for IgG in humans, we included transgenic mice expressing FcyRIIA to our in vivo mechanistic investigations. Platelet activation and mitochondrial release were monitored upon intravenous injection of synthetic ICs in wild type (WT) and transgenic (Tg) FcyRIIA mice.

**Results** We found that on activation, platelets relocate their mitochondria toward the cell membrane and then release respiratory-competent mitochondria into the extracellular milieu, both as free organelles and encapsulated within vesicles called microparticles (MP). Extracellular mitochondria were internalised by bystander leukocytes and, importantly, induced leukocytes rolling and adhesion to the blood vessel wall, suggesting that neutrophils and/or endothelial cells are activated by extracellular mitochondria. Activated platelets were more abundant in SLE patients than control subjects, and were associated with IgG. Extracellular mitochondria, both encapsulated in platelet MPs or naked, were also observed in blood circulation in SLE, and were frequently associated with IgG. Mechanistically, ICs present in blood induce profound cell activation, which is dependent on platelet FcyRIIA and its signalling cascade.

**Conclusions** Platelets represent an important source of mitochondria, which release in blood upon stimulation of FcyRIIA, might promote systemic inflammation in SLE. Whether the blockade of FcyRIIA might represent an attractive avenue in SLE research, and whether platelet activation markers and extracellular mitochondria might be utilised as potential biomarkers for the stratification of lupus patients needs to be further considered.

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## II-12 CSF-1 AND IL-34: DISTINCT POTENTIAL BIOMARKERS FOR LUPUS

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**Background** A noninvasive means to predict the onset and recurrence of lupus is needed to optimise and individualise treatment. Macrophages (Mø) are prominent in inflamed tissues targeted for destruction in SLE. We hypothesised that the principal molecules required for Mø survival and proliferation are biomarkers for SLE. CSF-1 and IL-34 are promising candidates as both (i) bind to cFMS expressed by Mø, thereby promoting Mø survival and proliferation and (ii) promote destructive inflammation. However, IL-34 and CSF-1 have differing functions, which may be related to IL-34, not CSF-1, binding to a second receptor and distinct spatial temporal expressions.

**Materials and methods** We analysed serum and urine CSF-1 and IL-34 levels in SLE patients with nephritis (LN), arthritis (LA), cutaneous and serositis compared with healthy controls in two large cohorts (ELISA). While serum and urine CSF-1 expression is elevated in each manifestation, CSF-1 is notably higher in LN. In contrast, serum IL-34 expression is dramatically higher in LA, not LN. Thus, we probed for CSF-1 and IL-34 expression in LN (kidney) and LA (synovium). Moreover, we longitudinally tracked serum CSF-1 and IL-34 prior to LN (biopsy proven), with disease activity including flares and during LA in comparison to disease activity

**Results**

- LN. CSF-1 and IL-34 are expressed in the same and different renal tubular epithelial cells in LN. Elevated serum or urine CSF-1, not IL-34, levels correlate with increasing intra-renal CSF-1 expression and histopathology index. Longitudinally tracking serum CSF-1, not IL-34, levels heralds the initial onset of nephritis and a rise in serum or urine CSF-1 predicts LN recurrences before clinical evidence of renal dysfunction and conventional serologic measures.
- LA. IL-34, not CSF-1, expression is higher in synovial fluid and synovium in LA compared to osteoarthritis and healthy controls and correlates with magnitude of intra-synovial leukocytes. Moreover, intra-synovial IL-34 expression is similar in LA and rheumatoid arthritis. Longitudinally monitoring serum IL-34, not CSF-1, levels track with clinical disease activity in LA and RA.

**Conclusions** Serial monitoring a rise in serum or urine CSF-1, not IL-34, in SLE reflects renal histopathology and clinical disease activity and the onset and reoccurrences of LN more accurately than conventional laboratory measures. While serial monitoring a rise in serum IL-34, not CSF-1, reflects clinical disease activity in LA. Thus, CSF-1 and IL-34 are inexpensive and accurate potential biomarkers for LN and LA, respectively.

## II-13 SUPPRESSION OF SYSTEMIC AUTOIMMUNITY BY THE INNATE IMMUNE ADAPTOR STING

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**Background** Cytosolic DNA-sensing pathways that signal via the adaptor Stimulator of Interferon Genes (STING) mediate immunity to pathogens and have also been known to promote autoimmune pathology in DNAseII/III-deficient mice. However, the role of these pathways in systemic models of autoimmunity is unexplored. We hypothesised that cytosolic DNA sensing pathways contribute to the pathogenesis of autoimmune disease. Surprisingly, we report here that STING *potently* suppresses inflammation in several models of systemic lupus erythematosus (SLE).

**Materials and methods** A controlled F2 intercross between heterozygote STING$^{\pm}$ lpr$^{\pm}$littermates generated STING-deficient lupus-prone mice homozygous for deficiency in Fas as well as STING (STING/lpr, n ≥10) or wild type for STING (WT/lpr, n ≥10). Mice were analysed at 16 wk of age. A similar F2 cross was set up for IRF3$^{-/-}$ and MRL/lpr mice as well as STING$^{-/-}$ and C57Bl/6$^{lpr/lpr}$ and analysed as above for STING/lpr mice (n ≥10 per group). C57BL/6, cGAS$^{-/-}$, Unc93b$^{3d/3d}$, and STING$^{-/-}$ mice were injected i.p. with TMPD and evaluated at day 14 and 6 months post injection.