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II-17 LUPUSHDL PROMOTES PRO-INFLAMMATORY RESPONSES IN MACROPHAGES THROUGH LOX1R BINDING AND ABROGATION OF ATF3 ACTIVITY

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Background Recent evidence indicates that high-density lipoprotein (HDL) exerts vasculoprotective activities by promoting activating transcription factor 3 (ATF3), leading to down-regulation of TLR-induced inflammatory responses. SLE is associated with increased cardiovascular disease (CVD) risk not explained by the Framingham risk score. Recent studies have indicated oxidised HDL as a possible contributor. We investigated the potential mechanisms by which lupus HDL may lose its anti-inflammatory effects and promote immune dysregulation.

Methods and results Compared to control HDL, SLE HDL activates NF_KB, promotes inflammatory cytokine production, and fails to block TLR-induced inflammation in control macrophages. This failure of lupus HDL to block inflammatory responses is due to an impaired ability to promote ATF3 synthesis and nuclear translocation. SLE HDL-induced pro-inflammatory responses in macrophages are dependent on its binding to lectin-like oxidised low-density lipoprotein receptor 1 (LOX1R), which promotes suppression of ATF3 activity in a ROCK1/2 kinase-dependent manner. This inflammation can be modulated *in vivo* as lupus-prone mice exposed to the HDL mimetic ETC-642 show improved ATF3 induction and significant abrogation of pro-inflammatory cytokines

Conclusions Lupus HDL promotes pro-inflammatory responses, increased NFκB activity and decreased ATF3 synthesis and activity, in a LOX1R- and ROCK1/2 kinase-dependent manner. ETC-642 inhibited both *in vitro* and *in vivo* SLE HDL-induced inflammation.

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II-18 CELL-BASEDTHERAPY IN SYSTEM LUPUS ERYTHEMATOSUS (SLE): EFFECTS ON NEUTROPHIL NETTING

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Background Evidence that mesenchymal stem cells (MSCs) derived from bone marrow, fat and umbilical cord can be used to treat refractory SLE and SLE nephritis is growing. MSCs were originally described as cells from bone marrow that have the capacity to differentiate into bone, cartilage and fat. More recently it has been recognised that all MSCs are peri-cytes and that their greatest potential is because they are pleiotropic and can both sense and repair their environment. We hypothesised that MSCs can reduce neutrophil activation in SLE by inhibiting neutrophil netting thus reducing induction of T-helper follicular cells that promote the development of long-living plasmablasts that can secrete autoantibodies.

Materials and methods We studied neutrophils derived from healthy donors and patients with SLE. Neutrophils were isolated using MACSxpress™ Neutrophil Isolation Kit (Miltenyi) and onto coverslips in 24-well plates and incubated for 1–2 hours with conditioned medium derived from MSCs or control medium. Netting was induced by culture *ex vivo* with 20 nM PMA for 2 hours. Coverslips were fixed in 4% paraformaldehyde and NETs were quantified using anti-human antibody directed against neutrophil elastase colocalizing with extracellular DNA using Hoechst 33342.

Results To date we have optimised the conditions of our assay. Studies are ongoing to determine the effect of MSCs and/or their products on neutrophil netting. Figure 1: seen below are netting neutrophils induced as described above. Assays are underway to determine the effect of MSCs on SLE netting neutrophils *ex vivo*.

Conclusion The possibility that MSCs and/or their products could act both on innate and adaptive immune responses in SLE is appealing. Demonstration of the effect of MSCs on neutrophils is critical in understanding the potential therapeutic role of MSCs in SLE and SLE related organ damage.

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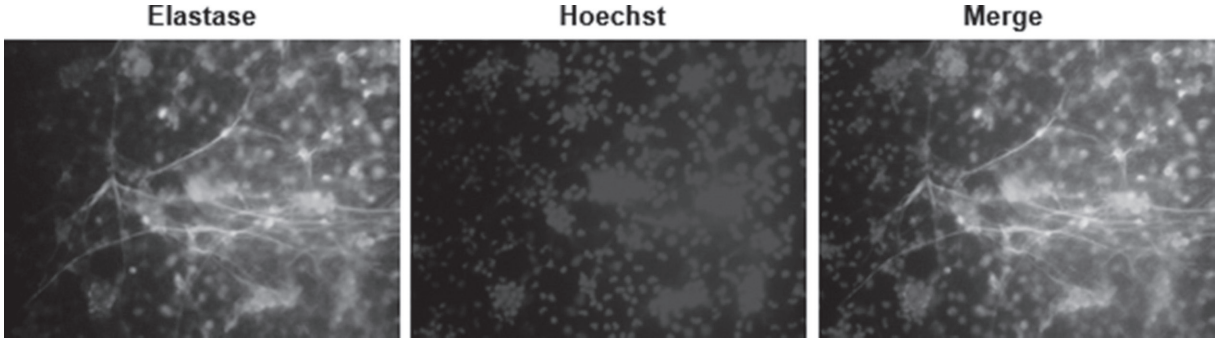

Abstract II-18 Figure 1 Neutrophil Elastase colocalized with extracellular DNA. Control neutrophils were isolated from peripheral blood and stimulated with 10nM PMA for 2 hr at 370C. Cells were fixed and stained for detection of neutrophil Elastase (green) and DNA was labeled with Hoechst 33342 (blue).