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 (ERαKO) resulted in significantly reduced renal disease and increased survival in murine lupus. Dendritic cell (DC) development, which requires both oestrogen (E2) and ERα is impacted, as is activation status and cytokine production. Due to altered hormonal feedback loops, ERαKO 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 ERαKO mouse following ovariectomy (OVX) ± E2 replacement to preserve a physiologic hormonal state. In parallel, we investigated the impact of an ERa complete knockout on lupus disease expression.

Materials and methods ERαKO (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 ERαKO 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+ ± 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 ERα). A protective effect was *not* observed in ERα 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 ERαKO protein (AF-1 mutant) confers protection from lupus disease expression, partially via impacting DC number and subset, compared to mice expressing full length ERα or a full-length knockout of ERα.

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

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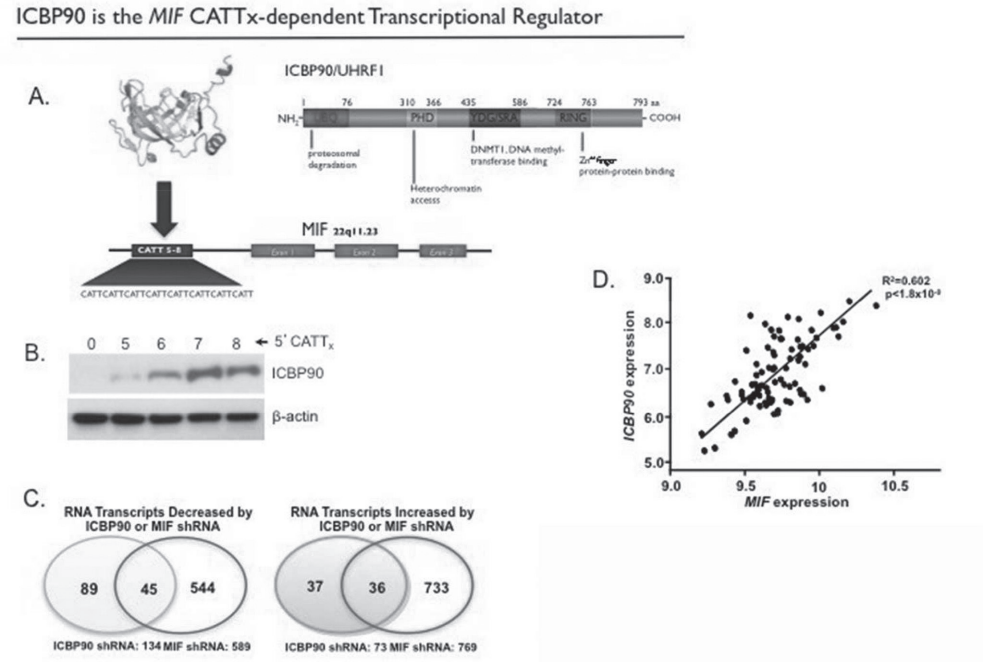
Background Gene association studies examining functional polymorphisms in the immunoregulatory cytokine MIF (macrophage macrophage inhibitory factor, *rs5844572*) have shown that SLE patients with end-organ sequelae have an increased frequency of high expression *MIF* genotypes when compared to patients 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



Abstract II-02 Figure 1 **A**). Ribbon and domain structure of ICBP90 and its MIF promoter target. **B**). -794 MIF $CATT_{5-8}$ 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.