports on the benefit of blocking IL-1 in mouse models of acute myocardial infarction (92–94), two clinical trials have been performed in patients with acute ST-elevated myocardial infarction (STEMI) (95,96). Both were randomized, placebo-controlled trials; anakinra (100 mg subcutaneously) or placebo was started within 24 h following standard of therapy for STEMI and continued for 14 consecutive days. Anakinra reduced the rise in CRP levels 72 h after the infraction, and 12 wks later, the anakinra-treated patients exhibited a statistically significant reduction in heart failure. It was concluded that blocking IL-1 during the immediate time of the infarct reduces the adverse effects on postinfarct remodeling.

Two other trials evaluated the role of IL-1 in patients with heart failure despite treatment with standard therapies. The first trial assessed a 2-wk course of anakinra (100 mg/d) on oxygen consumption and exercise tolerance in patients with classic systolic heart failure. Statistically significant improvements in these parameters were observed as well as a fall in CRP and IL-1β levels (13). A second trial was performed in patients with preserved ejection fraction heart failure. This condition is difficult to treat, and there is a predominance of women with preserved ejection fraction heart failure. Similar to the study in patients with systolic heart failure, there was significant improvement in inflammatory markers and physiologic parameters (97).

AUTOIMMUNE HEARING LOSS

In autoimmune inner ear disease, there is either sudden onset or progressive loss in hearing. Patients are usually treated with glucocorticoids; however, individuals not responding to glucocorticoid therapy have elevated IL-1β in the circulation, and peripheral blood monocytes release more IL-1β than monocytes from unaffected subjects (98). The pathogenic mech-

anisms for this disease remains unknown. Patients with this condition who are treated with corticosteroids and respond to the steroids are associated with an increase in circulating levels of the soluble form of the IL-1 decoy receptor type 2 (99); however, patients who do not respond to steroids do not exhibit the rise in the decoy receptor. At present, there is no effective treatment for patients who become unresponsive to steroids. In a phase I/II open-label trial of anakinra, subjects received 100 mg anakinra by subcutaneous injection for 84 d. Ten subjects completed the 84 d of treatment and 7 showed audiometric improvement (100). Circulating IL-1β levels decreased and correlated with improved hearing. The interpretation of these studies is that hearing loss due to this condition is reversible.

Patients with CAPS exhibit neurologic abnormalities such as aseptic leptomenigitis, thus reflecting IL-1–mediated inflammation in the brain. In a study of CAPS patients, 54% had sensorineural deafness (101). Treatment with either anakinra or canakinumab resulted in a complete resolution of symptoms (101–103). Children with severe CAPS show manifestations of elevated intracranial pressure and are believed to be mentally slow or even retarded. However, both mental and hearing impairment are reversed on treatment with anakinra (23,102,104–107) but also with specific neutralization of IL-1β with canakinumab (103,108–111). Meniere disease can also be characterized by progressive sensorineural hearing loss and is also associated with dysregulation of IL-1β (98,99,112).

WHY NO IL-1β?

Although the activity of IL-1β is such that a devastating systemic inflammatory state can be rapidly controlled with IL-1β blockade, there is no consistently statistically significant increase in the circulating levels of IL-1β between dangerously ill individuals and healthy subjects. There is one reliable clue to a disease that is likely mediated by IL-1β. Humans have been injected intravenously with IL-1, and even at doses of 1 or 2 ng/kg, IL-1β in-

creases the peripheral white blood cell count (113). Assuming a blood volume of 5,000 mL, the maximal plasma level of IL-1 at these doses is <0.5 pg/mL. After 2 h, the rise in white blood cells is due to an absolute neutrophilia with a greater percentage of band forms (25%). The rapid rise in neutrophils is associated with an increase in circulating granulocyte colony-stimulating factor (G-CSF). The subcutaneous route also resulted in a severalfold increase in neutrophils. IL-1β at 3 ng/kg has been injected intravenously during a 15-min infusion into subjects with melanoma but with normal bone marrow function. Within 1 h, the neutrophil counts increased progressively, reaching peak levels at 4 h (113). During the first hour, monocytes and lymphocytes were decreased. In some studies, daily injections of IL-1 increased circulating neutrophils after each injection. In humans injected with endotoxin, neutrophilia is a prominent observation, and similar to IL-1, peak levels of neutrophils including band forms occur at 4 h (114). Importantly, the endotoxin-induced neutrophilia is, in part, IL-1 mediated as a coinfusion of anakinra, which which reduces peak neutrophil counts by >50% (114). In both the juvenile (22) and adult Still disease (36), the prominent neutrophilia decreases rapidly with anakinra. Similarly, a fall in the neutrophilia characterizes the response to anakinra in patients with NOMID (23) or FCAS (115). A specific antibody to IL-1β reverses the neutrophilia that characterizes CAPS (111). Thus, neutrophilia is a consistent biological marker for IL-1β–mediated neutrophilia. Increases in platelets were also observed in patients with normal marrow reserves after one, two or seven injections of IL-1 (116). In patients injected with seven daily doses of 100 ng/kg IL-1α, there was a mean increase of 73% in platelet counts after 15 d (117).

IL-1 AND CANCER

Role of IL-1β in Multiple Myeloma

In the microenvironment of the bone marrow, IL-1β produced by myeloma pre-

cursor plasma cells stimulates the stromal cells to release much IL-6, which in turn promotes the survival and expansion of the pre-myeloma cells (118). It was reasoned that in the indolent stages of multiple myeloma, blocking IL-1β would reduce IL-6 activity (45). Patients with smoldering or indolent myeloma at high risk for progression to multiple myeloma were selected with the clinical objective of slowing or preventing progression to active disease. During 6 months of treatment with anakinra, there were decreases in CRP in most but not all patients, which paralleled a decrease in myeloma cell proliferation. After 6 months of anakinra, a low dose of dexamethasone was added. Of the 47 patients that received anakinra with dexamethasone, progression-free disease lasted over 3 years and in 8 patients over 4 years (45). Compared to historical experience, the findings indicate a significant failure to progress to active disease. Given the increasing incidence of multiple myeloma in the aging population, an option of anti–IL-1β as an early intervention treatment in the indolent stages of multiple myeloma might have a significant impact on this fatal cancer.

The Case for Treating Cancer with Anti–IL-1α

Sterile inflammation resulting from cell death is due to the release of cell contents, which are normally inactive and sequestered within the cell; fragments of cell membranes from dying cells also contribute to sterile inflammation. Endothelial cells undergoing stress-induced apoptosis release membrane microparticles, which become vehicles for proinflammatory signals. A population of large microparticles from endothelial cells contains nuclear fragments and histones and represents a class of inflammatory apoptotic bodies. These large apoptotic bodies contain full-length IL-1α precursor as well as a processed mature form of the cytokine (119). In vitro, these inflammatory apoptotic bodies induce monocyte chemotactic protein-1 and IL-8 chemokine secretion, which is independent of IL-1β. In vivo, the endothelium-
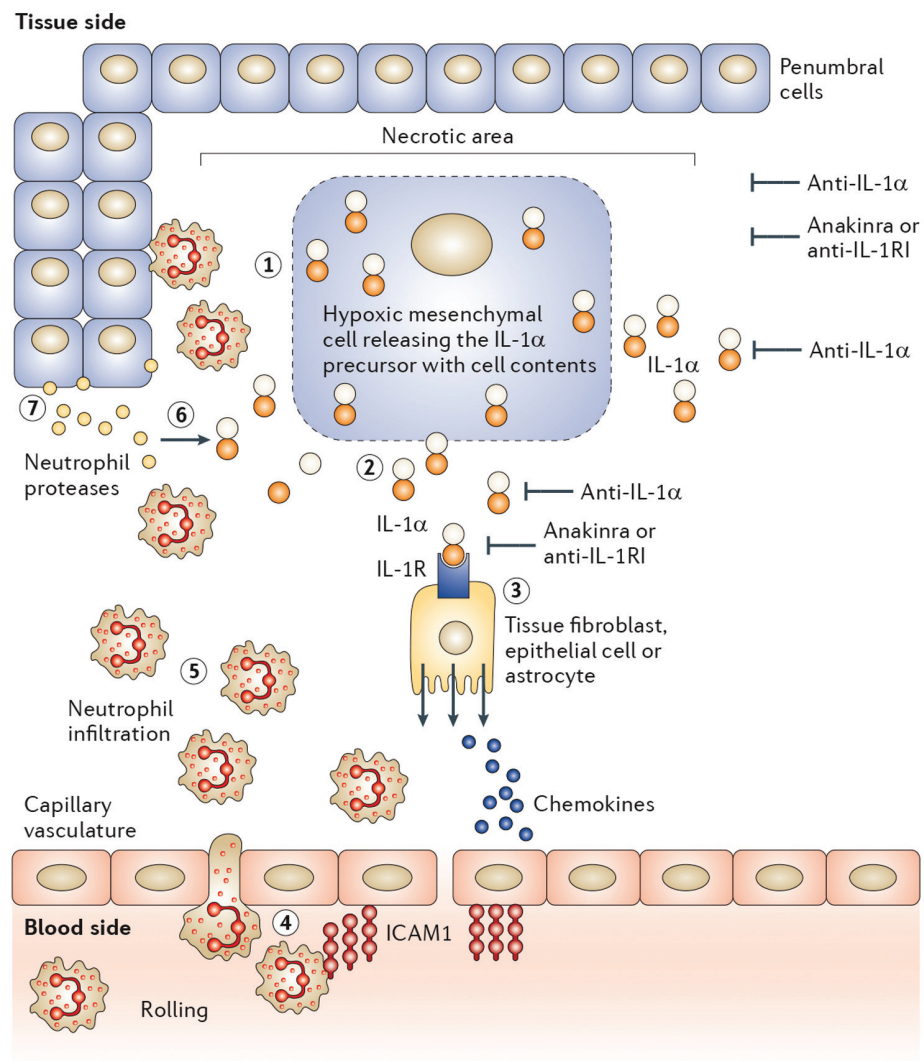

Figure 1. Initiation of sterile inflammation by IL-1α following an ischemic event. ①, In the necrotic area, dying cells lose membrane integrity. ②, Dying cells release their contents including the IL-1α precursor. Anti–IL-1α antibodies neutralize IL-1α at this step. ③, IL-1α binds to IL-1R type I (IL-1RI) on nearby resident fibroblasts, epithelial cells or in the brain astrocytes, releasing chemokines and establishing a chemokine gradient. Anakinra or anti–IL-1RI prevents this step. The chemokine gradient facilitates the passage to blood neutrophils into the ischemic area. ④, Capillaries in the ischemic tissues express the intracellular adhesion molecule-1 (ICAM-1). Circulating blood neutrophils roll on the endothelium, adhere to ICAM-1 and enter the ischemic tissue via diapedesis. ⑤, The number of neutrophils increases into the area of the necrotic event; the presence of local IL-1 prolongs the survival of neutrophils at this step. ⑥, Neutrophil proteases cleave the extracellular IL-1α precursor into mature, more active forms. ⑦, Neutrophils scavenge dying cells and release proteases that contribute to the destruction of penumbral cells. Image reproduced (no permission needed) from Dinarello *et al.* (137): Charles A Dinarello, Anna Simon, Jos W M van der Meer. Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. *Nature Reviews Drug Discovery.* 2012;11:633–52.

derived particles induce neutrophilic infiltration into the peritoneal cavity of mice that was prevented by IL-1 receptor blockade. Thus, nonphagocytosed en-

dothelial large apoptotic bodies are inflammatory, provide a vehicle for IL-1α and, therefore, constitute a unique mechanism for sterile inflammation.
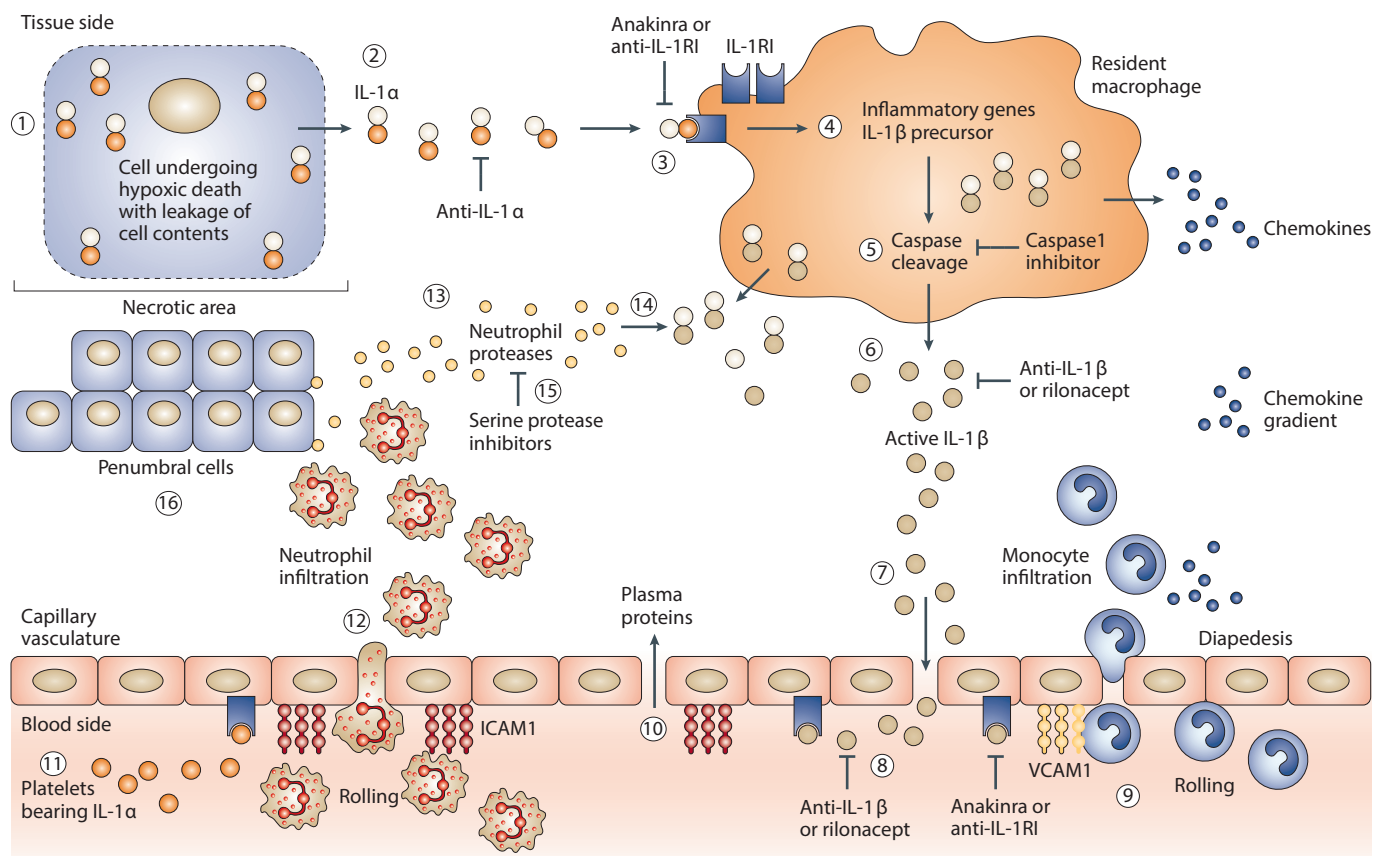
Figure 2. Role of IL 1β in sterile inflammation. ①, Following an ischemic event, cells undergo hypoxic damage, lose membrane integrity, and the dying cell releases cell content (see Figure 1). ②, The preformed IL-1α precursor is released. Anti–IL-1α antibodies neutralize IL-1α at this step. ③, IL-1α binds to IL-1 receptor type I (IL-1RI) on nearby resident macrophages. Anakinra or anti–IL-1RI antibodies prevent IL-1α activity at this step. ④, Triggered by IL-1α binding to the IL-1RI, resident macrophages synthesize inflammatory genes as well as the IL-1β precursor. ⑤, Intracellular processing of the IL-1β precursor by caspase-1. Caspase-1 inhibitors prevent the processing of IL-1β. ⑥, Active secretion of active IL-1β. Antibodies to IL-1β or rilonacept neutralize IL-1β in the extracellular compartment at this step. ⑦, With breakdown of the vascular integrity in the necrotic area, IL-1β gains access to the vascular compartment. ⑧, IL-1β binds to IL-1RI on capillaries and induces vascular cell adhesion molecule-1 (VCAM-1). ⑨, Blood monocytes roll along the endothelium and bind to VCAM-1, followed by emigration into the ischemic tissue via diapedesis. Increasing numbers of monocytes become a source of greater production of IL-1β. ⑩, Opening of the endothelial junction resulting in capillary leak with the passage of plasma proteins into the ischemic area. ⑪, Platelet-derived IL-1α binds to the endothelial IL-1RI and induces ICAM-1. ⑫, Large numbers of neutrophils enter the tissue space, and the presence of local IL-1 prolongs the survival of neutrophils. ⑬, Release of neutrophil proteases. ⑭, IL-1β precursor released into the extracellular space is cleaved by serine proteases generating active IL-1β. Natural inhibitors of serine proteases such as α₁-antitrypsin prevent the extracellular processing of the IL-1β precursor. ⑮, Increasing numbers of neutrophils surround the necrotic area, scavenging dead cells and debris. ⑯, Damaging neutrophilic proteases attack and injure penumbral cells, increasing the loss of function. Blocking IL-1 cannot restore the necrotic tissue but reduces the loss of the penumbral cells. Image modified (no permission needed) from Dinarello *et al.* (137): Charles A Dinarello, Anna Simon, Jos W M van der Meer. Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. *Nature Reviews Drug Discovery*. 2012;11:633–52.

Most sterile inflammation resulting from ischemic damage starts with the release of the IL-1α precursor from necrotic cells (Figure 1). The IL-1α precursor is active (120). Membrane IL-1α is also highly active (121,122), and IL-1α is also present on platelets (123). In several diseases responsive to anakinra, it remains unclear if the disease is mediated by IL-1α or IL-1β activity. From experimental models, supernatants from cells undergoing a necrotic cell death induce local inflammation, which is initially due to IL-1α and not IL-1β (124). Although anakinra will prevent the activity of IL-1α and IL-1β, there is a need to selectively block IL-1α but not IL-1β. The rationale for this concept is based on a model of inflammatory bowel disease in mice in which IL-1α mediates the inflammation, whereas IL-1β mediates healing (125).

Human Anti–IL-1α

Patients with autoimmune diseases as well as healthy subjects have circulating antibodies to IL-1α, as discovered by Klaus Bendtzen (126,127). A fully human monoclonal anti–human IL-1α has been isolated from human B-lymphocytes and developed for neutralizing IL-1α for human disease. The monoclonal antibody is being tested in Type 2 diabetes, cancer, cancer cachexia, leukemia, psoriasis, vascular disease and scarring acne vulgaris.

Similar to sterile inflammation after an ischemic event, tumors undergoing a necrotic cell death are also a cause of sterile inflammation, which in mice is due to IL-1α, but not IL-1β or TLR (128). In human cancers, inflammation mediated by IL-1α will have a negative influence on survival because of increased angiogenesis, metastasis, metabolic syndrome and immunosuppression. Anti–IL-1α monotherapy was administered to patients refractory to antitumor therapies and losing weight (18). Dual-energy X-ray absorptiometry (DEXA) was used to assess LBM. Plasma IL-6 levels and circulating CD14-positive monocytes declined. Twenty-one patients were evaluated with DEXA, and 71% (15/21) showed increases in LBM ($p < 0.001$). Patients with increased LBM had a median survival of 19.3 months versus 6.6 months for individuals with LBM loss (18).

Are These Data Consistent with Properties of IL-1α?

In the early 1990s, either IL-1β or IL-1α was administered to patients with suppressed bone marrow due to chemotherapy to stimulate hematopoiesis; although effective, picomolar concentrations of IL-1α were toxic with fever, severe fatigue, loss of appetite, myalgias and frank hypotension (129). The association of noncancer chronic inflammation with loss of LBM is well established, and IL-1 can directly induce muscle protein breakdown (130).

The rationale for blocking IL-1α in any disease should not be on the basis of elevated circulating serum levels, since IL-1α is not released from living cells and is active as an integral cell surface pro-

tein. IL-1α is also present on platelets, which may account for the systemic effects such as elevated IL-6. In fact, the longstanding reports of platelet involvement in metastasis, which would include platelet-endothelial cell interaction (123) may now be, in part, understood by neutralization of IL-1α. The findings in the Hong study (18) are the first clinical evidence that endogenous IL-1α–induced IL-6 contributes to the thrombocytosis in cancer (129). Additional possible mechanisms of action with neutralization of IL-1α include decreased angiogenesis (131) and decreased immunosuppression (132). IL-1α neutralization also includes direct antitumor properties by inhibition of tumor growth. With the IL-1α precursor present in noncancerous as well as in most cancerous cells and given the broad inflammatory properties of IL-1α, no one mechanism accounts for the clinical improvements in the study (18).

Immunosuppression of Cancer

Cytokine-mediated inflammation has a role in the immunosuppression of cancer (133). From the above studies, IL-1α–mediated systemic inflammation is also a debilitating aspect of cancer. Many tumors produce IL-1α, which promotes angiogenesis and tumor growth (134). Therefore, blocking a cytokine in cancer is a therapeutic opportunity, particularly because anticytokines are without symptoms or physiologic side effects, and tumors are unlikely to develop resistance to a cytokine blockade. Although blocking IL-1 with anakinra reduces the progression of smoldering myeloma into overt myeloma (45), patients with epithelial cancers are rarely treated with a specific anticytokine such as IL-1–blocking agents (135). A prevailing but misunderstood concept is that blocking IL-1 would contribute to the immunosuppression of cancer and be contraindicated (136). Anti–IL-1α therapy demonstrated that treatment reduces systemic inflammation, since a fall in circulating IL-6 levels remains one of the most consistent observations of blocking IL-1 (137). The source of the inflammatory trigger is likely the tumor itself, since all can-

cer cells of epithelial cell origin contain IL-1α in its precursor form. Inflammation is also due to invading stromal cells into the tumor microenvironment. As tumors outgrow their vascular supply, they become necrotic, and the IL-1α precursor is readily released and triggers local production of chemokines, which facilitate an influx of neutrophils and monocytes (137). Unlike precursors of IL-1β, the IL-1α precursor is fully active. Neutralization of local IL-1α likely reduces the infiltration of tumor-associated macrophages and myeloid-derived suppressor cells, which contribute to the immunosuppression of cancer mediated by inflammation (133). The study also reports a reduction in fatigue, which is consistent with the use of anakinra in patients with inflammatory diseases unrelated to cancer (137).

DISCLOSURE

The authors declare that they have no competing interests as defined by *Molecular Medicine*, or other interests that might be perceived to influence the results and discussion reported in this paper.

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