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Review Article

**MEDIATORS OF THE ACUTE PHASE RESPONSE:
THE ROLE OF CYTOKINES**

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ABSTRACT

Cytokines are polypeptides or glycopeptides involved in intercellular communication, functioning as key mediators alongside hormones and neurotransmitters. Acting through specific receptors, cytokines regulate gene activation, influencing cellular function and phenotype. Their activity is modulated by inhibitors that control biological effects and cellular responses. Classified based on function, cytokines include growth factors, proinflammatory cytokines, and anti-inflammatory cytokines.

Proinflammatory cytokines such as TNF- α , IL-1 β , and IL-6 play a crucial role in inflammation, mediating immune responses, fever, and metabolic changes. They induce leukocyte activation, protein catabolism, and alterations in endocrine function, contributing to immune regulation and systemic effects. Additionally, cytokines influence metabolism by modulating nutrient absorption, energy balance, and acute-phase protein synthesis.

This review highlights the fundamental properties, classification, and biological effects of cytokines, emphasizing their central role in immune function, metabolism, and inflammation. Understanding cytokine interactions is essential for developing therapeutic strategies targeting immune and inflammatory disorders.

Keywords: Cytokines, Inflammation, Proinflammatory cytokines, Immune response, Metabolism

FUNDAMENTAL PROPERTIES AND CLASSIFICATION OF CYTOKINES

Cytokines are polypeptides or glycopeptides with a molecular mass of 6–70 kDa, acting through specific receptors within the cell and on the cell membrane. Cytokines function as messengers and, together with hormones and neurotransmitters, are classified as key factors of intercellular communication. They transmit information to the target cell, which expresses the corresponding receptor. This leads to gene activation, resulting in phenotypic or functional changes in the target cell. The synthesis and release of cytokines can be halted by inhibitors that modulate cytokine biological activity or inhibit the target cell's ability to respond. The term "cytokines" is derived from two Greek words—"cytos," meaning cell, and "kine," from "kinein," meaning to move. This name was introduced to distinguish this group of immunomodulatory molecules from hematopoietic cell growth factors.

Cytokines act as potent molecules that are released from cells, transported to different parts of the organism, and influence the functions of other cells, leading to various biological effects (1). The effector functions of these proteins include cell activation and differentiation, chemotaxis, and proliferation of a broad spectrum of cells. Cytokine activity depends on their concentration in the microenvironment and the expression of specific receptors on the surface of the target cell. Every nucleated cell produces cytokines, and the type and amount of cytokine secretion depend on the cell type, differentiation stage, and activation status. The production of cytokines is stimulated by antigen-specific activation of T4 lymphocytes.

Cytokines are primarily secreted by leukocytes; those secreted by lymphocytes are called lymphokines, while those secreted by monocytes or macrophages are referred to as monokines. Many lymphokines are known as interleukins because, in addition to being secreted by leukocytes, they can influence leukocyte cellular responses. To date, 29 types of interleukins have been identified, designated from IL-1 to IL-29. Additionally, more than 30 different cytokines are known. Many of them are cell growth factors, some are hematopoietic growth factors, while others exhibit antiviral activity and are referred to as interferons (IFN). Cytokines regulate the growth and differentiation of immune system cells, including T and B lymphocytes and macrophages. They also influence the scope and duration of the inflammatory response, modulate biological responses, and are interconnected in a cytokine regulatory network. Increased cytokine secretion is associated not only with infections but also with autoimmune and neurodegenerative diseases (2).

Since most cytokines originate from various cells in the organism, they exhibit diverse functions (3). Cytokines are present in numerous animal species, including mammals, birds, fish, reptiles, and sea stars (4).

Depending on their function, cytokines can be classified into three main groups (5).

1. Cytokines that primarily act as positive or negative growth factors for a wide range of cells (IL-2, IL-3, IL-4, IL-7, IL-10, IL-11, IL-12, and granulocyte-macrophage colony-stimulating factor (GM-CSF)).
2. Cytokines with pro-inflammatory properties (tumor necrosis factor- α/β (TNF- α/β), IL-1 α/β , IL-6, interferon- α/γ (IFN- α/γ), IL-8, and macrophage inhibitory protein-1).
3. Cytokines with anti-inflammatory activity (IL-1 receptor antagonists, soluble IL-1 receptors, TNF- α binding protein, and IL-1 binding protein)

PROINFLAMMATORY CYTOKINES AND THEIR ROLE IN INFLAMMATION

During inflammation, inflammatory cells—mainly macrophages and neutrophils—are activated by bacterial damage or as a response to local tissue injury. Together with endothelial cells, they secrete cytokines from the second group, the so-called proinflammatory cytokines, in the following order: TNF- α , IL-1 β , and IL-6 (6). The order of cytokine secretion is crucial, as each has its specific role. These cytokines can be produced by various cells, including monocytes, macrophages, neutrophils, lymphocytes, fibroblasts, endothelial, and epithelial cells. However, it is clear that the primary source of cytokines consists of monocytes and macrophages from the site of inflammation (7).

In the bloodstream, these cytokines act together through multiple overlapping pathways, exerting local effects on the cells surrounding the damaged area. Additionally, they exhibit systemic effects due to the transport function of the blood, reaching various target organs. Proinflammatory cytokines cause fever and muscle catabolism, activate leukocyte precursors in the bone marrow, and stimulate fibroblast and macrophage growth (8). They are responsible for a broad spectrum of synergistic or antagonistic effects that influence the body's specific immune response to foreign antigens and microbial invasion. These cytokines also have pronounced behavioral, neuroendocrine, and metabolic effects (9). Proinflammatory cytokines trigger the release of secondary cytokines and chemokines (IL-6, IL-8, and monocyte chemoattractant protein) from local stromal cells. The chemotactic activity of some of these molecules attracts leukocytes, particularly neutrophils, to the site of inflammation, where they further release proinflammatory cytokines.

CYTOKINES AND THEIR EFFECT ON METABOLISM

Studies on laboratory animals have shown that IL-1, IL-6, and TNF- α influence the intermediary metabolism of carbohydrates, fats, and proteins, regulate the hypothalamic-pituitary axis, and act on the brain to reduce food intake (10). TNF- α , IL-1 β , and IFN γ are crucial for the production of other cytokines (IL-6 and IL-8) and noxious agents such as platelet-activating factor, prostaglandins, leukotrienes, and nitric oxide (11). After stimulation by proinflammatory cytokines, Kupffer cells in the liver produce IL-6 and present it to hepatocytes. Therefore, IL-6 is

considered the primary mediator of hepatocyte secretion of most acute-phase proteins (APP) (12). The acute-phase response and the release of proinflammatory cytokines can directly affect the process of bone growth (13).

Infections reduce food intake, impair nutrient absorption—leading to direct nutritional losses— increase metabolic demands by enhancing catabolic processes, and disrupt nutrient transport to target tissues. The concentration of interleukins in the serum rises within a few hours after stimulus exposure and disappears from circulation within several hours (14).

CLASSIFICATION OF PROINFLAMMATORY CYTOKINES

Based on their role in the acute-phase response, proinflammatory cytokines can be classified into two groups:

1. IL-1 type cytokines, including IL-1 and TNF- α
2. IL-6 type cytokines, which include IL-6

These two types of cytokines act through different receptors located on the hepatocyte membrane.

Cytokines and Protein Catabolism

During inflammation, increased protein catabolism is a common occurrence. This process is stimulated by catabolic hormones and proinflammatory cytokines IL-1, IL-6, and TNF. Proinflammatory cytokines stimulate prostaglandin synthesis, which activates lysosomal enzymes in muscles. This leads to proteolysis, releasing amino acids that are used for the synthesis of new proteins, including acute-phase proteins and immunoglobulins. Some of the released amino acids serve as an energy source, while gluconeogenic amino acids (especially alanine) act as precursors for glucose synthesis. Since protein breakdown exceeds intake and synthesis, a negative nitrogen balance occurs.

Cytokines and Leukocyte Changes

During the inflammatory process, proinflammatory cytokines cause changes in the leukocyte blood profile. In dogs, many inflammatory diseases are accompanied by leukocytosis due to neutrophilia and often monocytosis (15). The activation of leukocyte precursors in the bone marrow is directly influenced by proinflammatory cytokines (16). A positive correlation has been demonstrated between acute-phase proteins (APP) and the number of band and segmented neutrophils (17).

Cytokines and the Endocrine Response

IL-1, IL-6, and TNF stimulate the production of corticotropin-releasing factor, leading to increased synthesis of adrenocorticotrophic hormone (ACTH) and, consequently, glucocorticoids (cortisol).

While glucocorticoids promote protein synthesis in the liver, they enhance proteolysis in muscles and lymphoid tissue, potentially leading to asthenia and reduced immune response.

Besides increasing circulating cortisol levels, cytokines also reduce thyroid hormone levels and disrupt the concentration of trace elements, such as decreasing serum iron and zinc levels. This occurs to minimize tissue damage and promote healing. Additionally, they lower calcium levels, vitamin A, and α -tocopherol concentrations.

Cytokines and Fever

Fever (febrile response) is a phylogenetically ancient mechanism of the body's response to inflammation. It is induced by proinflammatory cytokines (IL-1, IL-6, TNF, and IFN), synthesized by activated macrophages during acute inflammation. These cytokines act on thermosensitive neurons in the preoptic nuclei of the hypothalamus, stimulating the synthesis of prostaglandins, which increase the "set point" of the thermoregulatory center, thereby raising body temperature (18).

Hyperthermia accelerates metabolic processes, contributing to a negative nitrogen balance, particularly when accompanied by reduced food intake. However, elevated body temperature negatively affects the causes of inflammation while also enhancing T lymphocyte proliferation, T-helper cell activation, antibody production, and IL-1 activity.

Proinflammatory cytokines stimulate the growth of fibroblasts in inflamed tissue and macrophages (19). At the liver level, TNF- α , IL-1, and IL-6 play a significant role. Namely, after the activation of hepatocyte receptors, the synthesis of certain acute-phase proteins begins.

Other effects of proinflammatory cytokines on the liver include suppression of the cytochrome P-450 enzyme system, the production of heat shock proteins (HSP), and the synthesis of metallothionein (20). Suppression of the cytochrome P-450 enzyme system significantly affects the metabolism and toxicity of various chemical substances and drugs. Heat shock proteins or stress proteins are beneficial components present in cases of cellular molecular damage. Metallothionein synthesis increases liver resistance to toxic metals and may enhance the intracellular capacity for metal ion binding. Reduced hepatocyte secretion of albumin (a zinc transporter), transferrin, and lactoferrin leads to decreased serum zinc and iron levels, which is considered beneficial for an infected organism, as iron is essential for microbial growth. The reduction in blood calcium levels during the acute-phase response is considered somewhat less beneficial.

Decreased appetite or anorexia is also caused by proinflammatory cytokines. Cytokines induce prostaglandin production and prostaglandin-dependent fever development. Immunological stress triggers adrenal medulla hormone secretion, including catecholamines, leading to blood flow

redistribution to the brain and muscles instead of the splanchnic system. Intestinal villi atrophy, and reduced intestinal absorption may result in diarrhea. Metabolic changes lead to a negative energy balance, further promoting growth retardation.

During the acute-phase response (APR), plasma viscosity increases due to changes in total blood protein concentrations, including fibrinogen, which is significant as it affects the erythrocyte sedimentation rate (ESR), a parameter used as a nonspecific marker of disease. Since fibrinogen is classified as a slow-reacting positive acute-phase protein, several days are required from the stimulus for its concentration to rise, and consequently, several days for ESR to increase.

Tumor Necrosis Factor- α (TNF- α)

Tumor necrosis factor- α , or cachectin, is classified along with IL-1 as one of the key cytokines in the immune response. It is a potent cytokine produced by macrophages, fibroblasts, monocytes, and T and B lymphocytes. Its most studied function is its ability to induce an inflammatory response. In addition to stimulating the production of other cytokines (IL-1, IL-6, IL-8, GM-CSF), it mediates the cytokine cascade that causes inflammation and joint destruction in rheumatoid arthritis through receptors localized on macrophages or synovial membrane cells (21). Like IL-1, TNF- α can cause hypoferrremia by increasing iron uptake in macrophages and monocytes. It exhibits both pro-inflammatory and antitumor effects. It induces muscle catabolism, which is mediated by glucocorticoids, as well as glucagon-induced hyperglycemia and amino acid uptake by the liver (22). Among its many effects, its ability to induce cell death has been described. TNF- α regulates the proliferation and differentiation of immune cells and is involved in processes related to septic shock, autoimmune diseases, and graft-versus-host disease (GvHD).

Indirectly, it regulates the inflammatory response by stimulating corticotropin release from the pituitary gland, which in turn stimulates the adrenal cortex to secrete cortisol, thereby inhibiting inflammation. Blocking TNF- α with antibodies significantly reduces the production of IL-1, IL-6, IL-3, and GM-CSF.

Interleukin-1 (IL-1)

Interleukin-1 (IL-1) refers to two distinct proteins, IL-1 α and IL-1 β , which recognize the same cellular receptor. IL-1 is the most important interleukin in the immune response. It plays a key role in either amplifying or suppressing the inflammatory reaction. It is essential for immune system function, as it affects macrophages/monocytes, T and B lymphocytes, NK cells, and lymphocyte-activated killer cells (LAK). It induces TNF and IL-6 synthesis and plays a fundamental role in the antitumor activity of macrophages (23). It is secreted by macrophages, fibroblasts, endothelial cells, keratinocytes, dendritic cells, astrocytes, B lymphocytes, activated T lymphocytes, smooth

muscle cells, and microglial cells. IL-1 production by these cells occurs exclusively in response to cellular stimulation.

IL-1 has an important immunoregulatory function, stimulating IL-2 synthesis in T lymphocytes and enhancing IL-2 receptor expression on activated T lymphocytes (24). Along with other interleukins, it stimulates B lymphocyte proliferation and maturation and enhances immunoglobulin synthesis. It also promotes amino acid flux in whole blood and activates the hypothalamic-pituitary-adrenal axis. Glucocorticoids significantly reduce IL-1 β mRNA levels, inhibiting IL-1 effects and exerting anti-inflammatory and immunosuppressive actions.

Interleukin-6 (IL-6)

This 26 kDa protein regulates the immune and hematopoietic systems. It is produced by immune cells as well as many non-immune cells and organs (25). Due to its role in inducing the expression of acute-phase protein (APP) genes, either alone or by enhancing the effects of other cytokines, it is considered a key cytokine, as it stimulates the production of all acute-phase proteins (25). Under normal conditions, circulating IL-6 concentrations are very low, and in some cases, they cannot even be detected (26).

IL-6 stimulates hepatocytes, promotes the production of immunoglobulins from activated B lymphocytes, enhances T lymphocyte production, and regulates IL-2R expression. It exerts its biological effects through membrane receptors for IL-6, which are found on many cells, including megakaryocytes. It suppresses TNF- α and IL-1 secretion, activates and stimulates the hypothalamic-pituitary-adrenal axis by acting on corticotropin-releasing hormone, and helps regulate inflammatory responses (25). IL-6 promotes the final maturation of B lymphocytes into antibody-producing cells, indicating its involvement in inflammatory processes following an immune response. During inflammation, IL-6 suppresses TNF- α and IL-1 secretion by stimulating the production of acute-phase reactants from the liver, and it stimulates the hypothalamus-pituitary-adrenal axis, thereby helping to control the inflammatory response. In this sense, IL-6 acts as both a pro-inflammatory and an anti-inflammatory cytokine.

IL-6 plays a crucial role in the stimulation of early hematopoiesis. The effects of this cytokine have numerous biological consequences, particularly influencing the hemostatic mechanism. It can increase platelet counts in both normal and thrombocytopenic animals and humans. It also influences megakaryocyte maturation by increasing cell size and number, as well as enhancing platelet protein synthesis. Serum IL-6 concentration increases in reactive thrombocytosis associated with rheumatoid arthritis or secondary thrombocytosis caused by iron deficiency anemia. These findings suggest that cytokines may be responsible for pathological megakaryocytopoiesis. IL-6 increases platelet size and enhances their function. Since IL-6 promotes platelet production, it is more likely that changes in platelet functionality arise due to the

entry of new, more potent platelets into circulation rather than as a direct effect of IL-6 on platelets (27).

Glucocorticoids inhibit IL-6 transcription, so corticosteroid treatment lowers IL-6 serum levels (28). Cortisol can increase IL-6 receptor expression in liver cells and thereby stimulate IL-6-mediated acute-phase protein synthesis (29).

Cytokine concentration has been studied during various inflammatory conditions. Determining their plasma concentration is challenging due to their short half-life and the presence of blocking factors (30). Plasma IL-6 concentrations are elevated in patients with inflammatory processes; however, aside from the speed at which these changes occur, measuring IL-6 plasma levels does not provide a significant advantage over measuring CRP levels.

The immune system maintains a dynamic balance between proinflammatory and anti-inflammatory cytokines. This regulation is complex due to redundant immune pathways where multiple elements have similar effects. Most anti-inflammatory cytokines, except IL-1 receptor antagonist (IL-1ra), also exhibit proinflammatory properties.

MAJOR ANTI-INFLAMMATORY CYTOKINE

IL-1ra

IL-1ra is produced by monocytes and macrophages, with levels increasing over 100-fold after lipopolysaccharide (LPS) stimulation. While bacterial LPS induces both IL-1ra and IL-1 β , anti-inflammatory cytokines like IL-4, IL-6, IL-10, and IL-13 suppress IL-1 β while promoting IL-1ra synthesis.

A genetic polymorphism in IL-1ra's intron 2 affects its synthesis and can influence susceptibility to infections like Lyme arthritis and tuberculosis. Conversely, insufficient IL-1ra in the lungs may exacerbate acute lung injury and acute respiratory distress syndrome (ARDS).

IL-4

IL-4 is a pleiotropic cytokine that influences T-helper (Th) cell differentiation. Produced by Th2 cells, mast cells, and basophils, IL-4 facilitates Th2 responses, mast cell activation, and IgE production by B cells. It also inhibits proinflammatory cytokines, such as IL-1, TNF- α , IL-6, IL-8, and MIP-1 α , while promoting IL-1ra synthesis (31). Additionally, IL-4 reduces macrophage cytotoxicity and nitric oxide production, impairing parasite clearance (32).

The role of IL-4 in bacterial infections is complex. It enhances *Pseudomonas aeruginosa* clearance in Gram-negative pneumonia models (33), but acts as a growth factor for *Staphylococcus aureus*, increasing sepsis lethality in Gram-positive infections. IL-4 also influences structural cell

behavior, promoting vascular endothelial and fibroblast proliferation while inhibiting astrocyte and smooth muscle cell growth.

IL-4 exhibits antitumor properties by inducing cytotoxic responses. A study on stage IV non-small cell lung cancer suggested IL-4 may stabilize disease, slow tumor growth, and induce tumor shrinkage with minimal side effects, highlighting its potential as an adjuvant therapy (34).

IL-6

IL-6 has traditionally been recognized as a proinflammatory cytokine, often used as a marker of systemic inflammation. However, it also exhibits anti-inflammatory properties. IL-6 mouse models suggest that IL-6 primarily acts as an anti-inflammatory cytokine. IL-6 suppresses IL-1 and TNF synthesis, while promoting IL-1ra and soluble TNF receptor production. It also induces glucocorticoid synthesis and inhibits proinflammatory mediators like GM-CSF, IFN- γ , and MIP-2 (34). Due to these immunomodulatory effects, IL-6 is classified as an anti-inflammatory cytokine.

IL-10

IL-10 is the most potent anti-inflammatory cytokine in the immune system. It inhibits Th1 cytokines, such as IL-2 and IFN- γ , earning its initial designation as a cytokine synthesis inhibitory factor. IL-10 also suppresses monocyte/macrophage proinflammatory cytokine production and is primarily secreted by Th2 cells, monocytes, and B cells. It binds to a high-affinity 110-kDa receptor, blocking TNF- α , IL-1, IL-6, IL-8, IL-12, and other inflammatory mediators (34).

Additionally, IL-10 inhibits neutrophil and NK cell cytokine production, and prevents NF- κ B nuclear translocation after LPS stimulation. It promotes TNF receptor shedding, modulating TNF- α responses. IL-10 levels correlate with disease severity in systemic inflammation. High IL-10 and low TNF- α expression are associated with increased mortality in meningococemia and other infections (34).

Inadequate IL-10 responses may also worsen inflammatory conditions, as seen in ARDS patients with low IL-10 levels.

IL-11

IL-11 is a cytokine initially identified in the hematopoietic microenvironment. Originally described as a hematopoietic growth factor, IL-11 is now used clinically to restore platelets after chemotherapy (34). Beyond hematopoiesis, IL-11 suppresses IL-1 and TNF by increasing inhibitory NF- κ B, preventing NF- κ B activation of proinflammatory cytokines. It also inhibits Th1 cytokines (IFN- γ , IL-2) while promoting Th2 responses. Though rarely found in circulation, it plays a role in localized inflammation, such as arthritis and inflammatory bowel disease (35).

IL-13

IL-13, secreted by activated T cells, modulates monocyte and B-cell function. Genetically linked to IL-4, it shares a receptor and many functional similarities, though IL-4 primarily regulates Th2 differentiation, while IL-13 has minimal effects on T cells. IL-13 suppresses proinflammatory cytokines (TNF, IL-1, IL-8) and alters monocyte/macrophage surface expression, reducing CD14 and Fc γ receptor levels. It inhibits NF- κ B activation and protects against LPS-induced lethality in animal models. IL-13 also reduces lung inflammation caused by immune complexes, with effects comparable to IL-10 (34).

TGF- β

TGF- β is a member of a protein superfamily, it regulates cell proliferation, differentiation, and extracellular matrix formation (36). TGF- β inhibits growth in ectoderm-derived cells and influences lung epithelial cell differentiation and surfactant protein expression (34). It contributes to lung fibrosis and modulates extracellular matrix turnover. TGF- β has dual inflammatory roles, shifting from pro- to anti-inflammatory depending on context (37). It suppresses T and B cell proliferation and cytokine production, acting as a monocyte/macrophage deactivator similar to IL-10 but with weaker effects.

CYTOKINES IN RHEUMATOID ARTHRITIS, PULMONARY DISEASES, AND CNS DISORDERS

Rheumatoid arthritis (RA) is a prevalent autoimmune disease in industrialized nations (38), with cytokine involvement extensively studied due to tissue accessibility (39). The first major success in anti-cytokine therapy was TNF- α blockade, which significantly improves disease outcomes and prevents joint damage (40). This approach has also shown efficacy in other chronic diseases. Brennan and McInnes review the development of TNF- α blockade in RA and explore the roles of additional cytokines (41). Given standardized clinical protocols, multiple cytokine blockade trials have been conducted in severe RA (42).

In mice, IL-1 blockade is as effective as TNF- α inhibition (43), but in humans, IL-1 receptor antagonist (IL-1Ra) is less potent and less frequently used (44). Barnes examines cytokine roles in asthma and chronic obstructive pulmonary disease (COPD) (45). Steinman discusses cytokines in central nervous system (CNS) disorders, including fever, multiple sclerosis (MS), and Alzheimer's disease (AD) (46). In MS, inflammation is prominent, and IFN- β is a standard therapy. Early trials showed IFN- γ worsens MS, implicating Th1 cells in pathogenesis. MS lesions contain elevated IL-6, IL-17, IFN- γ , and osteopontin, though clinical trials assessing their blockade are pending. Surprisingly, TNF- α blockade, effective in RA, worsens MS by increasing relapse frequency, possibly due to TNF- α 's neuroprotective role and its regulatory effect on IL-12 and T cells.

Unlike TNF- α or TGF- β modulation, IFN- β treatment benefits MS patients, though its mechanism remains unclear. In AD, inflammation plays a potential role (46). TGF- β overexpression in AD-model mice reduced plaque burden (34), yet paradoxically, inhibiting TGF- β signaling also reduced inflammation and plaques in other models, necessitating further research (35).

CYTOKINE SIGNALING IN LEUKEMIA AND CANCER THERAPY

Smith and Griffin chronologically examine the role of cytokines and their receptors in leukemic cell growth (47). In the 1960s–1980s, discoveries in cancer biology and immunology led to assays for T cell growth factors (48), purification of growth factor proteins, receptor identification (49), and development of receptor-specific antibodies (50). These tools reshaped the understanding of lymphocyte proliferation as a response to antigen-induced growth factor release rather than direct antigenic stimulation. Understanding normal cell growth pathways has clarified leukemia-related abnormalities. Smith and Griffin emphasize that insights into normal cytokine-regulated growth provide a foundation for identifying cancer-related abnormalities and therapeutic targets.

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