Polyclonal Immunoglobulin Free Light Chain and Chronic Inflammation

To the Editor: With great interest, we read the article by Dispenzieri et al[1] in the June 2012 issue of *Mayo Clinic Proceedings* in which they reported their investigation of the association of polyclonal immunoglobulin free light chains (FLCs) and the mortality rate in a large population of normal persons. The authors concluded that nonclonal elevation of FLCs is a significant predictor of worse overall survival in persons without plasma cell disorders. The increased risk of death was independent of renal function, sex, and age but not restricted to any particular cause of death. As also discussed in the editorial that introduced this paper,[2] normal immunoglobulin production is accompanied by an excess of FLC synthesis. Free light chains are secreted by plasma cells and can be found in body fluids such as blood, synovial and cerebrospinal fluid, urine, and saliva. Although FLCs have been considered spillover products of antibody synthesis, FLCs can also have diverse biological activities, including antiangiogenic, prothrombinase, proteolytic, and complement-activating activities.[3]

In addition, we have described that FLCs can trigger inflammation via activation of mast cells.[4] Passive sensitization of mice with antigen-specific FLCs followed by antigen challenge induces an immediate hypersensitivity-type response.[4] Mast cells may not be the sole cellular target for FLCs, because neutrophils and neural cells have also been found to respond to FLCs.[5,6] In previous work, we showed that FLCs may play a crucial role in the pathogenesis of disease in preclinical models for asthma, inflammatory bowel disease, and food allergy.[7-10] In extension to these studies, we found increased local or systemic FLC concentrations in patients with food allergy[10] inflammatory bowel disease,[8] rheumatoid arthritis,[11] viral myocarditis,[12] and upper and lower airway diseases such as rhinitis,[13] asthma,[7] idiopathic pulmonary fibrosis and hypersensitivity pneumonia,[14] and chronic obstructive pulmonary disease (Figure).[5] Therapeutic intervention with rituximab in patients with rheumatoid arthritis showed that decreases in FLCs correlate with a decrease in disease activity.[11] Our studies suggest that FLCs may be responsible for an antigen-specific initiation and perpetuation of chronic inflammation.

These findings may be of particular importance in relation to the study described by Dispenzieri et al.[1] Increased FLCs could stimulate the progression of chronic inflammatory responses via the activation of specific immune cells. It would therefore be of interest in future studies to investigate whether polyclonal FLC concentrations may also be associated with specific markers of cellular activation. These data, including those from *Mayo Clinic Proceedings*,[1] suggest that measurement of FLCs may not only be important to investigate aberrant FLCs leading to plasma cell disorders but may also give insight into ongoing inflammatory immune reactions.

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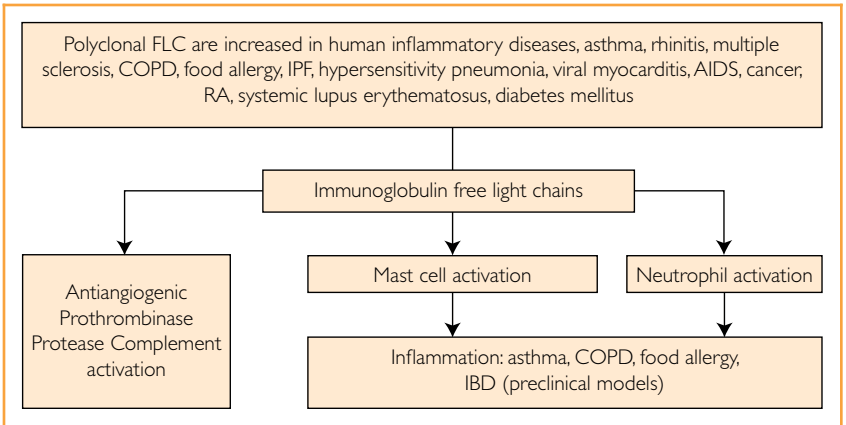

FIGURE. Immune disorders associated with increased immunoglobulin free light chains (FLC) and effector functions of immunoglobulin FLC leading inflammatory diseases via mast cell and neutrophil activation. COPD = chronic obstructive pulmonary disease; IBD = inflammatory bowel disease; IPF = idiopathic pulmonary fibrosis; RA = rheumatoid arthritis.

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In reply: We thank Dr Redegeld and colleagues for their thoughtful letter in response to our original article on the use of nonclonal serum immunoglobulin free light chains (FLCs) to predict overall survival in the general population.[1] The authors introduce several interesting hypothesis-generating concepts regarding potential mechanisms and associations between excess serum immunoglobulin FLCs and inflammation. Works such as theirs may bring further meaning to our observation that excess FLC is associated with poorer survival outcomes in the general population, clarifying whether FLCs are merely markers for more ominous events or whether they actually contribute to pathology.

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Changes in Serum Prostate-Specific Antigen Levels

To the Editor: I would like to comment on the study by Jacobsen et al[1] published in the January 2012 issue of *Mayo Clinic Proceedings* that documented the changes in serum prostate-specific antigen (PSA) values in a large group of men. The authors determined that the median annual change in PSA was about 4.8%, while the 95th percentile for PSA increase was about 50%. Interestingly, while the baseline PSA values and the absolute increases in PSA values increased with age, the increases in PSA were relatively constant across all ages when expressed as a percentage of the baseline value. They propose that PSA velocity, expressed as a percentage increase over the baseline PSA, may have more utility as an indication for biopsy than using a fixed annual increase in PSA. For example, men in their 50s had a median baseline PSA of 0.9 ng/mL, so the 95th percentile increase would be about 0.45. For men in their 70s, with a median baseline PSA of 2.1, the 95th percentile increase would be about 1.05. These examples show how using a percent increase in PSA as a biopsy threshold might prove more adaptive to age-related variations than using a fixed absolute annual increase of 0.75 points, as has been proposed in the past.

Much work needs to be done in this area to validate these findings. Many physicians will choose to follow the reasonable recommendation of the US Public Health Service not to screen for PSA in any category of healthy men until stronger evidence of benefit emerges.[2] But for those who believe that there is a useful signal buried in all the noise of PSA measurements, perhaps this study is the first step in developing a prostate cancer screening algorithm that will prove robustly beneficial for men across a range of ages and baseline PSA values. As a primary care physician who is stubbornly biased in favor of PSA testing, I would be interested to see further research into the utility of adaptive algorithms when testing PSA.

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In reply: We thank Dr Keller for his comments regarding our study of longitudinal changes in serum PSA levels published in the January 2012 issue of *Mayo Clinic Proceedings*.[1] As Dr Keller notes, our article shows that using changes in serum PSA levels expressed as percent change per year yields more stable findings across different ages and also provides a nomogram to aid clinicians in interpreting changes in serum PSA levels observed in a normal clinical practice. Much controversy currently surrounds the use of serum PSA measurements, and while PSA is not a perfect test, at this time it is still the only widely available option for screening for prostate cancer. Using a single cut point for serum PSA level or changes in serum PSA level irrespective of age or baseline PSA level has often been noted as a drawback of using serum PSA testing.[2,3] In order to prevent PSA history from repeating itself, either in the continued use of serum PSA measurements or in the development of future prostate cancer biomarkers, it is important to focus on an algorithm that is robust across different ages and baseline levels.

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Levamisole Toxicity

To the Editor: The review of levamisole toxicity by Lee et al[1] published in the June 2012 issue of *Mayo Clinic Proceedings* does not mention leukoencephalopathy as a well-