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EDITORIAL

Lupus nephritis - alarmins may sound the alarm?

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Abstract

A growing body of literature has documented the elevated levels of the alarmin HMGB1 in lupus skin and serum. Two recent reports highlight the increased expression of HMGB1 in lupus nephritis, within the diseased kidneys or in the urine. Taken together with previous reports, these findings suggest that the interaction of HMGB1 with a variety of receptors, including receptor for advanced glycation end products (RAGE) and Toll-like receptors, might play a role in the pathogenesis of lupus nephritis. These studies introduce urinary HMGB1 as a novel biomarker candidate in lupus nephritis. Whether alarmins would be effective in sounding the alarm at the incipience of renal damage remains to be ascertained.

The recent report by Abdulahad and colleagues [1] that urinary HMGB1 may be a maker of lupus nephritis is the latest addition to a growing body of literature implicating a central role for this molecule in systemic lupus erythematosus (SLE). HMGB1 is a prototype of the alarmin family of molecules, implicated as autoadjuvants that serve to amplify the immune response. Perhaps the first link to SLE emerged in 2005 when it was first reported to be expressed at high levels in the skin of cutaneous lupus [2]. Thereafter, it was noted to be elevated in the serum of SLE patients as well, using an immunoblot approach [3]. Following that, there has been a steady trickle of reports validating the elevated levels of serum HMGB1 in SLE, as in the latest two studies [1,4]. Indeed, elevated HMGB1 has been noted not only in the serum, but also in the kidneys of patients with lupus nephritis, as well as other chronic renal diatheses [4,5].

How HMGB1 impacts the pathogenesis of SLE has been extensively studied. We now know that cell death as well as cell activation by inflammatory triggers can promote the translocation of nuclear HMGB1 to the cytoplasm and its release into the extracellular milieu. Binding of released HMGB1 to a variety of receptors, including receptor for advanced glycation end products (RAGE), Toll-like receptor (TLR)2, TLR4, TLR9, Mac-1, syndecan-1, phosphacan protein-tyrosine phosphatase-ζ/β, and CD24, evokes the transcription and elaboration of several pro-inflammatory cytokines and type I interferons. Hence, the elevated levels of HMGB1 may, in part, explain the prominent type I interferon signature that characterizes SLE, as well as the documented increases in multiple pro-inflammatory cytokines. Based on the findings from multiple studies, elevated HMGB1 activity may also explain the phenotypic changes noted in dendritic cells and T cells in SLE, at least in part.

Two additional studies further incriminated HMGB1 in the pathogenesis of lupus. Tian and co-workers [6] demonstrated that the ability of DNA-containing immune complexes from SLE sera to stimulate plasmacytoid DCs and autoreactive B cells was contingent upon HMGB1 binding to immune complexes. Thus, HMGB1-DNA-anti-DNA complexes played a critical role in amplifying the auto-inflammatory cascade, by engaging the corresponding receptors for DNA (that is, the B-cell receptor and TLR9) and HMGB1 (that is, RAGE, TLRs or other receptors). A year later, Voll's [7] group demonstrated that the injection of nucleosomes from apoptotic cells could elicit lupus in mice, and implicated a role for HMGB1-bound nucleosomes in this process. Collectively, these studies substantiate the autoadjuvant role of HMGB1 in driving systemic lupus.

The recent reports on lupus nephritis [1,4] shift our focus to the kidneys, in the context of SLE. It is evident from these studies that HMGB1 can be expressed in the kidneys and urine of patients with lupus nephritis, correlating with disease activity. How HMGB1 expressed within the kidneys might amplify local inflammation is an open question. We know that the receptors for HMGB1 are expressed on multiple intrinsic renal cells, including proximal tubular cells, podocytes, mesangial cells and endothelial cells, in addition to their expression on the infiltrating macrophages. Indeed, increased expression of RAGE may play a role in several chronic kidney diseases, including lupus nephritis [8]. Moreover,

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genetic polymorphisms in RAGE have also been implicated in SLE [9]. Taken together, one can readily envision up-regulated HMGB1, RAGE and possibly other receptors working together to amplify inflammation within the glomerular and renal tubular milieu. In terms of the pathogenic mechanisms at play within the kidney, several questions remain. What are the dominant cells expressing HMGB1 and its receptors within a lupus-afflicted kidney? Is the HMGB1 predominantly bound to nucleosomes or anti-DNA/antigen complexes? What is the predominant source of the urinary HMGB1? If it is intra-renal, is HMGB1 arising from the apoptosis of particular resident cells, or from activation of particular cells? Could HMGB1/RAGE interaction be therapeutically targeted in lupus nephritis?

Besides its potential pathogenic role, urinary HMGB1 may also emerge as a useful biomarker of lupus nephritis, though many challenges remain. First, it would be important to transition to an assay platform that allows for large scale rapid diagnostics; this is particularly relevant given that most discriminatory assays for HMGB1 thus far have been based on immunoblots, not ELISA. Second, longitudinal studies are in order, to ascertain if urine HMGB1 levels can predict disease activity over time. Third, it would be of interest and importance to learn what parameters of renal pathology are best predicted by urinary HMGB1. Finally, it is critical to compare the predictive performance of urine HMGB1 against prevailing yardsticks and other competing biomarker candidates on the horizon.

The alarmin HMGB1 certainly looks attractive as a therapeutic target and disease biomarker, as discussed [10]. Alarmins were so named since they alert the immune system when danger is sensed. Whether they would be equally effective in sounding the alarm at the incipience of renal damage remains to be ascertained.

Abbreviations

SLE, systemic lupus erythematosus; TLR, Toll-like receptor.

Competing interests

The authors declare that they have no competing interests.

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