Check for updates



Comment on Ferrucci et al, page 2294

# Inflammation gone awry: aging or disease

**William B. Ershler** NATIONAL INSTITUTE ON AGING

In a cohort analysis of elderly Italians, Ferrucci and colleagues found that the dysregulation of proinflammatory mediators, considered by many to be at the root of aging, may more aptly be considered at the root of cardiovascular disease.

Now and again, unifying concepts emerge with relevance to diverse clinical domains. This is clearly true for the robust expansion of appreciation for inflammation gone awry, which has now been implicated in the pathogenesis of disease processes as diverse as gingivitis, diabetes, atherosclerosis, sarcopenia, osteoporosis, and dementia. For gerontologists interested in the biology of aging, the proinflammatory cytokine interleukin-6 (IL-6) has been particularly interesting, inasmuch as animal models and clinical series have time and time again demonstrated an age-associated rise in serum or tissue levels, with the most dramatic change observed in those who develop the phenotype of frailty. For example, in an epidemiologic study of more than 4000 community-dwelling elderly, IL-6 levels were positively associated with functional impairment (mobility and activities of daily living), depression, and mortality.[1] Other large cohorts, including the Health Aging and Body Composition Study (Health ABC)[2] and the Cardiovascular Health Study,[3] have demonstrated similar changes in IL-6 and other proinflammatory molecules or acute phase proteins, such as C-reactive protein (CRP) and fibrinogen. Invariably, to the extent that these factors are present, negative clinical consequences are observed.

Yet it remains to be determined whether the presence of these mediators of inflammation is the consequence of aging (ie, a decline in those factors that regulate proinflammatory cytokines) or a reflection of an underlying disease, such as atherosclerosis. If the former were true, one would expect increased cytokine levels in at least some individuals in the absence of demonstrable inflammatory disease. In this issue of *Blood*, Ferrucci and colleagues report data from a large cohort of thoroughly studied older adults. From their analysis, there appears to be a tight correlation of inflammatory signals with cardiovascular disease, as most (but not all) of the measured markers were not demonstrably correlated with age once the data were adjusted for cardiovascular risk factors or morbidity. As is typical from well-constructed epidemiologic studies, these findings will raise as many questions as they answer. And the big one still remains: which comes first—the cytokines or the disease? Do those factors that render an individual at risk for cardiovascular disease do so by altering proinflammatory cytokine regulation? Is there a genetic predisposition to cytokine dysregulation increasing susceptibility to atherosclerosis?

The study by Ferrucci and colleagues goes as far as a cross-sectional analysis can. At this point, what is sorely needed is a long-term longitudinal analysis of healthy individuals as they traverse from middle age to old age, with interval checks of these important markers and a cataloguing of clinical conditions and incipient disease processes. From there, rational experimental interventions in laboratory animals and humans can be derived with the ultimate goal of retarding either, or both, aging and age-related diseases. ■

## REFERENCES

1. Cohen HJ, Pieper CF, Harris T, Rao KM, Currie MS. The association of plasma IL-6 levels with functional disability in community-dwelling elderly. J Gerontol A Biol Sci Med Sci. 1997;52:M201-208.

2. Cesari M, Penninx BW, Newman AB, et al. Inflammatory markers and onset of cardiovascular events: results from the Health ABC study. Circulation. 2003;108:2317-2322.

3. Tracy RP, Lemaitre RN, Psaty BM, et al. Relationship of C-reactive protein to risk of cardiovascular disease in the elderly: results from the Cardiovascular Health Study and the Rural Health Promotion Project. Arterioscler Thromb Vasc Biol. 1997;17:1121-1127.



Comment on Hildebrandt et al, page 2249

# Cascading lung injury in allogeneic SCT

**Georgia B. Vogelsang** JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE

IPS is a frequently fatal noninfectious pulmonary process seen in up to a quarter of the recipients of myeloablative stem cell transplants. Treatment, high-dose steroids, antimicrobials, and supportive care are usually ineffective.

The pathophysiology of lung injury after stem cell transplantation (SCT) is poorly understood. Idiopathic pneumonia syndrome (IPS) has been attributed to many causes, including preparative regimen toxicity, culture-negative infection, immune-mediated injury, and graft-versus-host disease (GVHD). In this issue of *Blood*, Hildebrandt and colleagues report that donor leukocyte–derived RANTES (a chemokine ligand of the CC chemokine family of proteins that promotes migration of T cells, eosinophils, basophils, and macrophages to sites of inflammation) is significantly elevated in recipients of an allograft after irradiation, compared with syngeneic controls. Elevated mRNA and RANTES protein levels were associated with increased mRNA expression of CCR5 and CCR1 and increased inflammatory cell infiltration into the lung in this mouse model. The importance of donor RANTES was confirmed by the use of RANTES-deficient T cells, where lung injury was significantly reduced but not eliminated.

These data support the idea that IPS is a complex disorder due to a cascade of events. Preparative regimen toxicity (especially from irradiation) generates a proinflammatory environment that damages host tissues, augments the allostimulatory capacity of host dendritic cells, and alters the chemokine environment. Thus, donor T cells may act as effectors and facilitators of lung injury after allogeneic SCT,

Downloaded from http://ashpublications.org/blood/article-pdf/105/6/2247/1707426/zh800605002239i.pdf by guest on 25 January 2025