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Altered membrane expression levels of distinct CD45RB isoforms are associated with B cell hyperactivity in systemic lupus erythematosus (SLE).

Salvinia Mletzko[1], Marie-Michele Varin[1], Johan Duchene[2], Taher Taher[1], Gary Warnes[3], David A Isenberg[4], Rizgar A Mageed[1]

[1]Bone and Joint Research Unit, William Harvey Research Institute, Charterhouse Square, EC1M 6BQ, United Kingdom, [2]Clinical Pharmacology, William Harvey Research Institute, Charterhouse Square, EC1M 6BQ, United Kingdom, [3]Flow Cytometry & Imaging Core Facilities, Institute of Cell and Molecular Science, 4 Newark Street, E1 2AT, United Kingdom, [4]Centre for Rheumatology Research, Dvision of Medicine UCL, 46 Cleveland Street, W1T 4JF, United Kingdom

SLE is a chronic inflammatory disorder associated with B cell hyperactivity and the production of auto-antibodies. Previous studies have revealed diminished cellular levels of the Src family kinase Lyn, altered levels of CD45 isoform expression, and the translocation of a low MW isoform of CD45 into membrane signalling domains. In this study we report data showing that B cells in SLE patients are characterized by increased numbers of cells that express low levels of exon B containing isoforms of CD45, which are generated by alternative splicing of the gene. Further, we show that the majority of $CD45RB^{low}$ B cells in SLE are phenotypically immature B cells, $CD20^{+}IgD^{+}CD27^{low}$. The functional distinction between $CD45RB^{low}$ and $CD45RB^{high}$ B cells and potential relevance to disease were studied using FACS-sorted cells. Intracellular and extracellular Ca^{2+} mobilisation and cell proliferation upon B cell receptor (BCR) engagement were significantly higher in the $CD45RB^{low}$ population. In addition, confocal microscopy studies revealed co-localisation of CD45 and Lyn in $CD45RB^{low}$ but not in $CD45RB^{high}$ B cells. Further studies are underway to profile differences in cytokine and auto-antibody production between the two cell populations. To determine the molecular mechanisms that underlie this phenotype we established an isoform-specific RT-PCR and quantitative PCR assays. Results of these studies reveal that B cells from all individuals express mRNA of five CD45 isoforms. However, we report variations in the level of mRNA for the different isoforms between SLE patients and matched controls. The data also reveals that the level of isoform expression is regulated at transcriptional and translational levels. The relevance of our data to B lymphocyte biology and SLE immunopathology will be discussed.