

Innate Immunity

II-01 AN OESTROGEN RECEPTOR ALPHA FUNCTIONAL MUTANT IS PROTECTIVE IN MURINE LUPUS

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Background Systemic lupus erythematosus disproportionately affects females. We previously showed that a functional knockout of oestrogen receptor alpha (ER α KO) resulted in significantly reduced renal disease and increased survival in murine lupus. Dendritic cell (DC) development, which requires both oestrogen (E2) and ER α is impacted, as is activation status and cytokine production. Due to altered hormonal feedback loops, ER α KO mice have hypergonadism and partial endocrine sex reversal. Since elevated E2 and T2 levels may have immunomodulating effects, we studied the phenotype of the lupus-prone ER α KO mouse following ovariectomy (OVX) \pm E2 replacement to preserve a physiologic hormonal state. In parallel, we investigated the impact of an ER α complete knockout on lupus disease expression.

Materials and methods ER α KO (functional mutant) and Ex3a (null mutant) strains were backcrossed onto the NZM2410 lupus-prone background. Mice underwent OVX or not, and were E2-repleted or not. Urine and blood were collected at 2 week intervals, and mice were sacrificed at 32 weeks, or earlier if they had high proteinuria or >10% weight loss. Bone marrow was isolated and cultured for 7 days with Flt3L to enrich for DCs. Kidney and spleen single cell suspensions were also isolated. Cells were analysed by flow cytometry.

Results Lupus-prone ER α KO mice were protected from disease expression (no early deaths; no proteinuria at 32 weeks) if they were either unmanipulated or if they were both ovariectomized and E2-repleted (Figure 1). These mice also had fewer inflammatory cDCs (CD11c+ \pm CD11b+) from Flt3L-cultured bone marrow, or *ex vivo* spleen or kidney cells). Interestingly, protection was lost after OVX if no E2 pellet was administered, suggesting that the protective effect requires E2 in the system (despite the lack of a functional ER α). A protective effect was *not* observed in ER α null lupus-prone mice (Ex3a) when they were similarly OVX'd and E2-repleted.

Conclusions These data suggest that in an oestrogen-replete environment, the *presence* of the ER α KO protein (AF-1 mutant) confers protection from lupus disease expression, partially via impacting DC number and subset, compared to mice expressing full length ER α or a full-length knockout of ER α .

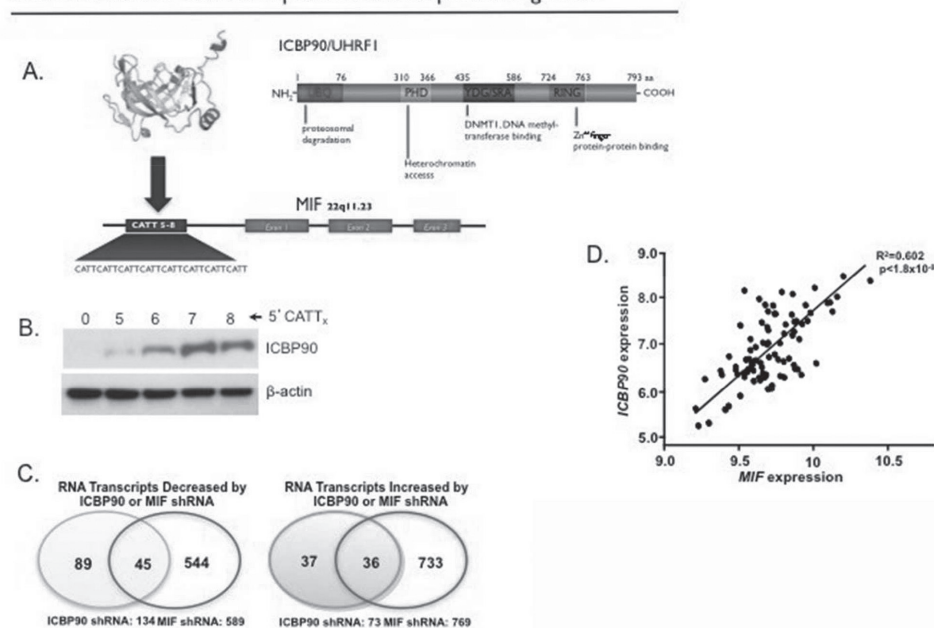
II-02 APPROACHING THE PRECISION THERAPY OF SLE AT THE MIF LOCUS

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Background Gene association studies examining functional polymorphisms in the immunoregulatory cytokine MIF (macrophage macrophage inhibitory factor, rs5844572) have shown that SLE patients with end-organ sequelae have an increased frequency of high expression MIF genotypes when compared to patients without end-organ involvement. Plasma MIF levels and TLR-stimulated MIF production also reflect underlying MIF genotype. Among activities relevant to autoimmunity, MIF counter-regulates the immunosuppressive action of glucocorticoids, inhibits

ICBP90 is the MIF CATTx-dependent Transcriptional Regulator



Abstract II-02 Figure 1 A). Ribbon and domain structure of ICBP90 and its MIF promoter target. B). -794 MIF CATT₅₋₈ length-dependent binding of ICBP90. C). High concordance between ICBP90 and MIF-regulated downstream transcripts. D). Correlation plot of ICBP and MIF expression in human autoimmune synovitis.