MACROPHAGE ACTIVATION IN POLYINOSINIC-POLYCYTIDYLIC ACID-ACCELERATED MURINE LUPUS NEPHRITIS

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Background and objectives The inflammatory phase of lupus nephritis is characterised by immune cell infiltrates and develops following the deposition of immune complexes in the kidneys. Immune complex deposition is not sufficient to produce nephritis as first shown by studies of FcRγ-/- NZB/W mice (Clynes R et al 1998, Bergtold A et al 2006). The authors have recently identified a population of kidney macrophages, characterised by low surface expression of the myeloid cell marker GR1, which was required for aggressive proliferative lesions and metalloproteinase activity in poly I:C-induced and interferon-α-mediated murine lupus nephritis. This population expressed IL-10, IL-1 receptor antagonist, metalloproteinases and growth factors (Triantafyllopoulou A et al PNAS 2010). Here, the authors aimed (A) to identify transcriptional mediators of macrophage activation in lupus nephritis kidneys and (B) to analyse blood monocyte expansion after the onset of proteinuria.

Materials and methods The authors used the poly I:C model of accelerated lupus nephritis, as previously described. NZB/W mice with spontaneous proteinuria of equal duration, as well as age-matched non-proteinuric mice were used as control groups. Proteinuria was measured by dipstick. Renal disease was assessed by histopathology. Monocyte/macrophage populations in peripheral blood or single cell suspensions of kidneys were analysed by flow cytometry. Gr1low macrophages were analysed by microarrays and real-time PCR (n=2-4 mice per group).

Results GR1 low monocytes preferentially expand in the peripheral blood of poly I:C-treated nephritic mice as early as after 4 days of proteinuria. Several transcription factors associated with myeloid cell differentiation and inflammatory regulation were identified. Upregulation of IRF-7 was of particular interest and was confirmed by real time PCR.

Conclusions The expansion of GR1low monocytes in a macrophage-driven model of crescentic lupus nephritis occurs at an early stage of disease in the peripheral blood compartment, thus suggesting that monocytes may be activated in lupus nephritis before their entry in the kidneys. Upregulated IRF-7
expression in infiltrating kidney macrophages suggests that macrophage-derived type I interferons may be crucial for proliferative lesions and accelerated glomerular damage.