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Polyclonal Immunoglobulin Free Light Chains as a Potential Biomarker of Immune Stimulation and Inflammation

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Clinical Biomarkers of Innate and Adaptive Immunity

C-reactive protein (CRP)[3] is an established biomarker of acute and chronic inflammation. The hepatic synthesis of CRP is closely regulated by inflammatory cytokines, in particular interleukin-6. The CRP concentration increases rapidly in response to an inflammatory event, peaks within 48 hours, and often increases 100-fold. Bacterial infections and large burns are associated with the largest increases in serum CRP, and serial measurements of CRP in patients with these conditions can allow assessment of disease progression or the response to treatment. More recently, the commercial introduction of nephelometric assays has allowed the detection of small changes in CRP, even within the reference interval, and such increases have been associated with cardiovascular disease (1) and cancer (2).

The assessment of inflammation by CRP measurement provides clinicians with a valuable tool to use across a number of clinical settings; however, CRP reflects only the activity of innate immunity. If the activity of both the adaptive and innate immune systems could be determined simultaneously, it is possible that additional diagnostic, prognostic, or monitoring information could be gained. The adaptive immune system consists of several specialized cell types and processes that allow protection from challenges by pathogens and the ability to recognize and remember each individual antigen. The individual identification of each antigen and the ability to mount a larger, more rapid response to the antigen on repeat exposure are essential to the success of this system of immunologic memory. A key

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component of this process is the production of antibodies by plasma cells of the B-cell lineage. Antibodies or immunoglobulins are proteins that consist of 2 identical heavy chains (HCs) and 2 identical light chains (LCs). Antibodies are typed by their HCs into 5 categories (IgA, IgD, IgE, IgG, and IgM), each of which has 2 isotypes, κ or λ LC. During the production of intact immunoglobulins, the LCs are produced in slight excess of the HCs at a rate of approximately 500 mg/day, total (3, 4). These excess free LCs (FLCs) are released into the circulation, where they are rapidly removed by glomerular filtration, with serum half-lives of 2–6 hours when renal function is normal (3–5). We have hypothesized that measuring polyclonal FLCs in the serum might gain new insight into the activity of the adaptive immune system, potentially allowing FLC measurement to serve as a novel clinically relevant biomarker.

Measurement of FLCs and Reference Intervals

In 2001, novel immunonephelometric assays for the measurement of FLCs in the serum were described (6). These assays use polyclonal antibodies (raised in sheep) that identify epitopes on the FLCs. These epitopes are exposed when the LCs are free but are hidden when the LCs are complexed with HCs. To date, work has focused almost entirely on the role of FLCs for the diagnosis and monitoring of patients with plasma cell dyscrasias (7), and these assays have been incorporated into a number of international clinical guidelines (8).

In addition to the assessment of monoclonal FLCs in plasma cell diseases, FLC assays also can be used to quantify polyclonal FLCs in blood. Katzmann et al. first described reference intervals for κ and λ FLCs and their ratio to determine the presence of a monoclonal paraprotein (Table 1) (9). In patients with polyclonal hypergammaglobulinemia (as determined by serum protein electrophoresis and immunofixation electrophoresis), nonspecific increases in FLCs occurred in a fashion similar to the nonspecific increases in CRP seen with inflammation. Such polyclonal FLC increases might be a nonspecific biomarker of adaptive immunity. The absolute serum concentrations of FLCs in a given patient are influenced by the rates of production and renal clearance. Hutchison et al. have reported strong correlations of FLCs with several biomarkers of renal function, thus supporting the inverse relationship of serum FLC concentrations with renal function and reinforcing the need for separate reference intervals for FLCs in the presence of renal impairment (Table 1) (10). This reduced renal clearance of FLCs may explain the increase in serum FLCs with age seen in the cohort of Katzmann et al.

Polyclonal FLCs as a Clinically Relevant Biomarker

The potential utility of measuring serial polyclonal FLC concentrations as a biomarker of activation of the B-cell lineage has raised interest in several clinical settings. The most obvious is in the field of autoimmune diseases. Preliminary studies have demonstrated that concentrations of polyclonal FLCs correlate with disease activity in patients with rheumatoid arthritis, Sjogren syndrome, and systemic lupus erythematosus (11). Additionally, FLC concentrations were predictive of hospitalization in 211 patients with lupus (12).

Another possible context in which the measurement of chronic immune stimulation with polyclonal FLCs might be informative is the identification and stratification of future risk for neoplastic disease. The relationship between chronic inflammation and cancer is well established, although not fully understood. In a cohort of patients with HIV, a polyclonal increase in FLCs was predictive of the future risk of non-Hodgkin lymphoma (13). When serum κ and λ FLC concentrations were 2-fold higher than normal, the risk of non-Hodgkin lymphoma was increased by 3.76-fold and 8.13-fold, respectively (13). Additionally, in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, a polyclonal increase in the serum FLC concentration was associated with an increased risk of chronic lymphocytic lymphoma (CLL). This association was present up to 9 years prior to the diagnosis of CLL but became stronger closer to the time of diagnosis (14).

A third scenario in which measurement of polyclonal FLCs might be useful is for patients with renal impairment (10). The complexity of measuring polyclonal FLCs in this setting is in determining the influence of reduced renal clearance vs increased production. As residual renal function is lost, the serum FLC concentrations will increase, so when a loss of residual renal function is coupled with a minor increase in production, an exponential increase in serum FLC concentrations might be seen. The potential relevance of investigating this relationship is the link between chronic inflammation and cardiovascular disease in this population. We hypothesize that assessment of rates of polyclonal FLC production might provide insight for risk stratification and management of these complex cases. In support of this concept, a provisional report for 1328 patients from the Renal Institute of Birmingham demonstrated that increased polyclonal FLCs are independently predictive of both overall patient survival and cardiovascular death (15).

Furthermore, Dispenzieri et al. reviewed a cohort of >15 000 patients for whom serum FLC measurements were available and determined that high polyclonal FLC concentrations were independently predictive of survival in the general population (16). Additional data from the German Heinz Nixdorf Recall health-screening study of 4350 patients demonstrated a clear independent association of increased polyclonal FLCs with overall patient survival (17).

In the settings of acute illnesses, CRP appears to be a more relevant biomarker of inflammation, except when the CRP response is limited. For instance, viral infections have a limited CRP response but are associated with increased polyclonal FLCs. Further work is needed to determine whether FLCs can provide a useful monitor of disease in this setting.

Barriers to Developing Polyclonal FLCs as a Clinical Tool

Before the measurement of polyclonal FLCs can be considered as a relevant tool, several unanswered questions need to be addressed. They include a better understanding of the intrapatient variation of FLCs and their changes in different diseases. More fundamentally, how should we measure and report polyclonal FLC concentrations and their production rates? Currently, only one commercial assay is available for the measurement of serum FLCs. This assay, Freelite (The Binding Site), consists of 2 assays—one to measure κ FLCs, the other to measure λ FLCs. It is unclear whether measurement of one of the FLC isotypes has greater utility over measuring the other or both.

The relationship of FLCs to CRP and other biomarkers of inflammation needs to be determined and, particularly, how their kinetics differ in various acute and chronic inflammatory conditions. We anticipate that CRP, as an acute phase protein, would have a more rapid on/off response compared with an indolent FLC response. This concept is supported by data from a small intensive-care case series (n = 14), which revealed poor intrapatient correlations for CRP and FLCs; results for a larger cross-sectional cohort also showed a limited correlation (18). Perhaps the most important question to address is how to develop a better understanding of the substantial influence of renal impairment on serum FLC concentrations and how to account for that in reporting results. Would an automated correction of FLCs with the estimated glomerular filtration rate or cystatin C provide more useful information than absolute concentrations alone?

As these early questions of how to measure and report polyclonal FLC results are answered, subsequent large clinical studies will then be required to demonstrate how these apparently nonspecific biomarkers of adaptive immunity might be applied in clinical practice. The results of these studies should be interesting to follow.

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Table 1.

Suggested reference values for serum free light chains.[a]

Population	No. of individuals	κ FLC, mg/L	λ FLC, mg/L	Total FLC, mg/L	Ratio
Healthy donors	282	7.3 (0.8–34.7)	12.4(2.7–37.4)	20.5 (3.5–72.1)	0.59 (0.26–1.65)
Renal impairment	688	43.8 (3–251)	38.0 (1.0–251)	82 (8.57–497)	1.12 (0.37–3.17)
Polyclonal hypergammaglobulinemia	25	19.6 (4.3–273)	28.8 (8.5–307)		0.55 (0.38–1.18)

[a]FLC data and the κ/λ FLC ratio are presented as the median (range). From Katzmann et al. (9) and Hutchison et al. (10).