Translational Article

Special Issue on Biomarkers, Inflammation, and Frailty

Guest Editorial

The “Cytokine for Gerontologists” Has Some Company

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FRAILTY has long been recognized as a complex syndrome of failure to thrive in the elderly adults. When Fried and colleagues (1) suggested the first comprehensive definition for frailty, they helped set in motion many studies of this complex condition; three more of these are published in this edition of the Journal. Even earlier, Rosenberg (2) had proposed sarcopenia as a term to describe the loss of muscle with normal aging, in parallel with osteopenia, and had suggested that sarcopenia was an important part of the pathophysiology of aging and frailty. The link between sarcopenia, frailty, and inflammation has beguiled researchers for decades, and remains central to our understanding of the pathophysiology of age-related decline in function.

Early work by Erschler suggested that interleukin (IL)-6 was an important cytokine in aging, and possibly causal to the development of sarcopenia and frailty (3). But 20 years on, the causal relationship of IL-6 to frailty remains unclear, and the picture has, predictably, gotten more complicated. Before turning to the new contributions to the field in the Journal, I suggest the following framework for evaluating what they mean:

1. Senescence of the immune system leads to loosening of the controls on autoimmunity, and the distinction between self and non-self in the immune system becomes less clear. This is supported by many articles demonstrating age-related changes in immune cell repertoire and function (4). Concurrently, there is an increase in markers of inflammation with age—C-reactive protein (5), sedimentation rate, etc. Whether this inflammatory reaction is driven by primary changes in immune function, by adipokines secreted by rising fat mass, by reduced physical activity and muscle loss, or by all or none of these remains unclear.

2. More recently, a phenotype of senescent cells has been implicated in various age-related disorders (6). The processes underlying cell senescence may play a protective role in preventing cancer, by identifying and isolating cells under genetic stress due to cancer transformation. However, senescent cells can also disrupt normal organ function, increase oxidative stress, promote vascular calcification, atheroma formation, and an osteoporosis-promoting bone microenvironment. A characteristic secretomic pattern produced by these cells, termed the senescence-associated secretory phenotype, is initiated by IL-1α, regulated by transforming growth factor-β, and mediated by the p38 mitogen-associated protein kinase and nuclear factor kappa B systems (6). These in turn promote secretion of IL-6, IL-8, and other cytokines.

3. IL-6 has both pro- and anti-inflammatory functions. In chronic inflammatory diseases such as rheumatoid arthritis, inhibiting IL-6 improves inflammatory markers and symptoms (7). On the other hand, muscle makes IL-6 in response to exercise (which is generally considered beneficial), and young people make more of it than old people despite the fact that older people have higher circulating IL-6, and young persons recover more quickly from muscle injury (8).
4. At least four other pathways besides IL-6 have been demonstrated to interact with sarcopenia, frailty, and survival in the elderly adults: tumor necrosis factor (TNF)-α; insulin-like growth factor-1; androgens (testosterone and dehydroepiandrosterone sulfate); and several members of the transforming growth factor-β superfamily. In the Framingham Heart Study, for example, IL-6, TNF-α, and insulin-like growth factor-1 each independently predicted survival in community-dwelling adults with a mean age of 78 years over a 4-year period (9). Recently, a rat model of sarcopenia suggested that there is cross-talk between inflammatory cytokines and muscle atrophy via activin A, a member of the transforming growth factor-β superfamily that inhibits muscle growth via the activin receptors, the same receptor family that binds myostatin (10).

In this issue of the Journal, three articles demonstrate that IL-6 has company in the claim for the title of cytokine for gerontologists. Varadhan and colleagues (11) studied a group of 15 cytokines regulated by the transcription factor nuclear factor kappa B, including C-reactive protein, IL-6, IL-1Ra, IL-18, and soluble TNF receptor-1 (a surrogate for serum TNF-α). They used two large populations: the InCHIANTI study (n = 1,155) to generate hypotheses, and the Cardiovascular Health Study (n = 5,600) to test them. They then compared various combinations of cytokines to see which predicted 1-year mortality best; the combination of IL-6 and soluble TNF receptor-1 worked best. Sanders and colleagues (12), using a subset of the oldest old in the Cardiovascular Health Study population (n = 900), asked whether there was a strong correlation among a group of the “usual suspects”—dehydroepiandrosterone sulfate, insulin-like growth factor-1 and two of its binding proteins, IL-6—as well as some new faces—adiponectin and total cholesterol. They then tested which of these markers correlated with grip strength, gait speed, and mental status. Not surprisingly, the correlations among the biomarkers were weak (<.2). As the authors point out, this suggests that frailty (and sarcopenia, though it was not specifically measured) probably reflect multiple inputs, with the importance of any single pathway being limited overall and variable between people. In terms of correlation with functional measures, dehydroepiandrosterone sulfate and IL-6 performed best. Finally, Darvin and colleagues (13), in a case–control study of elderly adults in an independent living retirement community, which was designed to confirm an earlier proteomic screening study, also found that IL-6, as well as transferrin and fibrinogen, correlated with frailty.

What do we conclude from the past two decades of research, and the new data presented now? It seems feeble to simply declare, “It’s complicated,” but perhaps that is the most legitimate conclusion. With more granularity, I think we can say that aging, in the absence of an overriding chronic disease, leads to muscle loss, fat gain, reduced physical activity, and increased insulin resistance and inflammation that probably reinforce each other. The idea of frailty as a multifactorial problem has become clear—now the stage is set for trying to reverse it. To that end, we have a host of possible treatments: inhibitors of IL-6 and TNF-α, agonists of insulin-like growth factor-1 and androgens, senescence pathway inhibitors, exercise, diet, antioxidants, and soon, inhibitors of various parts of the transforming growth factor-β superfamily. So far, all the data we have on causes of frailty and sarcopenia come from observational studies. Until we have rigorous interventional studies using specific inhibitors or activators of one part of these pathways or another, we will not be able to truly ascertain cause–effect relationships.

References