as compared to controls. A combination of inhibitors and gene expression studies showed that glucose oxidation rather than aerobic glycolysis is a major metabolic pathway of lupus T cells. In vitro, both metformin and 2-DG blocked IFNγ production and metformin increased IL-2 production. In vivo, a combined treatment with metformin and 2-DG normalised T cell metabolism and reversed disease phenotypes in all four lupus mouse models. Remarkably, the number of Treg cells, which correlates with disease severity in patients, was normalised by the combination treatment in every model. Further, excessive IFNγ production by CD4 T cells from SLE patients was also normalised by metformin. Finally, CD4+ T cells from lupus patients showed a metabolic signature with over-expression of genes promoting glucose utilisation, mitochondrial oxidative phosphorylation and sterol synthesis.

Conclusions The combination of a glucose inhibitor with metformin restores T cell function and reverses disease across diverse mouse models of SLE, and metformin treatment normalises the function of T cells from SLE patients. We propose that T cell metabolism may serve as a biomarker of disease activity and provides a novel target for immune intervention in SLE.

Acknowledgements This work was supported by NIH grants R01 AI045050 and ALR-TIL 000075018 to L. Morel.

Background Systemic lupus erythematous (SLE) is a multifactorial autoimmune disease, in which infections are considered to play a pathogenic role, but the cellular and molecular culprits remain unknown. Bacterial biofilms are multibacterial cellular communities important in the establishment of chronic infection by pathogens. Bacteria produce amyloids, complex proteins with a conserved beta sheet structure, that strengthen the extracellular matrix of their biofilms. We have reported that bacterial and eukaryotic DNA is incorporated into curli fibres, functional bacterial amyloids present in Salmonella and E. coli biofilms. We found that curli/DNA complexes from biofilms activate conventional dendritic cells leading to production of pro-inflammatory cytokines, including Type I interferons, in vitro and in vivo, indicating that curli are a new class of danger signals. Lp. infections with curli-expressing S. Typhimurium or E. Coli Nissle, and also systemic administration of curli/DNA complexes purified from Salmonella biofilms accelerated onset in lupus-prone NZBxW/F1 mice and triggered autoantibodies production in non-predisposed mice, suggesting curli/DNA complexes as novel players in SLE pathogenesis.

Materials and methods In order to determine the cellular and molecular players in the acceleration of lupus by curli-expressing infections, bone marrow-derived cultures of conventional dendritic cells and macrophages were generated in vitro and B cells were isolated ex vivo from NZBxW/F1 lupus-prone mice, TLR-deficient mice and wild-type mice and stimulated with curli/DNA complexes purified from Salmonella biofilms. Moreover, lupus prone and control mice were infected i.p. and oral gavage with curli-expressing or curli-deficient S. Typhimurium and the effects on dendritic cells, macrophages, and B cell activation, and production of autoantibodies were studied. A novel ELISA was developed to measure anti-curli antibodies in SLE patients and infected mice.

Results We found that Curli and DNA synergistically activate innate and adaptive immune cells, in vitro and in vivo, via TLR2 and TLR9, leading to a Type I interferon response. We found that curli/DNA complexes can directly stimulate proliferation and