New markers of disease activity in lupus nephritis:

Essay

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List of abbreviation

ACE	Angiotensin converting enzyme
ACR	American College of Rheumatology
AGP	Alfa 1-acid-glycoprotein
AGT	Angiotensinogen
AI	Activity index
AKL	Anticardiolipin antibody
ANA	Antinuclear antibody
ANCA	Anti-neutrophil cytoplasmic antibodies
Anti-C1q Abs	Anti-complement 1q antibodies
Anti-dsDNAAbs	Anti-double stranded DNA antibodies
Anti-GBM	Anti-glomerular basement membrane
Anti-nDNA	Anti-nativeDNA
APRIL	Aproliferation-inducing ligand
APSN	Antiphospholipid syndrome
ARB	Angiotensin receptor blockers
BILAG	British isles lupus Assessment Group
C3,C4	Complement3,4
CB-CAP	Cell-bound complement activation product
CCL3	Chemokine (C-C motif) ligand 3
CCL5	Chemokine (C-C motif) ligand 5
CCR5	C-C chemokine receptor 5
CD	Cluster of differentiation
CFH	Complement factor H
CI	Confidence interval
CNV	Copy number variation
CP	Ceruloplasmin
CR	Complete response
CRP	C-Reactive protein
CTR	Cardio thoracic ratio
CXCL16	Chemokine (C-X-C motif) ligand 16
DC	Dendritic cell
DNS	Dezoxiribonucleic acid
EBV	Epstein-Barr virus
ELISA	Enzyme-linked immunosorbent assay
ELNT	Euro-Lupus Nephritis Trial
Enos	Endothelial nitric oxide synthase
EPCR	Endothelial protein C receptor

ER	Estrogen receptor
ESRD	End stage renal disease
Fasl	Fas ligand
FCγR	Fcγ receptor
FLCs	Free light chains
FSGS	Focal segmental glomerulosclerosis
GFR	Glomerular filtration rate
GWAS	Genome-wide association studies
H	Histone
HDAC	Histone deacetylase
HLA	Humen leukocyte antigen
HPF	High power field
ICAM	Interacellular adhesion molecule
ICs	Immunocomplexes
I/D	Insertion/Deletion
IFN	Interferon
IFNγ	Gamma interferon
IgG	Immunoglobulin G
IL	Interleukin
iNOS	Inactivated nitric oxide synthase
IP-10	Interferon gamma inducible protein 10
ISN/RPS	International Society of Nephrology/Renal pathology Society
ITGAM	Integrin alpha M
KLK	Kallikrein
KT	Kidney transplantation
Kt/V	Residual renal function
LN	Lupus nephritis
L-PGDS	Lipocalin-type prostaglandin D-synthetase
MBL	Mannose binding lectin
MCP-1	Monocyte chemoattractant protein-1
MdM2	Mouse double minute 2 homolog
MIF	Migration inhibitor factor
MiRNA	MicroRNA
MMF	Mycophenolatemofetil
NF	Nuclear factor
NGAL	Neutrophil-gelatinase-assotiated lipocalin
NIH	National institutes of health
NKcell	Natrual killer cell
NPV	Negative predictive value
PAI-1	Plasminogen activator inhibitor-1

PD	Peritoneal dialysis
PDCD1	Programed cell death 1
PPV	positive predictive value
PSTR	Peritoneal solute transporter rate
RAAS	Renin angiotensin aldoserone system
RANTES	Regulated upon activation, normal T-cell expressed and secreted
RBC	Red blood cells
RNP	Ribonucleoproteins
ROC	Receiver operating characteristic curve
RRT	Renal replasment therapy
RT-PCR	Reverse transcription polymerase chain reaction
Sb2M/SCysC	Serum b2 microglobulin/cystatin c index
SDR	Sedementation rate
SELDI-TOF-MS	Surface enhanced laser desorption/ionization time of flight mass spectrometry
SIL-7R	Serum levels of soluble interleukin 7 receptor
Sirt1	Sirtuin-1
SLE	Systemic lupus erethmatoses
SLEDAI	SLE disease activity index
SLICC	Systemic lupus international collaborating clinics
SPP1	Osteopontin
STAT	Signal trasducers and activator of transcription
TF	Transferrin
TLRs	Toll like receptors
TNF	Tumor necrosis factor
TNFR1	Tumor necrosis factor receptor 1
TWEAK	Tumour necrosis factor like weak inducer of apoptosis
UG	Uteroglobin
WBC	White blood cells
WHO	World Heath Organization
VCAM	Vascular cell adhesion molecule
VEGF	Vascular endothelial growth factor
VNN1	Vanin-1

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Introduction

Lupus Nephritis (LN) is a common and serious feature of systemic lupus erythematosus (SLE).SLE itself is defined by a combination of clinical and laboratory features.The incidence and prevalence of lupus and LN are influenced by age, gender, ethnicity, geographic region, diagnostic criteria employed, and method of acertainment.The peak incidence of lupus is 15 to 45 years, with females outnumbering males by 9 : 1.This gender predominance is less pronounced in children and older individuals.Among lupus patients, LN affects both genders equally and is more severe in children and men and less so in older adults.Both lupus and LN are three to four times more common in African Americans, Afro-Caribbeans, Asians, and Hispanic Americans than in Caucasians. Additional risk factors for renal disease include younger age, lower socioeconomic status, longer duration of disease, family history of SLE, and hypertension**(Appel and Jayne2007).**

Despite the overall improvement in the care of SLE in the past two decades, the prognosis of lupus nephritis remains unsatisfactory.Up to 25% of patients still develop end stage renal failure 10 years after onset of renal disease**(Mok, 2006).**

Current laboratory markers for lupus nephritis such as proteinuria, protein-to-creatinine ratio, creatinine clearance, anti-dsDNA, and complement levels are unsatisfactory.They lack sensitivity and specificity for differentiating renal activity and damage in lupus nephritis.Significant kidney damage can occur before renal function is impaired and first detection by laboratory parameters.More sensitive and specific clinical markers for the onset or relapse of renal disease activity in patients with SLE may allow earlier institution of treatment and even preventive

strategies so that the efficacy of existing therapies can be enhanced while treatment-related complications can be minimized**(Mok, 2010).**

Monocyte chemoattractant protein-1 (MCP-1) is involved in mediating inflammation and injury in lupus nephritis. It is a promising biomarker for lupus nephritis as it can predict renal flares and correlates with their severity particularly in proliferative types(WHO class III & IV) of lupus nephritis**(Rovin, et al., 2007).**

Neutrophil Gelatinase-Associated Lipocalin (NGAL) belongs to a family of carrier proteins important for cellular ion transport, apoptosis and tissue differentiation. Both serum and urinary levels of (NGAL) correlate with residual glomerular filtration rate, protein-to-creatinine ratio and are good biomarkers of chronic kidney disease**(Bolignano, et al., 2008).**

Tumor Necrosis Factor-Like Inducer of Apoptosis (TWEAK) mediates cellular proliferation ,survival, differentiation,migration and angiogenesis**(Ortiz, et al.,2009).** Increased expression of TWEAK on activated lupus T cells has been shown to induce monocyte/macrophage apoptosis, which may contribute to the initiation of SLE through increasing the burden of apoptotic materials**(Gao, et al., 2009).** Overall, although urinary TWEAK is a promising biomarker for lupus nephritis because of its high specificity for lupus renal disease and good correlation with renal disease activity, it may not be sensitive enough to predict a renal flare early and cannot replace the need for a renal biopsy**(Mok,2010).**

Urine Proteomics

Suzuki et al.,(2009),utilitized the surface enhanced laser desorption/ ionization time-of-flight mass spectrometry (SELDI-TOF MS) technology to isolate a panel of urinary protein signature for patients with lupus nephritis.

Anti-C1q Antibodies

C1q plays a crucial role in the clearance of immune complexes and apoptotic bodies**(Tsirogianni, et al., 2009).**Elevation of anti-C1q titre had 50% positive predictive value and 100% negative predictive value for the subsequent development of class IV or V lupus nephritis**(Meyer, et al., 2009).**

Anti-*α*-Actinin Antibodies

These are expressed by podocytes and mesangial cells in renal tissues. Among patients with SLE, anti-*α*-actinin antibody levels were significantly higher in those with renal flares and correlated independently with anti-dsDNA titers **(Renaudineau, et al., 2007).** The performance of a panel of conventional and novel autoantibodies in the diagnosis, monitoring, and prognostic stratification of lupus nephritis has to be evaluated in the future**(Manson, et al., 2009).**Although a large number of novel biomarkers have been studied in lupus nephritis, none of them have been rigorously validated in large-scale longitudinal cohorts of patients with different ethnic background. It is unlikely at this juncture that acandidate biomarker stand-alone can replace conventional clinical parameters to monitor disease progress and detect early renal flares. Urine biomarkers appear to be more encouraging than serum biomarkers possibly because they are the direct products or consequences of kidney inflammation or injury.Future directions in SLE biomarker research should focus on a combination of novel markers with conventional clinical parameters to enhance the sensitivity and specificity for the prediction of renal flares and prognosis in lupus nephritis**(Mok, 2010).**

Genes and genetic variations associated with LN

Many studies have shown that the genetic basis of LN predisposition exhibits in two aspects.On one hand, some susceptibility alleles of candidate genes

are associated with LN disease severity. On the other hand, there exists a set of kidney-specific genes that are likely to amplify or sensitize patients to autoimmune pathology of LN**(Morel, 2007)**.

Aberrations in epigenetic regulation for LN

Immune-mediated LN is multigenic and/or multifactorial in origin. Epigenetic mechanisms get involved in a variety of autoimmune disorders, including LN, by regulating immunogenicity and autoantibody production. The influence of epigenetic mechanisms on LN has been investigated in many studies. Epigenetic modifications can influence gene expression and alter cellular function without modifying the genomic sequence. Three main epigenetic processes include DNA methylation,nucleosome repositioning by histone modifications and MicroRNA(miRNAs)**(Renaudineau, et al., 2011)**.

Aim of the work

The aim of this work is to:

1. Review the recent literature about lupus nephritis regarding: pathogenesis, updated classification, clinical manifestations, complications and recent investigations.
2. Emphasize the need for new reliable non invasive biomarkers of disease activity in patients with lupus nephritis which can predict disease flare and correlate positively with disease activity.
3. Review recent advances in treatment strategies of lupus nephritis.

Chapter 1

Lupus nephritis

Systemic lupus erythematosus

Introduction

SLE depicts a remarkable complex autoimmune disease with considerable heterogeneity in clinical manifestations and disease course. Classification of SLE was last edited by the American College of Rheumatology (ACR) in 1997**(Hochberg, 1997)**. Earlier diagnosis, more intensive treatment regimens and diverse alternative strategies and possibilities to treat co-morbidities have contributed to improvement of prognosis**(Cervera, et al., 2003)**. Negative predictive factors with respect to survival include male gender, positive lupus anticoagulant, glomerulonephritis and "severe" onset of SLE**(Doria, et al., 2006).** The incidence is much higher in young woman and the prevalence is two- to four-fold greater in non-Caucasian populations**(Pons-Estel, et al., 2010)**. Genetic,environmental and hormonal factors have been identified as possible risk factors for developing SLE**(Rubtsov, et al., 2010) and (Cooper, et al.,2010)**. It was suggested that the nucleosome might be the driving autoantigen in SLE. This hypothesis is supported by the finding that glomerular deposition of antidsDNA antibodies in lupus nephritis is mediated by nucleosomes**(van Bavel, et al., 2008)**.

Signs and symptoms

SLE is a chronic autoimmune disease that can affect almost any organ system; thus, its presentation and course are highly variable, ranging from indolent to fulminant. In childhood-onset SLE, there are several clinical symptoms more commonly found than in adults, including malar rash, ulcers/mucocutaneous involvement, renal involvement, proteinuria, urinary cellular casts, seizures,

thrombocytopenia, hemolytic anemia, fever, and lymphadenopathy**(Livingston, et al., 2011)**. In adults, Raynaud pleuritis and sicca are twice as common as in children and adolescents**(Livingston, et al., 2011)**.

Patients may present with any of the following manifestations**(Edworthy,2005)**:

- Constitutional (eg, fatigue, fever, arthralgia, weight changes)
- Musculoskeletal (eg, arthralgia, arthropathy, myalgia, frank arthritis, avascular necrosis)
- Dermatologic (eg, malar rash, photosensitivity, discoid lupus)
- Renal (eg, acute or chronic renal failure, acute nephritic disease)
- Neuropsychiatric (eg, seizure, psychosis)
- Pulmonary (eg, pleurisy, pleural effusion, pneumonitis, pulmonary hypertension, interstitial lung disease)
- Gastrointestinal (eg, nausea, dyspepsia, abdominal pain)
- Cardiac (eg, pericarditis, myocarditis)
- Hematologic (eg, cytopenias such as leukopenia, lymphopenia, anemia, or thrombocytopenia)

In patients with suggestive clinical findings, a family history of autoimmune disease should raise further suspicion of SLE.

Diagnosis

The presence of 4 of the 11 American College of Rheumatology (ACR) criteria yields a sensitivity of 85% and a specificity of 95% for SLE**(American College of Rheumatology, 2012)**.

When the Systemic Lupus International Collaborating Clinics (SLICC) group revised and validated the ACR SLE classification criteria in 2012, they classified a person as having SLE in the presence of biopsy-proven lupus nephritis with ANA