Immunopathogenesis of SLE and Rationale for Biologic Therapy

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Environmental Triggers, Gender, and Genetic Factors Contribute to SLE Pathogenesis

- Environmental Triggers
  - UV light
  - Cigarette smoking
  - Infection and toll-like receptor stimulation

- Multiple Genetic Polymorphisms Subjected to Epigenetic Regulation

- Sex Hormone Interactions
  - Female predominance

B-Cell Function in Immune Responses

Activate antigen presenting cell function

Antigen presentation

Regulate T cell activation, anergy or differentiation (Bregs)

Antibody production

Regulate FDC differentiation and lymphoid organisation

Produce cytokines

B Cells and Systemic Lupus Erythematosus

- Murine models show that genetic manipulations which enhance B-cell function in mice with specific genetic backgrounds can result in:
  - autoantibody formation
  - often an SLE-like disease
  - but not inflammatory arthritis
- In humans, a role for B cells in SLE can be proven by showing that interventions that target B cells specifically alter disease manifestations
- A role for B cells in SLE has been demonstrated by clinical improvement upon therapeutic B-cell targeting with belimumab
- However, besides the production of autoantibodies, the contribution of enhanced B-cell function to the pathogenesis of SLE remains uncertain and the specific B-cell subsets involved as well as the functions of B cells in SLE have not been resolved
Normal B Cell Maturation and Stimulation

Effector B Cell Subsets

Memory B Cells

- Generated during T cell-dependent responses
- Antigen specific
- Specialized for heightened secondary responses to antigen
- Usually express post-switch mutated B cell receptors
- Resistant to standard immunosuppressive therapy, rituximab and belimumab

Immunoglobulin Secreting Cells (Plasma Cells and Plasmablasts)

- Plasmablasts
  - Short-lived dividing cells that secrete large amounts of antibody transiently
  - Generated during T cell-independent and T cell-dependent responses
  - Antigen specific
  - Secrete IgM (TI) or IgG (TD) that is either minimally (TI) or heavily (TD)
  - Sensitive to immunosuppressive therapy, rituximab, belimumab

- Plasma Cells
  - Long-lived non-dividing cells that reside in specific niches and secrete large amounts of antibody continuously without antigenic stimulation
  - Generated during TD responses
  - Antigen specific
  - Secrete IgG and IgA that is heavily mutated
  - Resistant to immunosuppressive therapy, rituximab, belimumab
B-cell Hyper-reactivity: a Contributing Factor in SLE

B Cell Abnormalities in Active SLE

Normal

SLE

Naïve

Post-switch memory

Pre-switch memory

Plasma cells

Naïve

Immature cells

CD27-IgD-memory cells

CD27

IgD

T-Cell-Dependent Generation of High Avidity Autoantibodies within GCs

Antigenic stimulation

↑ T Cell help

(PTPN22, IL-21)

Naïve B cell activation

GC REACTION

Clonal expansion

Somatic hypermutation

Class switch recombination

Selection of autoreactive clones

↑ apoptosis

↓ clearance of apoptotic material

Intrinsic B Cell hyper-responsiveness

(BANK1, BLK, IL-21R, FcRGN2b, TLR7, PTPN22, CD40, Lyn, TNFAIP3, Blimp1)

AUTOANTIBODY SECRETING PLASMA CELLS

AUTOANTIGEN REACTIVE MEMORY B CELLS

Generation of Ig Secreting Cells

T Independent Response

- Short-lived low avidity IgM secreting plasmablast

T Dependent Response

- Short-lived low/high avidity IgM/IgG secreting plasmablast
- Long-lived high avidity IgG secreting plasma cell

Bone marrow/MALT

**Generation of Ig Secreting Cells**

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Anti-dsDNA

Anti-Sm/RNP

**ICOS:ICOSLigand**

- ICOS (Inducible T cell Stimulator(CD278) is a member of the CD28/CTLA-4 family expressed on activated T cells
- ICOS Ligand (CD275) is a member of the CD80/86 family and is expressed on B lineage cells, dendritic cells, macrophages, endothelial cells
- Critically involved in the generation of $T_{FH}$ Cells by upregulating bcl6
- In mice, absence leads to markedly decreased germinal center reactions and decreased levels of IgG1 and IgE following immunization. In humans, loss of function mutations associated with a subset of CVID
- Over expression of ICOS results in a lupus like syndrome

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**CXCR5: CXCL13**

- CXCR5 (CD185) is a G protein-coupled seven transmembrane receptor expressed by B cells, central memory CD4 T cells and T\_FH cells
- CXCR5 specifically recognizes CXCL13 produced by FDC and stromal cells
- CXCR5:CXCL13 interactions control co-localization of activated T\_FH cells and B cells in the initiation of GC reactions
- In the absence of CXCR5:CXCL13 interactions, GC formation and T cell dependent antibody responses do not occur

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**Nat. Rev. Rheumatol.** doi:10.1038/nrrheum.2011.108
CD40: CD154

- CD40 (TNFRSF5) is expressed by B cells, antigen presenting cells and endothelial cells
- CD40 interacts with CD154 (CD40L, TNFSF5) expressed on activated T cells, platelets
- CD40-CD154 interactions are essential for GC formation
- In the absence of CD154 in mice or humans (HlgM1), there is no GC formation, class switch recombination, somatic hypermutation or generation of memory B cells

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IL-21

Discovered 2000
Type 1 Cytokine
Common-Cytokine-Receptor γ-Chain

Properties of IL-21/IL-21R

1. IL-21, a type 1 cytokine is produced by CD4+ T cells after antigen activation and also CD8+ T cells and NKT cells. It is constitutively expressed by CXCR5+ T Follicular Helper Cells (T_{FH}, T_{H21}). The IL-21 gene is located in 4q27.

2. IL-21R is a composite receptor composed of the specific IL-21R and the γC chain. Signaling involves STAT3 >STAT1>>>STAT5. IL-21R is expressed by lymphohemopoietic cells, but also by epithelial cells, keratinocytes, and synovial fibroblasts and is induced by antigen/mitogen stimulation and IL-21. The IL21R gene is located in 16p11.
Major Actions of IL-21

- T Cells/NK Cells
  - Promotes survival and expansion of CD8\(^+\) T Cells and NK Cells
  - Promotes differentiation of Th17 Cells
- B Cells
  - Promotes expansion and differentiation of naïve and memory B Cells into Ig secreting plasma cells.

IL-21 and SLE

- IL-21 drives extensive plasma cell differentiation and Ig production from stimulated murine and human naïve and memory cells
- Levels of IL-21 are markedly elevated in BXSB mice, sanroque mice and SLE patients
- SLE is associated with a polymorphism in the IL-21 gene and the IL-21R gene
- Blocking IL-21 is effective therapy in MRL\(^{lpr/lpr}\) mice, and lupus in BXSB\(^{yaa}\) mice is prevented by deletion of the IL-21R
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Anti-Sm/RNP

The BAFF/BlyS-APRIL System

PMNs, Myeloid cells, Stromal cells, T cells

BAFF/BlyS (TNFSF13B)

APRIL (TNFSF13A)

Belimumab, BAFF-R-Ig

Atacicept

BAFF-R (TNFRSF13C)

Naive

TACI (TNFRSF13B)

Memory

BCMA (TNFRSF17[13A])

Plasma cells

B CELLS


The Roles of BAFF/BlyS and APRIL and Their Receptors in B-Cell Biology: Lessons from Genetically Altered Mice

Cytokines:
- BAFF/BlyS controls the development and survival of conventional (B2) B cells and marginal zone (MZ) B cells
- APRIL is involved in the switch to IgA and in plasma cell survival
- Optimal plasma cell survival requires both BAFF/BlyS and APRIL
- B-cell memory does not depend upon either BAFF/BlyS or APRIL

Receptors:
- BAFF-R controls the development and survival of conventional (B2) and MZ B cells
- TACI, BCMA are involved in regulating the expansion of the B-cell pool
- BCMA contributes to plasma-cell survival

BAFF/BlyS and Autoimmunity

- In mouse models, overexpression of BAFF/BlyS can lead to the development of an SLE-like disease
- BAFF/BlyS and APRIL blockade suppresses some animal models of SLE and inflammatory arthritis
The Rationale for BAFF/BLyS and APRIL Blockade in SLE

- Data from murine models
- Elevated levels of BAFF/BLyS and APRIL in subjects with SLE
- In SLE, BAFF/BLyS levels correlate with anti-DNA titers and disease activity

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Belimumab Induced Changes in B-Cell Subsets in Subjects with SLE

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Belimumab versus Placebo

The Effect of Belimumab on Circulating Plasma Cells

CD19<sup>+</sup> / CD27<sup>BR</sup>/CD38<sup>BR</sup> plasma cells

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<th>Study week</th>
<th>Placebo</th>
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Median % change

[BLISS-76] *p<0.001; †p<0.01; *p<0.05


The Effect of Belimumab on Serum IgG Levels

Serum IgG levels

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The Effect of Belimumab on Autoantibody Titers

BAFF/BLYS Blockade in SLE

- 2 replicate studies show significant, although moderate benefit
- These results demonstrate a role for B cells in some patients with SLE
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IL-6 in Human SLE

Systemic
• Increased serum IL-6 levels in active lupus
• Increased IL-6 production by T and B cells
• Increased expression of IL-6R by B cells in active lupus
• Blocking IL-6 decreases spontaneous Ig and anti-dsDNA production ex vivo

Effects on kidney
• IL-6 increases mesangial cell proliferation
• Increased IL-6 expression in lupus kidneys
• Increased urinary IL-6 levels during active lupus nephritis
Tocilizumab in SLE: Phase I study

- Open label, inter-group dose escalating design
  - 2 mg/kg: 4 subjects
  - 4 mg/kg: 6 subjects
  - 8 mg/kg: 6 subjects
- Seven bi-weekly infusions
- 2 months follow-up
- Patients with mild-to-moderate disease
- No other immunosuppressive therapy except moderate doses of prednisone (< 0.3 mg/kg)
- Primary outcome: safety
- Secondary outcomes:
  - Clinical efficacy
  - Biologic effect
- 16 patients completed the study

Impact of Tocilizumab: Acute Phase Reactants

ESR

Fibrinogen

Impact of Tocilizumab in SLE: Anti-dsDNA

Impact of Tocilizumab: Disease Activity

Blockade of IL-6R with Tocilizumab Normalizes Circulating Plasma Cells in SLE

Efficacy of Tocilizumab in SLE

- Prompt decrease in acute phase reactants
- Decrease in anti-dsDNA antibodies
- Improvement in overall disease activity
- Normalization of circulating B cell subsets

These results indicate:

IL-6 plays an important role in lupus pathogenesis
IL-6 may be a good target for therapeutic intervention.
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