paramount importance. In addition to enhance our basic knowledge of podocyte biology, our results may provide novel targets for intervention and new urinary biomarkers to monitor therapeutic responses.

Interferons

I-01 NOVEL MECHANISM OF ACTION OF ANTI-MALARIAL DRUGS IN THE INHIBITION OF TYPE I INTERFERON PRODUCTION

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Background Anti-malarial drugs (AMD) such as Hydroxychloroquine (HCQ) and Quinacrine (QC) are effective in the treatment of skin rash and arthritis in systemic lupus erythematosus (SLE). However, which mechanism(s) are responsible for their beneficial action is uncertain. Type I interferon, (IFN-I) is strongly implicated in the pathogenesis of SLE and 'interferonopathies' such as Aicardi-Goutieres Syndrome (AGS) A new DNA activated IFN-I pathway, cyclic GMP-AMP (cGAMP) synthase (cGAS), was recently discovered and linked to AGS and mouse models of Lupus. Preliminary data indicate that a subset of SLE patients also have elevated cGAs and cGAMP (the cyclic dinucleotide responsible for activation of STING and IFN-I.
Materials and methods *In silico* structure-based drug screening were provided by the CANDO docking algorithm. Predictions made by CANDO were confirmed by Autodock Vina and analysed via PyMOL. cGAS activity/cGAMP production was analysed by Thin Layer Chromatography (TLC). DNA-binding to cGAS in the presence or absence of AMD was determined by an Electrophoretic Mobility Shift Assay (EMSA). Following DNA cell transfections, cytokines were quantified by qPCR, ELISA or an ISRE-luciferase reporter assay. cGAMP in patient samples was quantified by mass spectrometry.
Results In silico screening of drug libraries identified several antimalarial drugs (AMD) which could potentially inhibit cGAS activity by interacting with cGAS/DNA dimer complex. Electrophoretic Mobility Shift Assay revealed that AMD disrupted the double stranded DNA-cGAS complex in a dose dependent manner. These AMD also inhibited IFN-I expression in THP1 cells transfected with dsDNA and in 293 T cells transfected with cGAS/STING plasmids validating that cGAS is a target of AMD. We synthesisedsynthesized several new AMD. One of these compounds, X6, had excellent water solubility and cell penetration. X6 localised to the cytosol and had a lower toxicity profile compared to QC. Biochemical and cellular assays revealed that X6 was a more potent inhibitor of IFN-I production than HCQ. We also validated mechanism of action and proof of concept in the animal model of AGS.
Conclusions Our studies identify new DNA sensor cGAS as a target of AMD activity, which provide a novel mechanism of action of these AMD. We have synthesised new AMD like drugs that are also able to inhibit cGAS as well as Toll pathways. These drugs could be beneficial for the treatment of AGS and/or Lupus.

I-02 INCREASED INTERFERON β EXPRESSION AND SENESCENCE ASSOCIATE SECRETORY PHENOTYPE IMPAIR THE IMMUNOMODULATORY FUNCTION OF BONE MARROW MESENCHYMAL STROMAL CELLS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background Interferon I (IFN-I) signature is an important feature of systemic lupus erythematosus (SLE). Our previous study identified an IFN-I signature in both bone marrow (BM) and peripheral blood of SLE patients. The overlapping roles of IFNα subtypes and disappointing results with IFNα subtype blockade in clinical trials calls for alternative targets and recent findings centred on IFNβ suggest that it is an important candidate molecule in SLE. IFNβ has distinct features as compared to IFNα: higher affinity binding to the shared IFN-I receptors, IFNβ specific gene transcripts, induction of senescence in fibroblast. As a critical non-hematopoietic component in BM, MSCs create a microenvironment for hematopoiesis and immunity. MSCs display robust immunomodulatory properties. MSC defects have been suggested in autoimmune diseases. Taking into consideration the importance of IFNβ and MSCs in autoimmune diseases, here we set out to investigate the role of IFNβ and MSC in SLE pathogenesis, and the underlying mechanisms.
Materials and methods BM MSCs were isolated with FicollPaque gradient centrifugation (1.073 ± 0.001 g/ml) and phenotyped using flow cytometry. Various *in vitro* approaches including confocal immunofluorescence immunocytochemistry, real-time PCR, western blotting, comet assay, beta-galactosidase assay and RNA interference were applied.
Results We compared 6 age paired BM aspirates from healthy controls and SLE patients. SLE MSCs show reduced proliferation rate, increased production of reactive oxygen, and increased DNA damage and repair (DDR), which leads to p53 mediated senescence associate secretory phenotype (SASP) and inhibited immunomodulatory factors production. IFNβ increased 5 folds and IFNβ specific genes are significantly elevated ($p < 0.05$) in SLE BM MSCs and are closely correlated to the level of Mitochondrial Antiviral Signalling Protein (MAVS) ($r > 0.9$, $p < 0.01$), an intracytoplasmic nucleic acid sensor. Silencing MAVs inhibits IFNβ expression and reverses SASP in SLE MSCs.
Conclusions SLE is associated with elevated IFN-I in BM. BM MSCs produce IFNβ, have increased DDR and SASP. Thus an IFNβ positive feedback loop forms in SLE BM MSCs. By silencing MAVS, also named Interferon Beta Promoter Stimulator Protein 1, IFNβ expression is inhibited and IFNβ positive feedback loop is disrupted. Moreover, SASP is rescued by MAVs blockage in SLE BM MSCs. Our novel findings of the IFNβ positive feedback loop and related SASP in SLE BM MSCs shed light on SLE pathogenesis. In addition, our study has also revealed the essential role of MAVS in IFNβ positive loop, and thus provided a new potential therapeutic target for SLE treatment.