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Editorial

Cytokine-Related Aging Process

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CYTOKINES are soluble peptide messengers that are synthesized by lymphocytes (thus, they were originally called lymphokines), neutrophils, macrophages, and neuronal cells. The first experimental evidence that circulating factors could modulate the immune system was published in 1932 (1). It was not, however, until more than 30 years later that peptide mediators of lymphocyte activity were identified (2). Two years later, Gery and colleagues (3) isolated soluble peptide messengers from macrophages, and the concept of cytokines as ''the great communicators'' between immune and somatic cells in response to inflammation was born. Today, it is recognized that cytokines can be both proinflammatory and antiinflammatory and have a wide range of effects on organ systems throughout the body (Figure 1). Originally, each cytokine was named after the function it was recognized to perform. However, it soon was realized that cytokines produced multiple functions, and, thus, in 1979, a consensus committee decided to rename the cytokines ''interleukins'' followed by a number (4). Nonetheless, some cytokines have retained other names, for example, tumor necrosis factors (TNFs) (originally cachectins), interferons, and, most recently, the adipocyte-produced cytokines, or adipocytokines, such as adiponectin and leptin. Recently, there has been an increasing awareness that the cytokine response to nonspecific inflammation may be a component of the pathophysiology of frailty, functional decline, and death in older persons (5,6). Some cytokines, such as interleukin-10 (IL-10), are antiinflammatory and oppose the actions of the proinflammatory cytokines. Westendorp has suggested that the balance between proinflammatory and antiinflammatory cytokines favors either a long life or reproductive success (7). Thus, persons with high levels of tumor necrosis factor alpha (TNFα) and low levels of IL-10 will have few children but live a long time. This is the modern version of Thomas Kirkwood's ''disposable soma'' theory, which stated that investment in maintenance and repair comes at the expense of investment in reproduction.

Tissue destruction or infection leads to a nonspecific acute-phase response. Markers of this nonspecific response are C-reactive protein (CRP) and serum amyloid protein, which increase rapidly (within 6 hours and peak within 48 hours) following an acute-phase stimulus. CRP derived its name from its ability to precipitate the C-polysaccharide of *streptococcus pneumoniae* (8). Both CRP and serum amyloid protein are members of the pentraxin family (Gk. penta = five; ragos = berries). When CRP binds to damaged cell membranes or lipids, it activates the classical complement pathway through C1q. CRP is increased after acute and chronic infection, in arthritic and other inflammatory disorders, tissue necrosis, neoplasia, cardiovascular disease, insulin resistance syndromes, obesity, smoking, stress, atrial fibrillation, oral estrogen intake, smoking, and coffee consumption (9). Liver disease, weight loss, exercise, moderate alcohol intake, and hepatic hydroxymethyl glutaryl coenzyme A (HMGCoA) reductase inhibitors are associated with lower CRP levels. Autoimmune diseases, such as systemic lupus erythematosus, fail to produce a CRP response. Thus, while CRP is a sensitive marker of disease processes, it is notoriously nonspecific. In older persons, CRP has been shown to be a marker of functional decline and mortality (10–13). Because of the nonspecificity of CRP, there has been a search for more specific markers that could explain the pathophysiology of functional deterioration with aging, sarcopenia, and the anorexia of aging (6,14–21).

Interleukin-6 (IL-6) was one of the first cytokines to be linked to the aging process, and has been termed the ''geriatric cytokine'' (22). IL-6 is released from macrophages and T lymphocytes. Both TNFα and interleukin-1 beta (IL-1β) are potent releasers of IL-6. IL-6, on the other hand, once released, feeds back to down-regulate the release of TNFα and IL-1β giving it an antiinflammatory, as well as a proinflammatory role. Increased IL-6 leads to loss of muscle and bone mass, fever, activation of the hypothalamic-pituitary-adrenal axis, activation of the hepatic acute phase response, and hemodilution, resulting in a decline in hemoglobin levels (23–26). In bone, IL-6 is produced by osteoblasts and promotes osteoclast activity and subsequent bone resorption (27). Testosterone, which declines with aging in men (28,29), suppresses IL-6 production from bone (30). Parathyroid hormone levels, which increase with the age-associated decline in vitamin D (31), increase the production of IL-6 from osteoblasts (32). Parathyroid hormone also results in hepatic production of IL-6 and its soluble receptor (33). In older persons, elevated IL-6 levels have been shown cross-sectionally to be inversely associated with muscle mass and strength, physical performance, balance, and walking speed, and positively associated with death (13,35–37). Ferrucci and colleagues (38) reported in a cross-sectional study that elevated IL-6 levels predicted

Table 1. Cytokines and Their Actions

Cytokine	Primary Source(s)	Actions
Tumor necrosis factor-α	Macrophages Adipocytes	Proinflammatory Cardiodepressant Anorexia Cachexia Lipolysis Apoptosis Osteolysis Insulin resistance Anemia
Interleukin-1β	Macrophages Endothelial cells Astrocytes	Proinflammatory Fever Liver acute-phase response Cognitive decline Anorexia
Interleukin-2	T lymphocytes	Growth factor for NK-cells and T lymphocytes
Interleukin-6	Macrophages Myocytes T lymphocytes	Pro- and antiinflammatory Endogenous pyrogen Liver acute-phase response Osteolysis Activation of hypothalamic-pituitary-adrenal axis Anemia Proteolysis Loss of muscle mass Anorexia
Interleukin-8	Macrophages	Neutrophil recruitment
Interleukin-10	T lymphocytes	Antiinflammatory inhibits TNFα/IL-1 production
Interleukin-11	Endothelial cells Fibroblasts	Antiinflammatory Hematopoetic growth factor
Interleukin-12	Macrophages Dendrite cells Neutrophils	Proinflammatory
Interleukin-13	T lymphocytes	Allergic inflammation
Interleukin-17	T lymphocytes	Proinflammatory
Interleukin-18	Macrophages	Proinflammatory Atherosclerotic plaque growth Inhibits osteoclast formation Induces interferon gamma
Interleukin-21	T lymphocytes	Stimulates T cells and NK cells Antitumor activity Inhibits dendritic cell activation Stimulates B-cell activity
Interleukin-23	Dendritic cells Macrophages	Increase IL-17 Autoimmune Inflammation in the brain
Interleukin-25	T-helper cells Mast cells	Induces IL-4, IL-5, and IL-13 Proinflammatory
Adiponectin	Adipocytes	Modulates insulin sensitivity
Leptin	Adipocytes	Enhances memory Anorexia Increased resting metabolic rate

Note: NK = natural killer; TNFα = tumor necrosis factor alpha; IL = interleukin.

development of disability over the subsequent 4 years. It has been known for several years that IL-6 stimulates muscle protein degradation in diseases such as cancer, end-stage renal disease, and AIDS via effects on both lysosomal (cathepsin) and nonlysosomal (ubiquitin-proteasome) pathways (39–43). The association of lower levels of IL-6 with the gradual loss of muscle during normal aging (sarcopenia) is a more novel finding.

Interleukin-1β is a proinflammatory cytokine that induces TNFα and IL-2 by activating T-helper cells, and produces tissue inflammatory actions by activating cyclooxygenase-2 to produce prostaglandin E_2, inducible nitric oxide, and intercellular adhesion molecules such as ICAM-1 (intercellular adhesion molecule-1) (44). IL-1β also induces its own release, creating a vicious inflammatory cycle. Biochemically, IL-1β activates, after phosphorylation by a kinase, the tumor necrosis factor receptor-associated factor-Y, which then activates nuclear factor kappa β to bind to the DNA in the nucleus and produce its effects. IL-1β produces fever, sickness behavior, and anorexia. In addition, it causes a decline in the ability to acquire and retain new memories. This occurs both indirectly, by activating ascending fibers in the autonomic nervous system, and directly, by crossing the blood–brain barrier (45). IL-1β can be considered the trigger for the inflammatory cascade, and, as such, results in an increase in CRP and serum amyloid protein (44). Within the central nervous system, IL-1β may be the trigger for increased amyloid precursor protein and the development of subsequent Alzheimer's disease (46,47). Cytokines are also involved in the pathogenesis of delirium (48).

Tumor necrosis factor alpha is produced from macrophages and adipocytes. It is proinflammatory, working in concert with IL-1β. It produces anorexia, stimulates lipolysis, and inhibits lipoprotein lipase, thus leading to the cachexia syndrome (49,50). It has direct effects resulting in decreased function of the myocardium and produces apoptotic cell death (51). TNFα appears to be one of the mediators of receptor activator of nuclear factor kappa β ligand's (RANKL) effects in promoting osteoporosis (52). As noted previously, it stimulates release of IL-6, which causes increased protein degradation.

Numerous other cytokines have been identified and their effects are listed in Table 1.

Soluble cytokine receptors are produced either through proteolytic cleavage from the membrane-bound form, or, alternatively, they are produced by alternative splicing of mRNA, which leads to the formation of a transcript, which encodes a soluble receptor (53). These circulating soluble receptors then act as cytokine-binding proteins, which can down-regulate the effects of circulating cytokines. However, soluble receptors, either in combination with the cytokine or by themselves, can activate certain cells. Thus, IL-6/SIL-6R (soluble IL-6 receptor) complex is a particularly potent proinflammatory mediator, as it induces secretion of IL-8 and IL-6 from leukocytes and synthesis of adhesion molecules in endothelial cells (54,55). Overall, soluble cytokine receptors tend to have longer half-lives than their cytokines, and as their secretion appears to parallel that of the cytokine, they may be better markers of chronic cytokine activity.

A word of caution is necessary regarding the measurements of cytokines and their soluble receptors. Firstly, the analytic enzyme-linked immunosorbent assay kits have been shown to have widely differing standards, and even

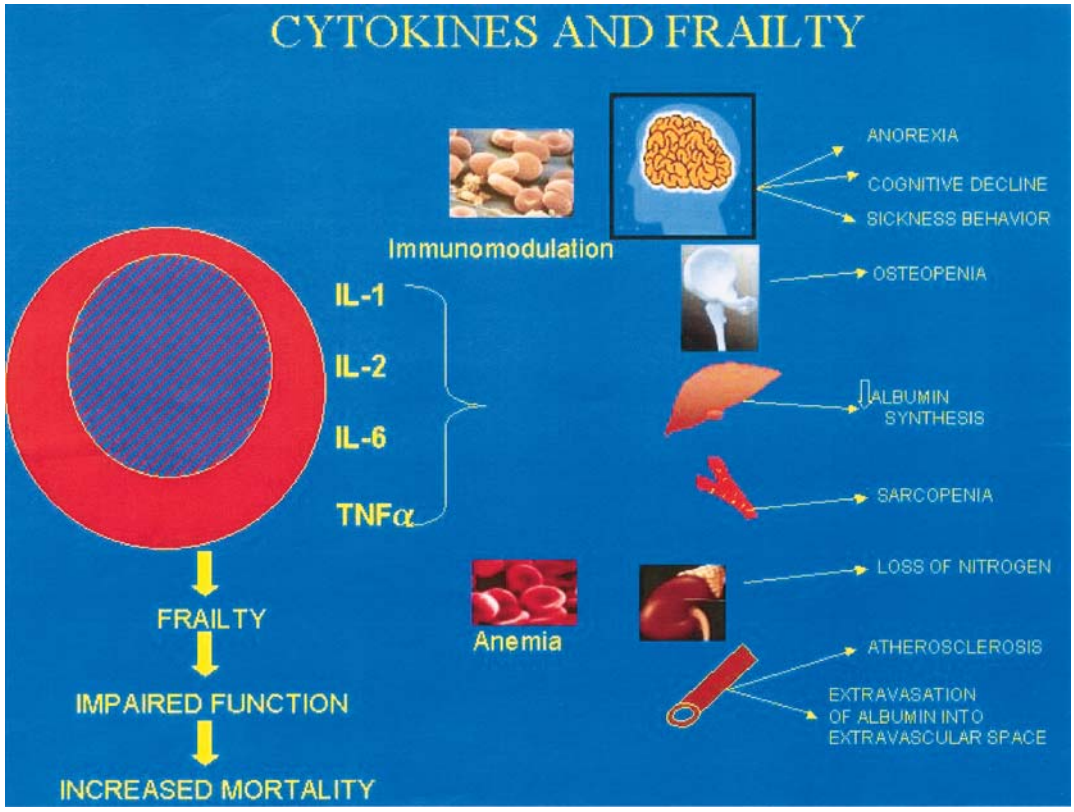

Figure 1. Effects of cytokines on multiple organ systems, which can result in the development of frailty. IL = interleukin; TNF = tumor necrosis factor.

kits from the same manufacturer may have standards that differ by as much as 50% (56). The quality of laboratory performance can also markedly affect the assay outcome. Samples can be frozen at −70°C and assayed at a later date. The exact length of time the samples can be stored, however, is uncertain. It is important that authors report interassay and intraassay coefficients of variation for all their assays. International reference standards for cytokines should be used and, where available, external proficiency testing should be put in place for a laboratory measuring cytokines.

From the geriatrician's viewpoint, a major role of cytokines is in their ability to accelerate the loss of muscle mass in sarcopenia and/or cachexia. The multiple mechanisms by which cytokines can lead to the severe tissue wasting seen in cachexia are outlined in Figure 2 (57). Megestrol acetate, which is used to treat anorexia, reduces IL-6 (58), and its orexigenic effects have been shown to be related to circulating cytokine effects (59). The role of cytokines in sarcopenia is less well established (19,20,60,61). It would appear that lower levels of circulating cytokines interact with hormone deficiency (62–64), the decline in physical activity (65), obesity, and the anorexia of aging (15,16,66–68) to lead to the loss of muscle that characterizes the occurrence of sarcopenia. An article in this issue of the Journal suggests that sarcopenia, like osteoporosis, is dictated to some extent by the development of muscle mass in youth (69). While osteoporosis can be considered a pediatric disorder, both genetic and environmental factors, for example, obesity or early menopause, can modulate the rate at which osteoporosis eventually develops (70,71). A similar constellation of factors may be involved in the pathogenesis of sarcopenia.

The relationship of inflammatory markers to muscle mass, muscle strength, and physical performance has been investigated in a number of studies (11–13,35–38,72–78). These results are summarized in Table 2. Overall, these studies suggest that nonspecific markers of inflammation (e.g., CRP and IL-6) are strongly associated with the loss of muscle mass and decline in performance. Other cytokines, particularly TNFα and its soluble receptors, have been inadequately studied to determine their role in the pathogenesis of frailty and disability. However, the suggestive role of TNFα in cardiac cachexia and its overproduction in obese persons suggests a potential role for this cytokine (79,80). Other cytokines, such as adiponectin and leptin, which appear to play a role in the insulin resistance syndrome, also deserve further study to determine their long-term role in the development of frailty (81–86).

In conclusion, we suggest that the Cytokine-Related Aging Process should be considered a true, and potentially reversible, syndrome. The Cytokine-Related Aging Process appears to be related to a constellation of age-related findings including loss of muscle and bone mass, anemia, cognitive decline, and immune dysfunction. This raises the possibility that cytokine modulators such as thalidomide, soluble cytokine receptors, or antibodies to cytokines, may

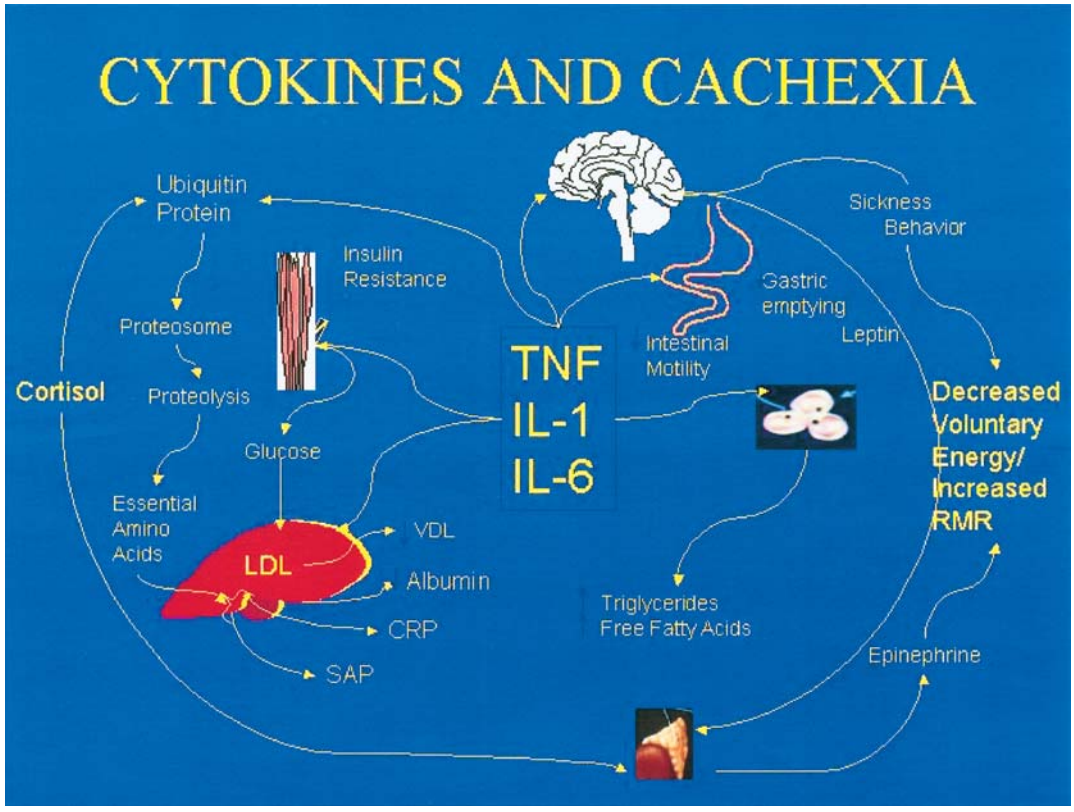

Figure 2. The role of cytokines in the pathophysiology of cachexia. TNF = tumor necrosis factor; IL = interleukin; LDL = low-density lipoprotein; VDL = vasodepressor lipid; CRP = C-reactive protein; SAP = serum amyloid protein; RMR = resting metabolic rate.

modulate the aging process. The role of antiinflammatory cytokines is also potentially exciting in this regard.

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Table 2. Correlations of Cytokines With Frailty-Associated Factors in Older Persons

Author	Date	Reference	Age (Y)	No. of Participants	Association
Cesari et al.	2004	12	65–102	1156	CRP, IL-6, and IL-1RA associated with physical performance, CRP and IL-6 associated with hand-grip
Tilvis et al.	2004	13	75, 80, 85	650	CRP-predicted cognitive decline at 5 but not 10 years
Abbatecola et al.	2004	72	22–104	1146	IL-6 and IL1ra correlated positively and sIL-6R negatively with insulin resistance adjusted for age
Payette et al.	2003	35	72–92	558	IL-6 predicted sarcopenia in women but not men
Reuben et al.	2003	73	70–79	870	High levels of recreational activity was associated with lower levels of CRP and IL-6
Ferrucci et al.	2002	38	65+	620	High IL-6 was associated with development of mobility disability, decreased walking speed, and reduced activities of daily living
Leng et al.	2002	26	74+	30	Frailty was associated with higher levels of IL-6
Visser et al.	2002	36	70–79	3075	Elevated IL-6 and TNFα was associated with smaller muscle area, less appendicular mass, lower knee extensor strength and lower grip strength
Reuben et al.	2002	11	70–79	870	Inflammation is associated with increased mortality
Taaffe et al.	2000	74	70–79	880	IL-6 and CRP was not associated with change in performance but higher levels were present in those that died
Bruunsgaard et al.	1999	75	100+	126	High levels of TNFα
			81	45	correlated with
			55–65	23	dementia in
			18–30	38	centenarians
Dentino et al.	1999	76	70+	1686	Depression correlated with IL-6
Rosenthal et al.	1998	77	60+	72	Soluble IL-2R correlated negatively with albumin, prealbumin, cholesterol, transferin, and hemoglobin; no effect on TNFα, IL-1 beta, IL-6, or IL-2
Rosenthal et al.	1997	78	60+	72	sIL2-R predicted 1-year mortality
Cohen et al.	1997	37	65+	1727	IL-6 correlated with functional disability and self-rated health

Note: CRP = C-reactive protein; IL = interleukin; TNFα = tumor necrosis factor alpha.

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