Lipid-Antigen Presentation by CD1d+ B Cells is Essential for the Maintenance of iNKT Cells: Aberrant B cells from Patients with Systemic Lupus Erythematosus Impair iNKT Cell Homeostasis

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Invariant Natural Killer (iNKT) cells

- In human 0.01-0.6% of total lymphocyte population (but very potent).
- Specialised T cell subset sharing markers with both NK cells and T lymphocytes and express a semi-invariant T cell receptor (iTCR).
- The iTCR recognizes glycolipid antigens (such as αGalCer) presented by CD1d on antigen presenting cells.
- Engagement of the iTCR by CD1d-lipid complexes leads to iNKT cell activation and rapid production of a wide range of cytokines/chemokines.
- Play very potent immune-regulatory role in many immune responses. Act as a "bridge" between adaptive and innate immunity.

iNKT cells are important for B cell antibody production and memory

B cell receptor-mediated uptake of CD1d-restricted antigen augments antibody responses by recruiting invariant NKT cell help in vivo

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Invariant NKT cells sustain specific B cell responses and memory

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B-iNKT cell interactions

Overview

1. The role of B cells for the maintenance of iNKT cells in healthy individuals
2. Phenotype and function of iNKT cells in SLE
3. Using B cell depletion therapy (BCD) as a "tool" to dissect the in vivo function of B cells in iNKT cell biology
Depletion of B cells in healthy PBMCs inhibits iNKT cell expansion

Whole PBMCs

B cells

iNKT cells

α-GalCer

α-GalCer + IL-2

PBMCs - B cells

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B cells activate iNKT cells in a CD1d-dependent manner

Whole PBMCs

B cells

iNKT cells

α-GalCer

α-GalCer pulsed B cells

Reduced number of invariant NKT cells in human autoimmune disease

Invariant NKT cells limit activation of autoreactive CD1d-positive B cells

Profound invariant natural killer T-cell deficiency in inflammatory arthritis

Rituximab treatment overcomes reduction of regulatory iNKT cells in patients with rheumatoid arthritis

SLE iNKT cells are reduced in number

OAD = Other Autoimmune Diseases

iTCR = invariant TCR
SLE iNKT cells are functionally impaired

Whole PBMCs

iNKT cell expansion (day 7)

α-GalCer + IL-2

ns

IFN-γ

TNF-α

IL-10

IL-4

IL-6

IL-2

Healthy SLE

MFI

Overview

1. The role of B cells for the maintenance of iNKT cells in healthy individuals

2. Role of iNKT cells in autoimmunity

3. Using BCD therapy as a "tool" to dissect the in vivo function of B cells in iNKT cell biology

Utilizing rituximab treated SLE patients as an in vivo model

Healthy

Expansion
Cytokine production

Healthy

Expansion
Cytokine production

SLE

BCD therapy

Anti-CD20 therapy

Expansion
Cytokine production

Utilizing rituximab treated SLE patients as an in vivo model

Healthy

Expansion
Cytokine production

SLE

BCD

Expansion
Cytokine production

Utilizing rituximab treated SLE patients as an in vivo model

Healthy

Expansion
Cytokine production

SLE

BCD

Expansion
Cytokine production

Disease Activity

pre-BCD

BCD

repopulated

Disease Activity

non-responders

% Boeils

BCDrr

BCDnr

Disease Activity

responders

BCDrr

BCDnr
iNKT cell numbers remain low during B cell depletion but are restored upon return of B cells in responding patients.

Differential CD1d expression in B cells

Longitudinal analysis of patients and healthy donors over time confirms the effect of rituximab on iNKT cell numbers.

iNKT cells reacquire the capacity to respond to lipid stimulation only after repopulation of B cells.

CD1d expression in SLE patients is reduced on B cells, but not on other APCs.
Increased CD1d internalisation-rate on B cells from SLE patients

**Conclusions from studies in SLE patients**

- B cells sustain the *in vitro* expansion and activation of iNKT cells in healthy individuals via CD1d
- SLE iNKT cells were numerically and functionally impaired
- iNKT cell and B cell CD1d defects in SLE patients were exclusively reversed in patients responding to BCD treatment

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