# HDL influences CD4 T cell proliferation in SLE and increases TGF-β1 expression: a potential role in the protection from atherosclerosis and autoimmunity

Authors: Fernandes das Neves[1], M; Jury E. C.[2]; Delgado Alves, J[1,3]

[1] Fernando Fonseca Hospital, Medicine 4

[2] University College London, Medicine

[3] CHRC, Campus Nova Medical School, Chronic Diseases Research Center

Dear editor,

Lipid metabolism is crucial for immune cells function in systemic lupus erythematosus (SLE) (1). This is further supported by the associated increased cardiovascular risk (2). Increased levels of plasma membrane cholesterol is known to promote an inflammatory T helper response (3). Animal studies showed that HDL, the main responsible for reverse cholesterol transport from peripheral cells to the liver, can inhibit T and B cell proliferation in stimulated splenocytes (4). In humans, HDL (at the concentration of 50 μg/mL) from healthy young individuals increased the proliferation of in vitro stimulated T cells (5). Animal and human studies on cytokine production have also given diverse results, with some reporting a decrease in proinflammatory cytokine production by monocytes/macrophages in the presence of HDL (6) and others demonstrating that HDL can have pro-inflammatory effects (7). In SLE, HDL levels inversely correlate with disease activity (8). We performed an exploratory study of the role of HDL (pooled from healthy donors) on T cell response in frozen PBMCs from healthy donors and patients with SLE. PBMCs preincubated with and without HDL at different concentrations (50, 100, 300 and 600 μg/mL) were stimulated to measure Ki-67, a proliferation marker, through flow cytometry (figure 1). In healthy donors, HDL did not change CD4+ T cell Ki-67 expression. However, CD4+ T cells from patients with SLE showed a statistically significant reduction in proliferative response with increasing HDL concentration (50 vs 600 μg/mL, $p = 0.019$). PBMCs from patients with SLE showed a decrease in proliferation with the HDL concentration of 600 μg/mL, in comparison with healthy donors, on the brink of significance ($p = 0.068$). This suggests that while T cells from healthy donors are more able to resist alterations in lipid metabolic flux, in patients characterized by cardiometabolic disease such as SLE, alterations in HDL concentration could influence T cell function. HDL increased TGF-β1 in CD4+ T cells from healthy donors and patients with SLE, with a dose-dependent effect (figure 2). The expression of IFN-γ, TNF-α and IL-10 in stimulated CD4+ T cells treated with HDL was not significantly different from untreated cells. This finding suggests an important regulatory role for HDL, without compromising the immune response. This is the first demonstration of an effect of HDL in the production of TGF-β1 by healthy and SLE T cells. The only previous study on the effects of HDL on TGF-β demonstrated that HDL subfraction 3 specifically induces TGF-β2 expression in human endothelial cells (HUVECs) (7). In SLE, several studies showed that TGF- β1 is one of the few cytokines that is downregulated in serum, with a negative correlation between TGF-β1 levels and disease activity and organ damage (8). There is also evidence that lymphocytes from patients with SLE are more resistant to TGF-β1 (9). TGF-β1 was shown to be negatively correlated with the carotid intima-media thickness in these patients (10). Our study identifies a TGF-β-associated link through which HDL can modulate the

immune response and may help understanding why patients with SLE are more prone to accelerated atherosclerosis.

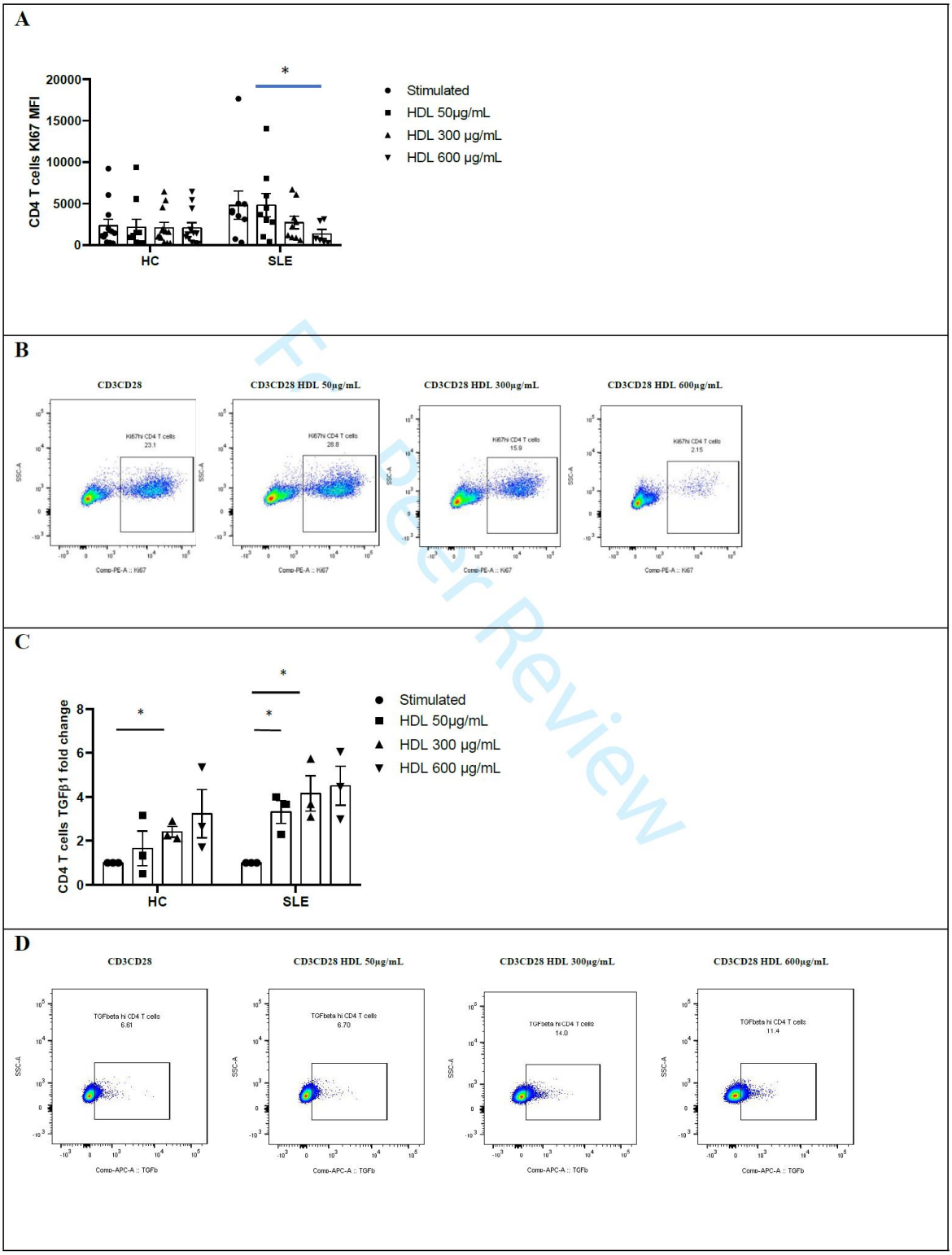


Figure 1: A) Healthy controls (n = 12) and SLE (n = 9) CD4 T cells proliferation measured by Ki-67 MFI, after CD3CD28 stimulation; B) Flow cytometry plots from a sample of a patient with SLE showing an evident decrease in proliferation with crescent HDL concentration in CD4 T cells; C) TGF-β1 expression in CD4 T cells after PMA/ionomycin stimulation.. The fold change in the percentage of

CD4 T cells highly expressing TGF-β1 was calculated to normalize interindividual variations; D) Representative cytometry plots of TGF-β1 expression. Statistical analysis was performed using student t test. Statistical significance was considered when $p < 0.05$ (* $p < 0.05$).

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