The inflammasome of activated human B-cells regulates IL-1β and IgM: A crosstalk between the innate and the adaptive immune response

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The less well-known function of B cells

- Activated B-lymphocytes secrete cytokines that participate in cellular innate host response
  - TNF$_\alpha$, Lymphotoxin $\beta$, IL-10
  - IL-8

- These cytokines play also a role in autoimmune diseases

- Acute exacerbations of many autoinflammatory diseases are preceded by infectious illness

Fungal β-glucans and immune activation

Nature Reviews Microbiology 14, 163–176 (2016)
β-Glucans are potent immunomodulators

Complement

Beta-glucan

AP-1 NF-κB

IL-8

IL-17

IL-8

IL-1β

IL-6

TGF-β

IL-23

TGF-β

IL-22

IL-17

Th17

Th1

B

IgM

IFN-γ


Modified from Carmona EM and Limper AH. Int J Clin Rev 2012:03:01
B-cells responses to fungal β-glucans


IL-8

IL-6

Beta-glucan

AP-1

NF-κB

IL-8

IL-17

MMP-7


Modifed from Carmona EM and Limper AH. J Clin Rev 2012;03:01

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**CpG**

Bacterial DNA has unmethylated CpG motifs that are released during infection and recognized by PRR (TLR9)

Synthetic oligodeoxynucleotides (ODN) contain CpG motifs similar to those found in bacteria.
**IL-1β**

- IL-1β is essential in the clearance of fungal and bacterial infections
- Increase levels can also be found in several autoimmune diseases
- Il-1β and IL-18 are secreted as inactive precursors

Cleaved by the inflammasome

Pre-IL1β  IL1β

Netea MG et al. Plos Pathogens. 2010
Inflammasome

Macrophage

TLR

ATP

K+

Activation of Caspase-1

Pro-caspase-1 CARD

Transcription mRNA IL-1β

Pro-IL-1β

Caspase-1 CARD

Mature IL-1β

Mature IL-1β

Monocyte

TLR

Pro-IL-1β

Caspase-1 CARD

Transcription mRNA IL-1β

Mature IL-1β

Active Caspase-1

Mature IL-1β

Mature IL-1β

Netea MG et al. Plos pathogens 2010
IL-1β after 1,3 β-glucan stimulation
IL-1β secretion after β-Glucan but not CpG stimulation
β-Glucan and CpG stimulate the NLRP3 Inflammasome
IL-1β Secretion is Dependent on NLRP3 and Caspase-1
β-glucan signaling
Dectin-1 is Required for β-glucan-Induced IL-1β Secretion
SYK and NF-κB are Required in β-glucan-Induced IL-1β Secretion
Decreased IgM levels in NLRP3 deficient mice

Kumar H et al. J. Immunol. 2015
NLRP3 mediates IgM Production

- NLRP3
- ASC (oligomer)
- ASC (monomer)
- proCASP1
- CASP1 p20
- ACTB

- IgM (µg/ml)

- TNFα (pg/ml)

- IL-6 (pg/ml)
IgM induction by CpG is Mediated by ATP, K+ Depletion and CASP1
mTOR is Required for IgM Production in CpG Stimulated B-Lymphocytes
How does mTOR regulate IgM?
Proposed Mechanism

Glucan

Dectin-1

CARD9

ASC

NLRP3

Procaspace 1

Caspase 1

IL-1β

ProIL-1β

TLR9

MyD88

mTOR

?NF-κB

CpG

IgM

(1)

(2)
Questions & Discussion
mTOR is Required for IgM Production in CpG Stimulated B-Lymphocytes
β-Glucans are potent immunomodulators

complement

Beta-glucan

AP-1

NF-κB

IL-8

IL-17


MMP-7

IL-6

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Th1

Th17

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IL-6

TGF-β

IL-23

IL-17

IL-22

IFN-γ

B

β-glucans

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