DELETION OF THE BAFF RECEPTOR TACI FULLY PROTECTS AGAINST SLE WITHOUT REDUCTION OF B CELL NUMBERS AND FUNCTION

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10.1136/lupus-2017-000215.345

Background and aims B cell-activating factor of the TNF family (BAFF) is an essential B cell survival factor. However, high levels of BAFF promote systemic lupus erythematosus (SLE) in mice and humans. Belimumab (anti-human BAFF) limits B cell survival and is approved for use in patients with SLE. Surprisingly, the efficacy of rituximab in SLE remains controversial, despite depleting B cells more potently than belimumab. This raises the question of whether B cell depletion is really the mechanism of action of belimumab. In BAFF transgenic (BAFF-Tg) mice, SLE development is T cell-independent but relies on innate activation of B cells in cooperation with the BAFF receptor TACI. Therefore, in this study we tested whether TACI, a BAFF receptor dispensable for B cell survival may have a role in the pathogenesis of SLE.

Methods To test the role of TACI in driving BAFF-mediated autoimmunity, we reconstituted BAFF Tg mice with a TACI-deficient bone marrow and also crossed BAFF Tg mice onto TACI-/- mice.

Results We show that loss of TACI on B cells protected against BAFF-mediated autoimmune manifestations while preserving B cells, suggesting that loss of BAFF signalling through TACI, rather than loss of B cells, may underpin the effect of belimumab in the clinic. Moreover, a multimeric form of BAFF, is very effective at activating TACI, suggesting that this abnormal form of BAFF may also be a pathogenic factor in SLE.

Conclusions B cell-sparing blockade of TACI may offer a more specific and safer therapeutic alternative to broad B cell depletion in SLE.

THE CONTRIBUTION OF INTERFERON LAMBDA TO SLE

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10.1136/lupus-2017-000215.346

Background and aims Interferon lambda (IFN-lambda) is a novel type of interferon produced by dendritic cells (DC). Despite its binding to a different receptor, IFN-lambda shares functional similarities with type I IFN (IFN-I) by upregulating the expression of IFN-stimulated genes. The role of IFN-lambda in DC biology and in autoimmunity remains unknown.

- to identify the DC subsets producing IFN-lambda.
- to investigate the role of IFN-lambda in DC functions.
- to investigate the role of IFN-lambda in SLE.

Methods

- Mouse and human DC subsets were stimulated ex vivo and the IFN-lambda expression was measured.
- The maturation and the capacity of DC to cross-prime T cells was compared in WT and IFN-lambda-/- mice. T cell cross-priming by human DCs was measured ex vivo in the presence of exogenous IFN-lambda.
- Serum levels of IFN-lambda was measured in lupus-prone mice and in SLE patients. The phenotype of the blood DC subsets from SLE patients was also characterised.

Results

- Mouse plasmacytoid DC (pDC) and CD8+ DC highly secrete IFN-lambda. In humans, the CD141+ DC are the major IFN-lambda producers.
- IFN-lambda enhances the capacities of mouse and human DCs to mature and to cross-prime T cells.
- High serum levels of IFN-lambda were detected in lupus-prone mice and in some SLE patients. SLE patients display increased activation of the IFN-producing DC subsets: the pDCs (producing IFN-I) and the CD141+ DCs (producing IFN-lambda).

Conclusions IFN-lambda is produced by some DC subsets and enhances their functions. Furthermore, IFN-lambda is expressed during SLE, suggesting a potential role of the cytokine in the aetiology of SLE.

DECTIN-1 ON MONOCYTIC CELLS MEDIATES ABERRANT INNATE AND ADAPTIVE IMMUNE RESPONSES IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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10.1136/lupus-2017-000215.348

Background and aims Abnormal expression of CD200/CD200R1 may contribute to the immunologic abnormalities in patients with systemic lupus erythematosus (SLE). This study aimed to assess the function of CD200/CD200R1 and impact of CD200-Fc on dendritic cells in lupus-prone NZB/WF1 mice.

Methods Female NZB/WF1 mice were treated with CD200-Fc or control for 4 weeks. Plasma samples were collected to measure autoantibody levels. The expression levels of CD200/CD200R1 in peripheral blood mononuclear cells (PBMCs) and splenocytes were examined.

Results The percentage of CD200/CD200R1-positive cells in splenocytes from NZB/WF1 mice was lower than that of C57BL/6 mice (p<0.05). The plasma level of anti-dsDNA was significantly higher in NZB/WF1 mice than C57BL/6 mice (p<0.001). However, the anti-dsDNA levels decreased (p=0.047) after CD200-Fc treatment. Finally, CD200-Fc reduced the levels of IL-6 (p=0.017) and IL-10 (p=0.03) in the dendritic cell culture supernatant.

Conclusions The immunosuppressive CD200/CD200R1 signaling pathway might be involved in the immunopathology of NZB/WF1 mice; the present results merit further exploration of agents that can modulate the CD200/CD200R1 pathway as a therapy for human lupus.
Background and aims Dectin-1 is a c-type lectin like receptor that signals via syk and is involved in anti-fungal immunity. Dectin-1 was found to trigger experimental inflammatory arthritis, and likely play a role in the pathogenesis of some autoimmune diseases. This study aimed to examine dectin-1 expression and function of circulating CD14+ monocytes and monocyte-derived dendritic cells (MDDCs) in patients with systemic lupus erythematosus (SLE)

Methods SLE patients with active and inactive diseases and healthy subjects were recruited. Dectin-1 agonists including curdlan, zymosan and toll-like receptor agonists Pam3CSK4 (TLR2) and LPS (TLR4) were used to stimulate monocytes and/or MDDCs. Dectin-1, ROS and phosphorylated-syk (p-Syk) were measured by flow cytometry. Cytokine profile was measured by and multi-bead immunoassay.

Results Dectin-1 expressing monocytes was significantly lower in active SLE patients compared to inactive patients and healthy controls. The absolute count of dectin-1 expressing monocytes correlated significantly and inversely with SLEDAI, anti-dsDNA antibody level and C4. Despite this, ROS production upon stimulation by dectin-1 agonists was comparable. Stimulation of dectin-1 led to activation and maturation of MDDCs. SLE MDDCs showed higher p-Syk activation compared to normal MDDCs upon dectin-1 stimulation. Curdlan-stimulated MDDCs produced higher levels of IL-1β, IL-23 and TNF-α. Adding TLR2 agonist to curdlan, SLE MDDCs produced significantly higher level of IL-1β compared to normal MDDCs.

Conclusions Active SLE patients had significantly lower circulating dectin-1 expressing monocytes which produced comparable level of ROS compared to inactive patients and healthy subjects. Dectin-1 agonists led to significantly higher Th17 promoting cytokines upon co-stimulation with TLR2 in SLE MDDCs.

Background and aims Toll-like receptor 7 (TLR7) has been implicated in B cells activation and the generation of pathogenic autoantibodies. Newly-formed transitional (TR) B cells are enriched in autoreactive specificities and are increased in some SLE patients. This study was undertaken to examine activity of TR B cells and the possible link between the TR B cells expansion/activation and TLR7 levels in SLE.

Methods PBMCs were collected from SLE patients and healthy donors and analysed for the expression of TLR7, TR9 and IFN-responsive genes by RT-PCR. The frequencies of B cell populations were analysed by flow cytometry. BAFF titers were analysed by ELISA. TLR7 variant rs3853839(C/G) was detected by Taqman 5’-allele discrimination assay. TR B cells were primed with IFNα and stimulated with TLR7 ligands in vitro.

Results High expression levels of TLR7 in SLE patients positively correlated with IFN signature and disease activity, but not with BAFF titers. SLE patients with high levels of TLR7 (TLR7hi group) showed an expansion of CD19+CD38highCD24highCD10+ TR B cells. Overall, frequencies of TR B cells positively correlated with the levels of TLR7, but not TLR9. SLE patients, carrying a risk G allele, had increased TLR7 expression and TR cell frequencies, compared to non-risk allele carriers. TLR7hi SLE patients showed increased autoantibody titers and skewing towards Sm/RNP antigens. Upon IFNα priming, TR B cells up-regulated TLR7 and differentiated into plasmablasts in response to TLR7 ligand stimulation.

Conclusions Our findings suggest that dysregulation of TLR7 in SLE might drive the expansion and promote the activation of TR B cells, which might be a source of autoantibodies.