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Lupus nephritis biomarkers

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ABSTRACT

Lupus nephritis (LN), a potentially destructive outcome of SLE, is a real challenge in the management of SLE because of the difficulty in diagnosing its subclinical onset and identifying relapses before serious complications set in. Conventional clinical parameters such as proteinuria, GFR, urine sediments, anti-dsDNA and complement levels are not sensitive or specific enough for detecting ongoing disease activity in lupus kidneys and early relapse of nephritis. There has long been a need for biomarkers of disease activity in LN. Such markers ideally should be capable of predicting early sub-clinical flares and could be used to gauge response to therapy, thus obviating the need for serial renal biopsies with their possible hazardous complications. Since urine can be readily obtained, it lends itself as an obvious biological substrate. In this review, the use of urine and serum as sources of lupus nephritis biomarkers is described, and the results of biomarker discovery studies using candidate and proteomic approaches are summarized.

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1. Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disorder with exceedingly diverse clinical manifestations. Lupus nephritis (LN) is one of the commonest and most serious manifestations of SLE leading to significant morbidity and mortality among patients [1–3]. Despite overall improvement in the care of SLE patients and an increase in 5-and 10-year renal survival rates of LN, its prognosis remains unsatisfactory particularly in certain ethnic groups such as African Americans and Hispanics [3–5]. Improving the prognosis of LN needs developing newer strategies which are more sensitive and specific for the onset or relapse of renal disease activity, thus allowing earlier initiation of management plans [2]. Late diagnosis of LN correlates with a higher frequency of renal insufficiency and ESRD, underlining the importance of early diagnosis. [6].

Current conventional laboratory markers for detecting and assessing LN such as proteinuria, urine protein:creatinine ratio, creatinine clearance, anti-dsDNA, and complement levels are unsatisfactory for several reasons. They lack the ability to differentiate renal activity from renal damage in LN, which is cardinal for planning treatment strategy. The pathogenic processes underlying LN may begin well before renal function becomes impaired and detectable by laboratory parameters [2].

Although renal biopsy is still the gold standard for diagnosing and classifying the degree of renal inflammation and scarring, its invasiveness as a procedure with potential complications makes it unsuitable for serial monitoring [3,7]. For these reasons, novel biomarkers are clearly warranted. A biomarker is a biologic, biochemical, or molecular substance that can be detected qualitatively and quantitatively by laboratory techniques, that correlates with disease pathogenesis or activity at various time points. With respect to LN, an ideal biomarker should have as many of the following properties: 1- specific for renal involvement in SLE patients, 2- has established correlation with renal activity or damage, 3- efficient for serial monitoring of disease status longitudinally, 4- superior to conventional clinical or laboratory parameters in predicting oncoming renal flares early enough in order to initiate prompt treatment and prevent renal damage, 5- able to gauge severity of renal involvement, so that clinicians can identify patients who might benefit from more aggressive therapies, 6- has been validated in two or more independent cohorts and 7- easy to perform, with minimal infrastructure needs, and above all, inexpensive [2]. It is certainly conceivable that different biomarkers may meet different needs in the field. (See Table 1)

There have been a number of studies focusing on the utility of biomarker panels versus individual biomarkers in predicting renal disease activity and LN outcomes. Most recently, Wolf et al. analyzed urine samples from a number of biopsy-proven LN patients for a panel of urine biomarkers. Models developed with the combined traditional and novel biomarker panels demonstrated clinically meaningful predictive power. Markers most predictive of response were chemokines, cytokines and markers of cellular damage [178]. Brunner et al. developed a novel Renal Activity Index for Lupus (RAIL) that is based solely on laboratory measures, for predicting histologic LN activity, assessed by the National Institutes of Health activity index (NIH-AI) and the tubulointerstitial activity index (TIAI). Using stepwise multivariate

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Table 1
Summary of biomarkers reviewed[1].

	Specific for renal involvement in SLE patients	Correlation with renal disease activity	Correlation with renal damage	Suitable for serial monitoring of disease status longitudinally	Prediction of LN flares	Correlation with renal histology
Traditional biomarkers						
Anti-dsDNA Antibodies	+	+	−	±	±	−
Complement C3 and C4	−	+	−	+	−	−
Proteinuria	+	+	+	+	−	±
Active sediment	+	+	−	±	±	−
Newly emerging biomarkers						
MCP-1 (urine)	+	+	−	+	+	±
NGAL (urine)	+	+	+	+	+	±
TWEAK (urine)	+	+	ns	+	+	−
IP-10(CXCL-10) (serum, urine)	+ (urine but not serum)	+	±	+	ns	+ (Class IV nephritis)
CXCL-16 (serum, urine)	+ (urine but not serum)	+	ns	ns	ns	ns
IL-6 (serum, urine)	+ (urine but not serum)	+	ns	+	ns	+ (Class III/IV nephritis)
IL-17 (serum, urine)	+ (urine but not serum)	+	ns	+	ns	+ (Class III/IV nephritis)
VCAM (serum, urine)	+ (urine but not serum)	+	ns	ns	ns	+ (Class III/IV nephritis)
TGF- ß1 (urinary mRNA)	+	+	ns	ns		+ (Class IV nephritis)
L-PGDS (urine)	+	+	+	+	±	±

[1] A summary of several promising biomarkers reviewed in this article. (+) Denotes a positive and statistically significant relationship being documented in at least one study. Biomarkers with (−) in a category have not been shown to have a statistically significant relationship in that category. (±) Denotes equivocal outcomes, while "ns" denotes "not studied". It should be kept in mind that for several molecules, data is only available from 1 to 2 studies, and these findings need to be updated as further validation trials are conducted.

logistic regression, the RAIL algorithms predicted LN-activity status for both NIH-AI and TIAI, utilizing traditional biomarkers and UBMs as candidate components. The differential excretion of 6 UBMs (neutrophil gelatinase–associated lipocalin, monocyte chemotactic protein-1, ceruloplasmin, adiponectin, hemopexin, and kidney injury molecule 1) standardized by urine creatinine was factored into RAIL. These UBMs predicted LN-activity (NIH-AI) status with >92% accuracy and LN-activity (TIAI) status with >80% accuracy with minimal influence by concomitant LN damage. However, further independent validation is required [179].

Over the past decade, several new biomarkers, such as serum and urinary cytokines, chemokines, adhesion molecules and growth factors, have been evaluated for monitoring treatment response and detecting early renal flares in LN [8]. In particular, urinary biomarkers appear to be more promising than serum biomarkers, possibly because the former arise directly from the inflamed tissue. In this review, we highlight these biomarkers and discuss their potential utility in LN.

2. Conventional (traditional) biomarkers

2.1. Anti-dsDNA antibody

Anti-dsDNA antibodies constitute a cardinal diagnostic tool for SLE and have been implicated in the pathogenesis of SLE renal disease as well as other disease manifestations [9]. Anti-dsDNA antibodies are present in higher concentrations in renal tissue compared to systemic circulation [10]. It has been shown that increases in serum anti-dsDNA antibodies often precede lupus flares. Furthermore, prophylactic treatment of patients following rises in anti-dsDNA antibody levels has reduced the occurrence of subsequent disease flares [11–14]. In addition, increases in anti-dsDNA antibody levels are associated with an increase of renal flare in patients with previous history of renal disease [9]. However, other studies have reported that anti-dsDNA does not predict or correlate well with LN or flares [15,52]. The clinical usefulness of anti-DNA assays depends on their ability to determine pathogenic autoantibody subtypes (based on fine specificities) and to measure them using a standardized quantitative approach. The sensitivity and specificity of anti-dsDNA antibody for the diagnosis of SLE vary depending on the assay platform used. For example, the CLIFT assay (indirect immunofluorescence on Crithidia luciliae) shows a sensitivity and specificity of 47–55% and 98–100%, respectively, while the Farr (Farr radioimmunoassay) shows a sensitivity and specificity of 42–85% and 95–99%, respectively, and the ELISA (enzyme-linked immunosorbent assay) exhibits a sensitivity and specificity of 56–67% and 91–96%, respectively [189,190].

2.2. Complement

The complement system has been related intimately to SLE than other autoimmune diseases [16]. Measurements of C3 and C4 have traditionally been used as the best laboratory assessment of SLE disease activity. Reduction of C3/C4 at initial diagnosis is associated with poor prognosis [17]. Circulating C5b-9 correlates strongly with disease activity scores [18]. Complement activation products such as C3a, C3d, C5a, C4d have been investigated as possible biomarkers. Although they show correlation with disease activity, they have not been able to replace measurement of total C3/C4 in daily clinical practice, due in part to their short half-life requiring special sample handling [18]. To the contrary, a few studies have shown that C3/C4 do not predict or correlate well with LN or flares [19,20]. Overall, the sensitivity/specificity profiles for C3 (75%/71%) and C4 (48%/71%) for identifying renal flares are low [191].

2.3. Proteinuria, GFR and urine sediments

Until today, proteinuria- measured in 24 h urine samples or as protein:creatinine ratio in the urine- is the principal urinary biomarker for assessing LN. In spite of its correlation with the eventual renal outcome, it is not necessarily related with histological index activity changes in LN, and, hence, cannot be considered the most reliable marker of LN disease severity or activity [17]. Along with serum creatinine, glomerular filtration rate (GFR), estimated by the use of the Schwartz formula, is a standardized tool for assessing renal function in LN [21]. Urinary sediments included in both SLEDAI and BILAG disease activity indices have also been considered as useful measures of disease activity [17]. Although all of these are well accepted indicators of renal damage,