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

Materials and methods ER\(_\alpha\)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\(_\alpha\)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+ ± 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\(_\alpha\)). A protective effect was not observed in ER\(_\alpha\) 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\(_\alpha\)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\(_\alpha\) or a full-length knockout of ER\(_\alpha\).