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Investigation of the role of estrogen-regulated microRNAs in SLE pathogenesis

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterised by the overproduction of inflammatory mediators such as cytokines (e.g. IL-17, IL-23, IL-16), chemokines (CXCL11, IL-8) and type I interferons (IFN) which contribute to disease pathogenesis. The cause of SLE is unknown, but is thought to be multifactorial, with genetic, hormonal and environmental factors all playing a role. Of particular interest, there is a gender bias associated with this condition with females affected at a 9:1 ratio compared to males, implicating a role for estrogen in disease development. A growing number of SLE-associated regulatory RNA species, microRNAs (miRNA), have recently been identified including miR-155, miR-21 and miR-342, all of which are regulated by estrogen and altered in SLE, potentially contributing to disease development and pathogenesis. Thus strong links exist between estrogen-regulated miRNAs and their altered expression in SLE therefore suggesting that understanding what pathways these microRNAs regulate will help our understanding of the role of estrogen in SLE and identify microRNAs that may hold potential as therapeutic targets in SLE. Preliminary studies have identified a panel of 87 novel miRNAs regulated by estrogen in human monocytes. Using qPCR we validated 4 estrogen–regulated miRNAs whose expression was altered in SLE patients. Whilst the targets for these miRNAs have not yet been identified, bioinformatic analysis suggests that a number of these microRNAs target essential components of inflammatory signalling pathways including the proinflammatory cytokine IL-16, levels of which are altered in SLE. Despite this, the exact role, function and regulation of IL-16 in SLE has not yet been determined.

In keeping with this, we aim to investigate the exact pathways through which IL-16 acts in SLE peripheral blood mononuclear cells following stimulation with recombinant IL-16 utilizing PCR, western blots and flow cytometry analysis techniques. This will require the use of numerous flow cytometry antibodies including CD4, CD8, CD11b, CD86, CD14 and CD69 to investigate specific cell subsets on which IL-16 is eliciting a response. Furthermore, we will investigate the effect of IL-16 and associated microRNAs on a murine model of pristane-induced lupus. We therefore hypothesise that alterations in estrogen-regulated miRNA expression in SLE patient immune cells may contribute to disease pathogenesis through the regulation of key inflammatory pathways such as IL-16 production.

Current SLE therapies are aimed at management of symptoms and do not address the underlying mechanisms of disease pathogenesis. Our aim is to elucidate the mechanisms associated with altered estrogen-regulated gene expression and cytokine production in SLE patients with an emphasis on the role of microRNAs here. The long-term aim of this would be the development of more targeted therapeutics. It is also expected that the presence of certain estrogen-regulated miRNAs will then be used as predictors of particular disease phenotypes and related abnormalities. Additionally identification of key estrogen-regulated miRNAs associated with an altered cytokine profile/immune dysfunction in SLE offers the potential to devise novel targeted therapeutics to ameliorate disease inflammation. This may then warrant the repurposing of estrogen modifying drugs such as Fulvestrant approved for use in the treatment of metastatic breast cancer as a potential therapeutic for the treatment of SLE.