Update on Immune Mechanisms in Systemic Lupus and Lupus Nephritis

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease defined by immune response affecting multiple organs of which lupus nephritis (LN) is most common and a predictor of poor overall outcome of SLE patients [1-3]. The immunopathological features of SLE are based on a loss of tolerance for nuclear antigens, which becomes clinically detectable by the presence of anti-nuclear antibodies with specificities against Ro, -Sm, dsDNA, histones antibodies, etc. The presence of these autoantibodies signifies autoimmunization and can act as diagnostic marker. Of a note, a diagnosis of SLE needs further clinical signs and symptoms of autoimmune disease such as fever, fatigue, skin rashes, and arthralgia [4,5]. With the advancement of knowledge, lupus is no longer considered the 'chameleon of medicine'. Significant progress has been made in decoding the pathogenesis of SLE and lupus nephritis. Here we provide an update on the immunomolecular and pathological aspects of lupus and lupus nephritis.

Extra renal Pathomechanism of Lupus Nephritis

Dysregulation of apoptosis and dead cell opsonisation

As mentioned before SLE develops as a consequence of loss-of-tolerance to self, ubiquitous nuclear autoantigens, which could be considered as an outcome of the immunization process. Some variants in the genome can compromise the processes of immunologically silent death (apoptosis) [6,7], and dead cell clearance (opsonisation) [4], e.g. the deletion of lymphocyte precursors during thymic-negative selection. Any impairment of these processes can lead to secondary cell necrosis, which implies rupture of the plasma and nuclear membranes and the release of nuclear autoantigens into extracellular tissue compartments and in the circulation (Figure 1). Additional factors such as trauma or sunburns enhance the burden of necrotic cells in the extracellular compartment due to which some individuals fail to clear these extracellular nuclear materials by phagocytic cells [4]. This feature also attributes to the insufficient clearance of neutrophil extracellular traps (NETs) during infections or sterile forms of inflammation [5]. Genome-wide association studies revealed a link between genetic susceptibility and LN in SLE and also demonstrates that this susceptibility varies from one individual to another individual [7]. For example, podocyte genes, primarily affecting the glomerular filtration barrier, may also incline to proteinuria, or hematuria can be affected by collagen IV gene variants [8,9].

Molecular mimicry of antiviral immunity

During the viral infection, Toll-like receptors recognizes the viral particles and elicits antiviral immunity. Dysregulation of apoptosis releases extracellular nuclear elements (nucleic acids and proteins) which mimic structural and molecular features of virus and elicits antiviral like immunity also known as ‘pseudo’ antiviral response [10,11]. Therefore, clinical manifestations of viral infections and SLE resemble each other [12]. Release of small nuclear RNA by pathogens activates dendritic cells and macrophages [13,14]. Renal glomerular endothelial cells and mesangial cells do perceive nucleic acids and also release type I interferons, which inside the glomerulus promote podocyte loss and glomerular scarring [15-19].

Aberrant lymphocyte immunity

Dendritic cells overcome their limited lifespan by the persisting activation by endogenous RNA and DNA autoantigens via TLR7 and TLR9, which also makes them resistant to glucocorticoid-induced death [20]. These nuclear autoantigens also activate clonal expansion of the respective autoreactive T and B cell subsets, involving affinity maturation of germinal center B cells, maturation into plasma cells and immunoglobulin class switch from IgM to high-affine IgG [21]. Memory T cells and long-lived plasma cells residing in bone marrow niches assure a life-long memory that is resistant to standard immunosuppressive therapies (Figure 2). This process is conceptually identical to any immune memory obtained by previous vaccinations [22].
Environmental contributors of LN

The major contribution of the environment comes from viral and bacterial infections. IFN-α is the primary cytokine released upon viral infection triggering antiviral immunity and lupus activity [23]. In contrast, bacterial infections induce a nonspecific immunostimulatory effects, with transient expansion of autoreactive lymphocyte clones. Bacterial infections also contribute to proteinuria and renal damage through their products stimulating both intrarenal immune cells and other renal cell types. Ultraviolet rays act as another environmental factor contributing to SLE activity by inducing keratinocyte cell death [24]. This cell death in patients with a significant dead cell clearance defect increases the burden of extracellular nuclear antigens [2]. Drug induced SLE involves inhibition of methyl-transferases, a process that enhances the unmasking of endogenous nucleic acids and the activation of TLR7 and TLR9 [25,26]. It has been observed that hormones do play role in the manifestation of LN, progesterone and estrogens stimulate the sex hormone–dependent immunoregulatory pathways [27].

Intrarenal Pathomechanisms of Lupus Nephritis

Various intrinsic renal immunological mechanisms attribute to the development of LN. These include in situ immune complex (IC) formation, complement cascade activation, and pathological manifestations due to compartment-specific glomerular injury.

LN pathogenesis due to immune complex formation

Immune complex depositions with various components such as polyclonal autoantibodies, complement cascade contributes to the intrarenal pathogenesis of LN [28]. Compartment-specific deposition of IC determines the class and severity of the LN [29]. Mesangium being the primary site of IC deposition designates the class I and II lesions with mesangial cells injury and mesangial cell hyperplasia. Subendothelial IC classify class III and IV with endothelial cells protuberance and coalesce, which will contribute to decline in glomerular filtration rate and promotes to endstage renal disease Subepithelial IC deposits account for class V lesions contributing to podocyte injury and its related glomerulosclerosis with extensive proteinuria (Figure 3) [30].

Leukocyte infiltration and intrarenal inflammation

During the disease pathogenesis, various cytokines, chemokines, and adhesion molecules induce immune cell infiltration into the kidney namely cytotoxic T cells, Th17 T cells, macrophages and B cells [31]. The kind of cytokine or chemokine involved determines compartment-specific recruitment of leukocytes. For example, the CC-
chemokine CCL2 promotes CCR2+ proinflammatory macrophages and T cells into the glomerulus and the tubulointerstitium, whilst CCR1+ cells home to interstitial compartment only [32]. Infiltrating leukocytes also may form de novo perivascular tertiary lymphoid organs within the kidney and allow the clonal expansion and somatic hypermutation of B cells at T-cells vicinity followed by local inflammation [33-35]. Necroinflammation, a process of necrosis related inflammation or inflammation related necrosis may be initiated by these infiltrating leukocytes [36]. Extracellular histones act as another important element in initiating necroinflammation [37]. During necrosis histones are released into the extracellular space and evoke cytotoxic effects on nearby cells by plasma membrane disruption [38]. Another important source of extracellular histones comes from the neutrophils undergoing NETosis resulting in the damage of endothelial cells, eg, in crescentic glomerulonephritis [39,40]. This process is under tight regulation. For instance, interaction of pentaxin-3 produced by renal cells with P-selectin expressed on endothelial cells regulates leukocyte recruitment [41,42].

**Dual facets of fibrosis/scarring**

Renal functional compartments are stabilized by mesenchyma. Glomerular tuft capillaries are stabilized by mesangial cells, the tubular part of the nephrons by interstitial fibroblasts, and pericytes of mesenchymal origin protect vascular structures upon kidney injury [43]. Tissue injuries activate mesenchymal elements to proliferate and to produce extracellular matrix components to stabilize the injured tissues as a scaffold for [44]. If irreversible loss of parenchymal elements occurs, the task of refilling the injured space will be taken up by mesenchymal elements [45].

Mesenchymal healing involves multiple elements, as for instances mesangial cells, extraglomerular mesangial cells or even derived from the bone marrow [46-50]. Upon glomerular injury, mesangial hyperplasia occurs as a hallmark [51], parietal epithelial cells (PEC) contribute to scar formation when podocyte regeneration remains insufficient. Inability of PECs to replace the lost podocytes, lead to Bowman’s capsule focal adhesion formation followed by PEC migration and extracellular matrix formation at glomerular tuft resulting in segmental sclerosis also known as focal segmental glomerulosclerosis (FSGS) [52]. These observations imply a dual nature of PECs [53]. Glomerular capillaries and Bowman’s capsule adherence prevents the protein loss at denudated GBM by stabilizing the glomerular tuft [54]. This process promotes further podocyte loss due to additional stress by hyperfiltration and commute to global glomerulosclerosis [55].

**Summary**

The pathogenesis of LN is based on extra- and intrarenal mechanisms. Loss-of-immune tolerance and systemic autoimmunity against nuclear autoantigens are based on variable genetic variants, which differ from one patient to the other. These genetic variants interfere with vital aspects of cells, such as cell death (apoptosis) and dead cell clearance, resulting in loss of tolerance to self-antigens. Another important contribution to lupus nephritis comes from the pseudo viral immunity or molecular mimicry of viral immunity, which provokes innate and adaptive immunity by Toll-like receptors such as TLR-3, 7 and 9. Intrarenal inflammation and the its binding of autoantibodies to intrarenal nuclear autoantigens, complement cascade and FcR activation resulting in local inflammation, tissue scaring.

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