

MAYO
CLINIC



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

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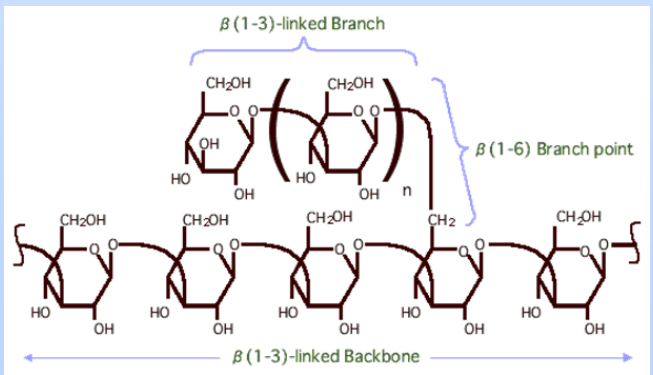
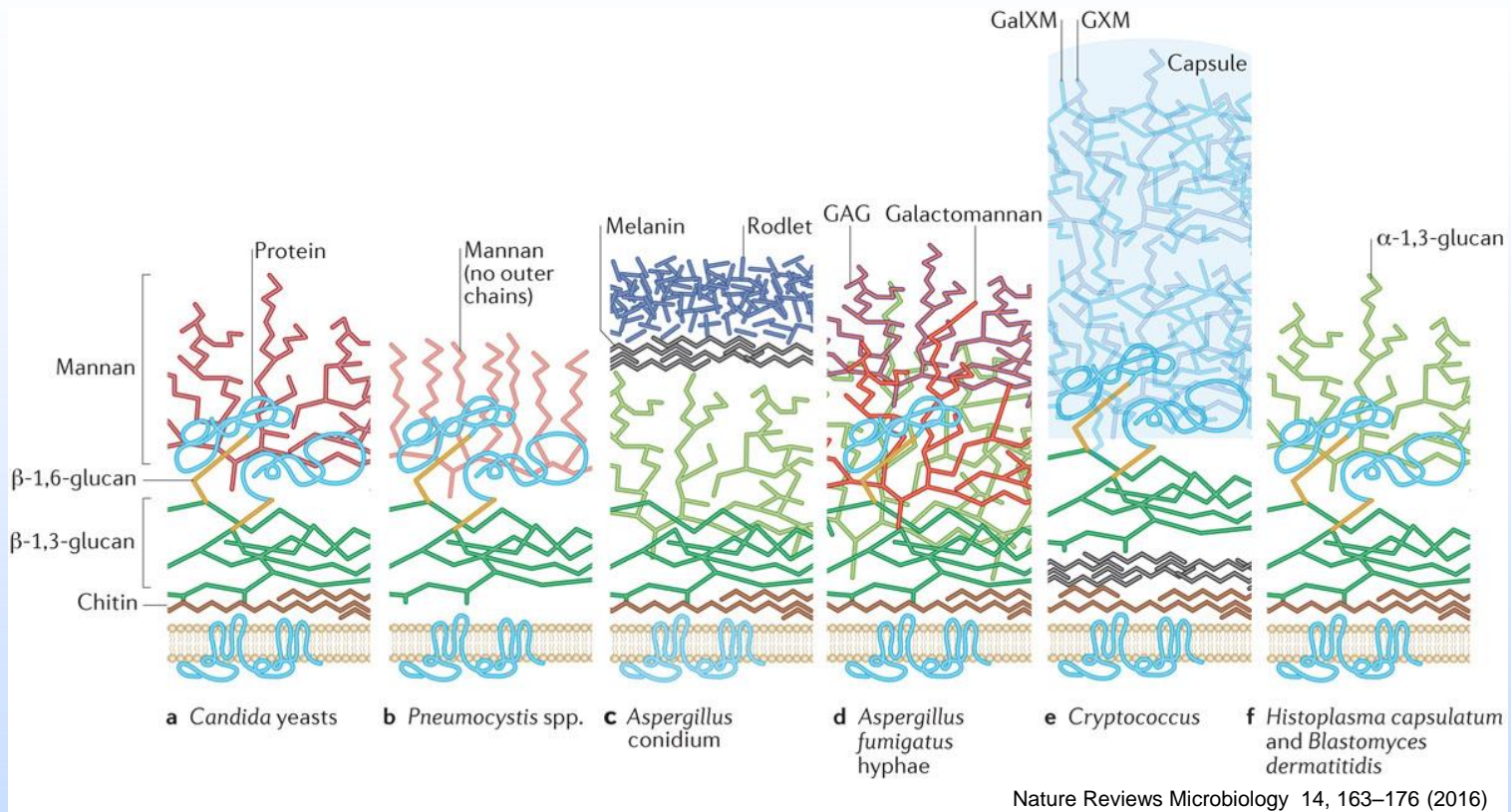


The less well-known function of B cells

- Activated B-lymphocytes secrete cytokines that participate in cellular innate host response
 - $\text{TNF}\alpha$, Lymphotoxin β , IL-10
 - IL-8
- These cytokines play also a role in autoimmune diseases
- Acute exacerbations of many autoinflammatory diseases are preceded by infectious illness

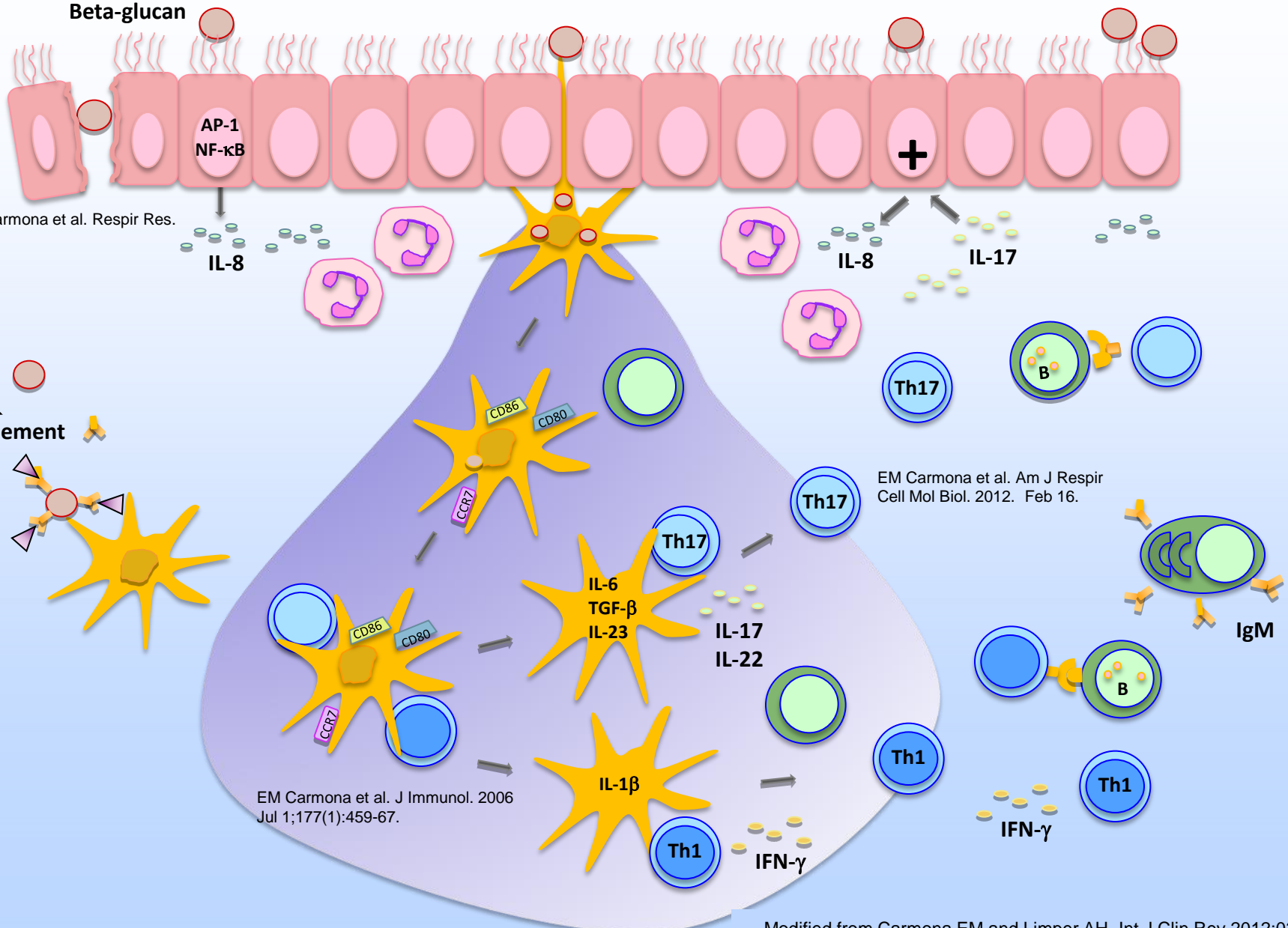
FE Lund. *Curr Opin Immunol.* 2008
Duddy M *et. al.* *J. Immunol.* 2007
Ali MF *et. al.* *J. Immunol.* 2015

Fungal β -glucans and immune activation



β -Glucans are potent immunomodulators

Beta-glucan



EM Carmona et al. Respir Res. 2010.

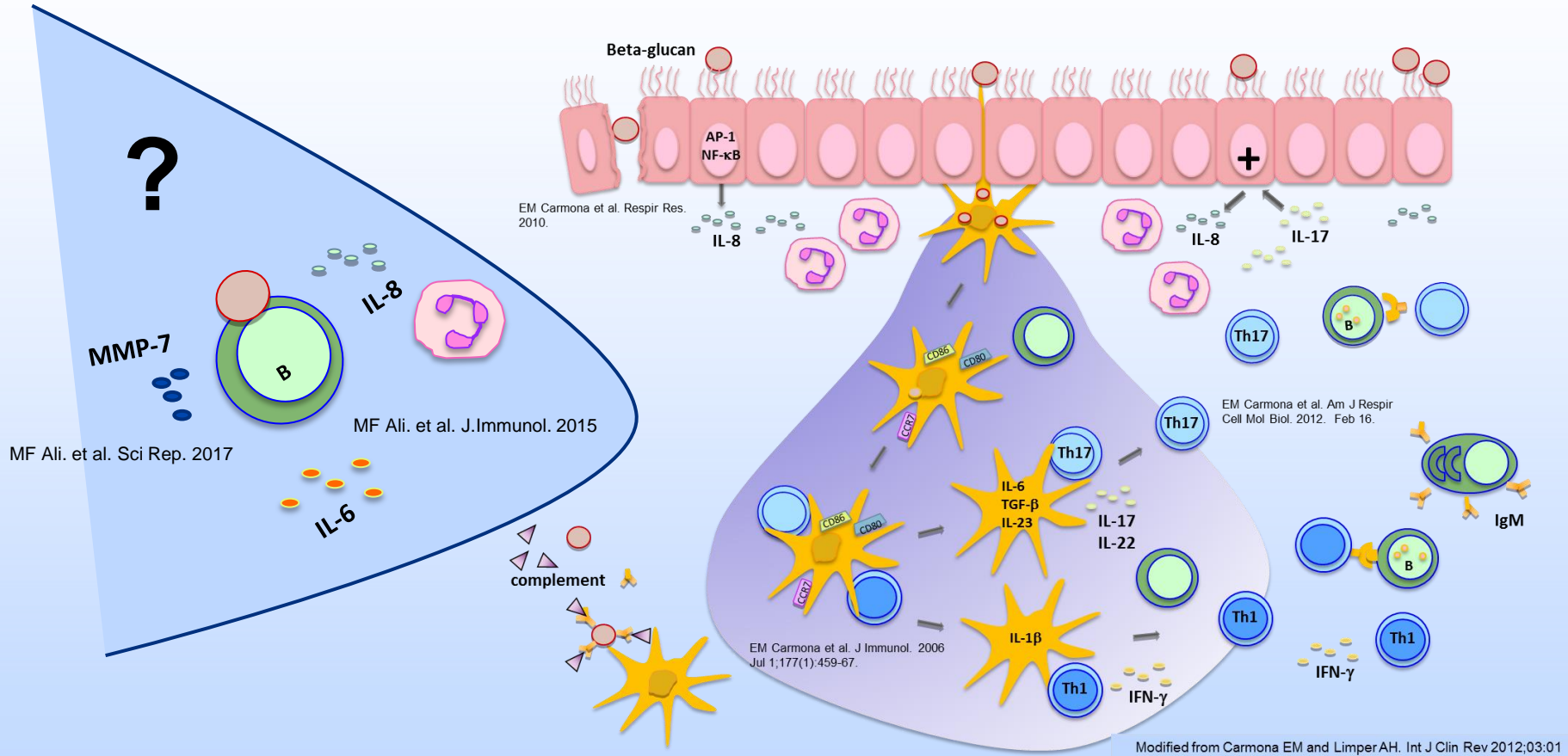
complement

EM Carmona et al. Am J Respir Cell Mol Biol. 2012. Feb 16.

EM Carmona et al. J Immunol. 2006 Jul 1;177(1):459-67.



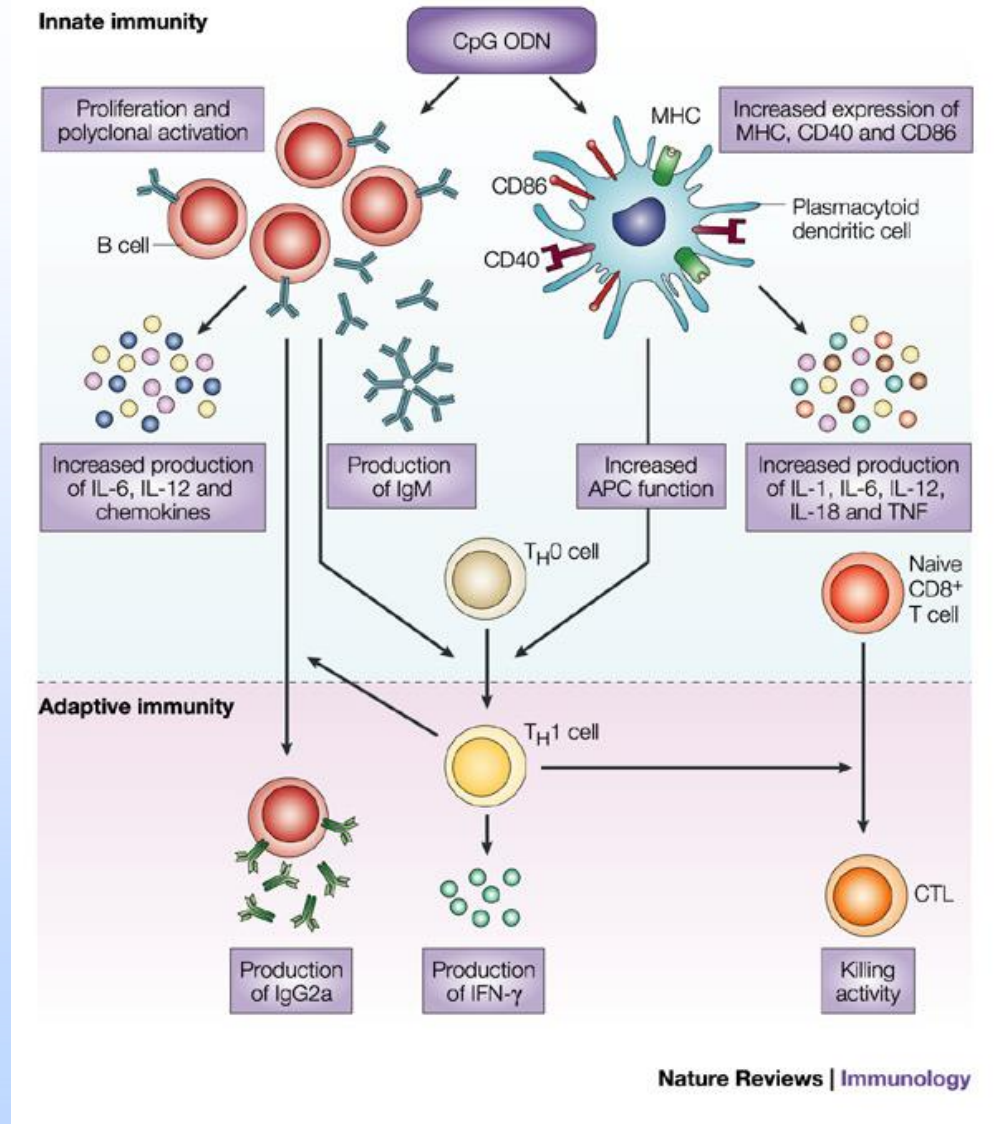
B-cells responses to fungal β -glucans



CpG

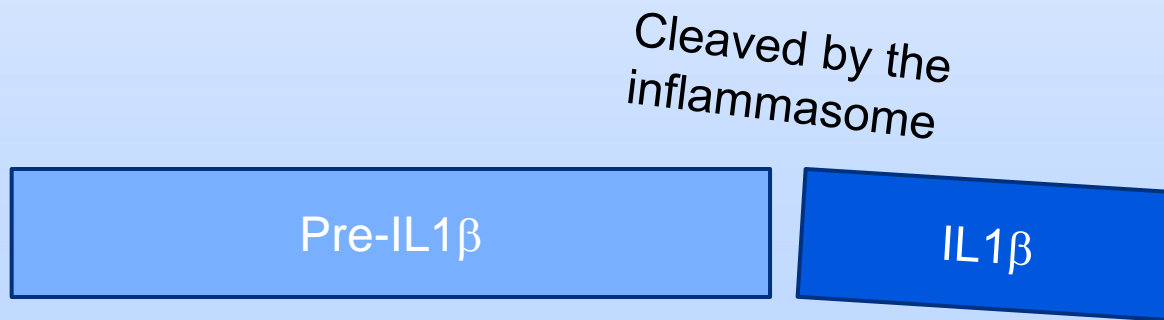
Bacterial DNA has unmethylated CpG motifs that are released during infection and recognized by PRR (TLR9)

Synthetic oligodeoxynucleotides (ODN) contain CpG motifs similar to those found in bacteria.

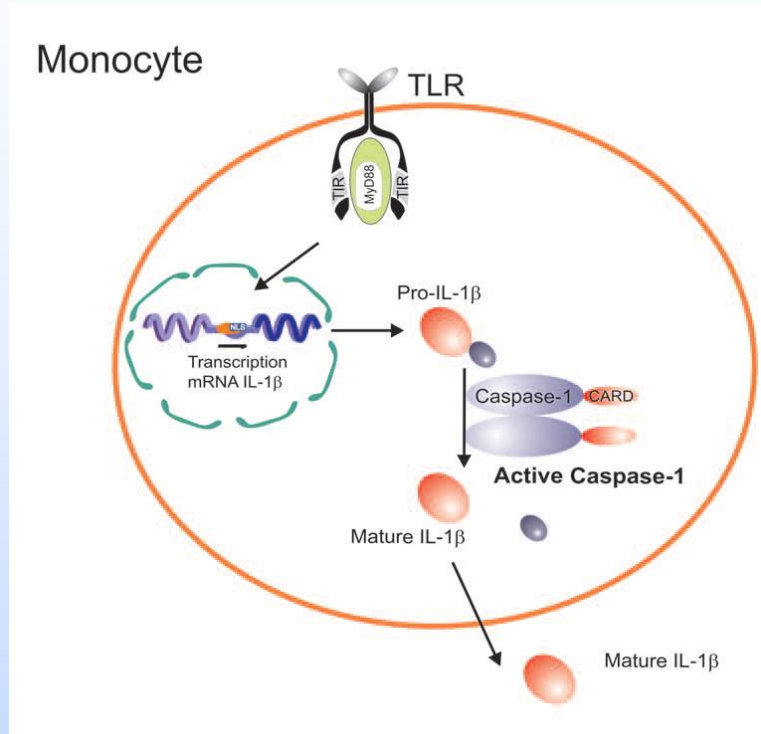
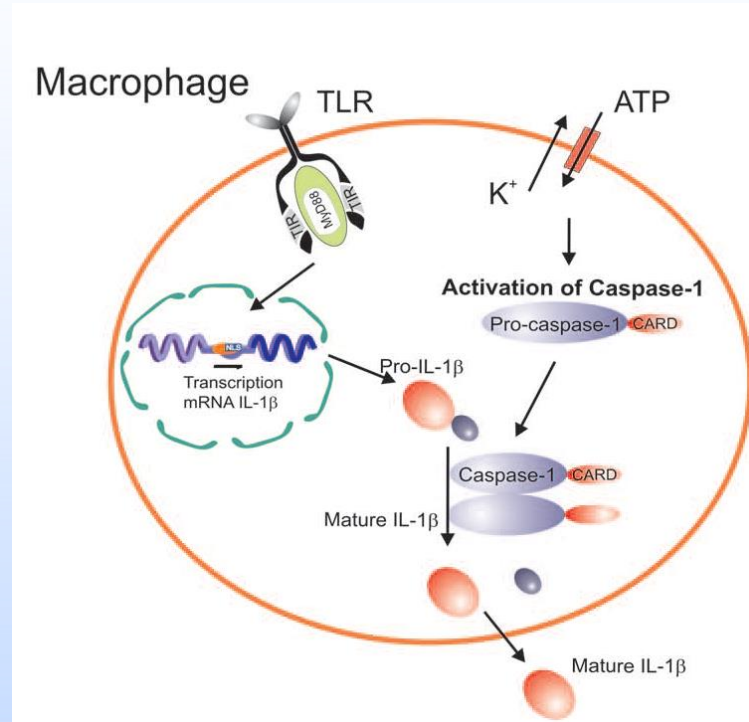


IL-1 β

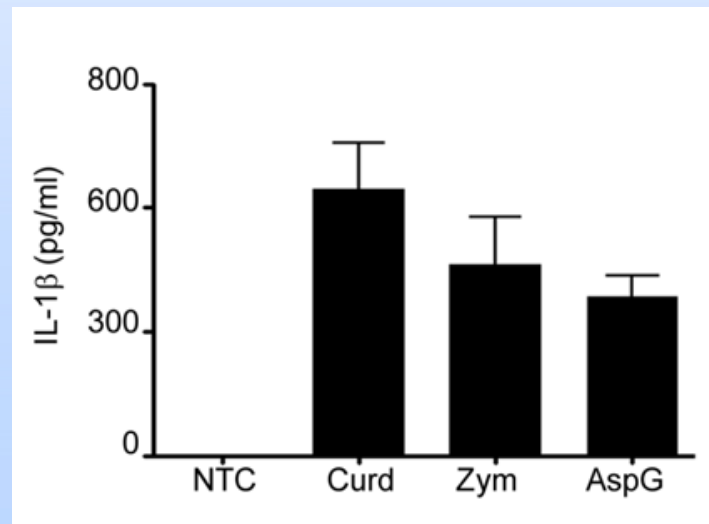
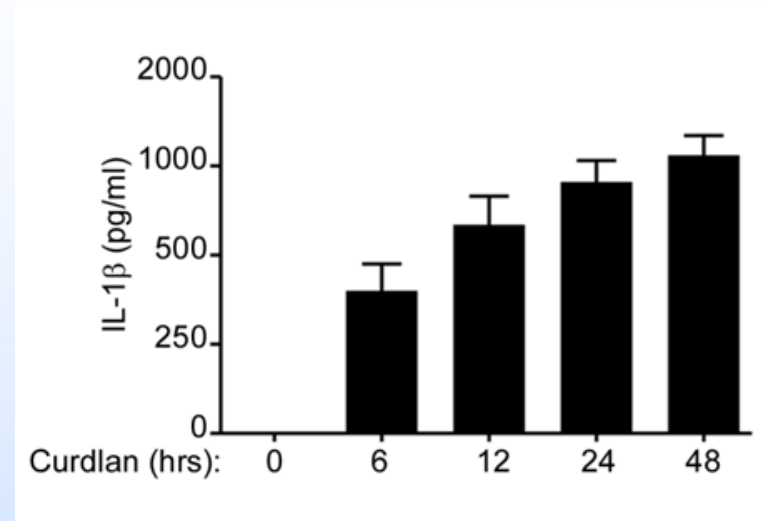
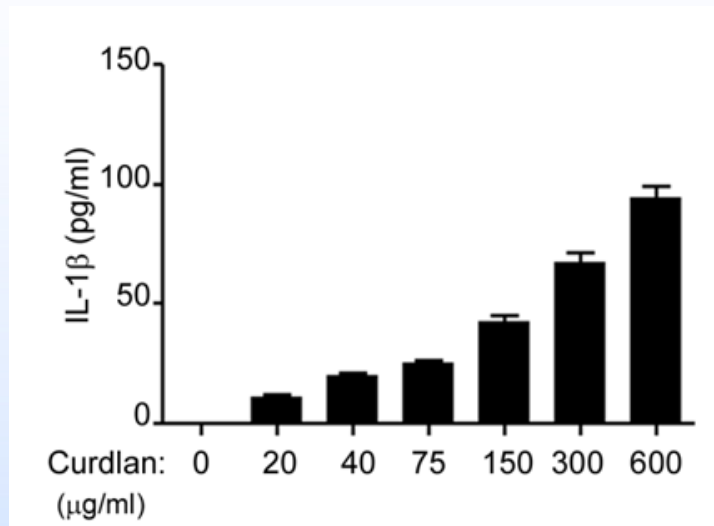
- IL-1 β is essential in the clearance of fungal and bacterial infections
- Increase levels can also be found in several autoimmune diseases
- IL-1 β and IL-18 are secreted as inactive precursors



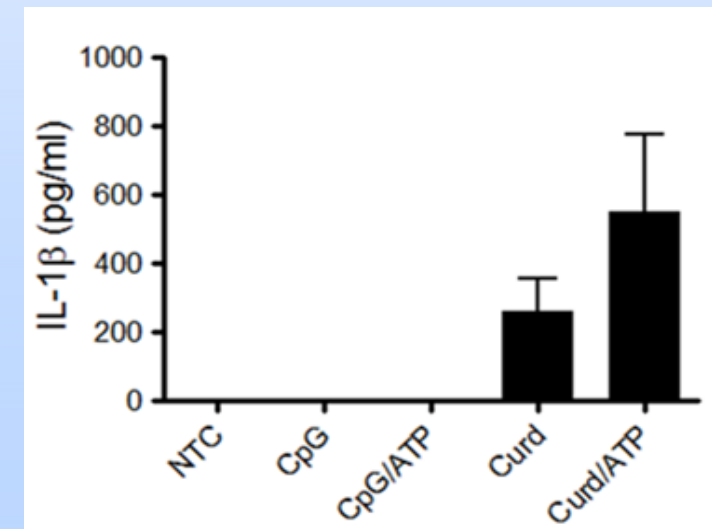
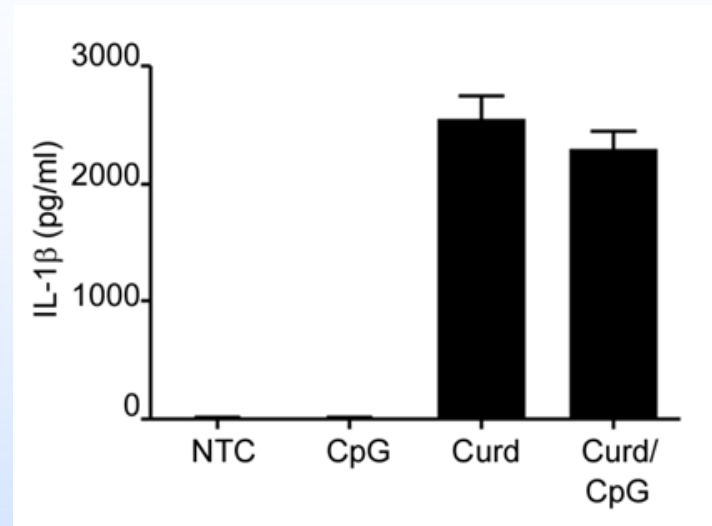
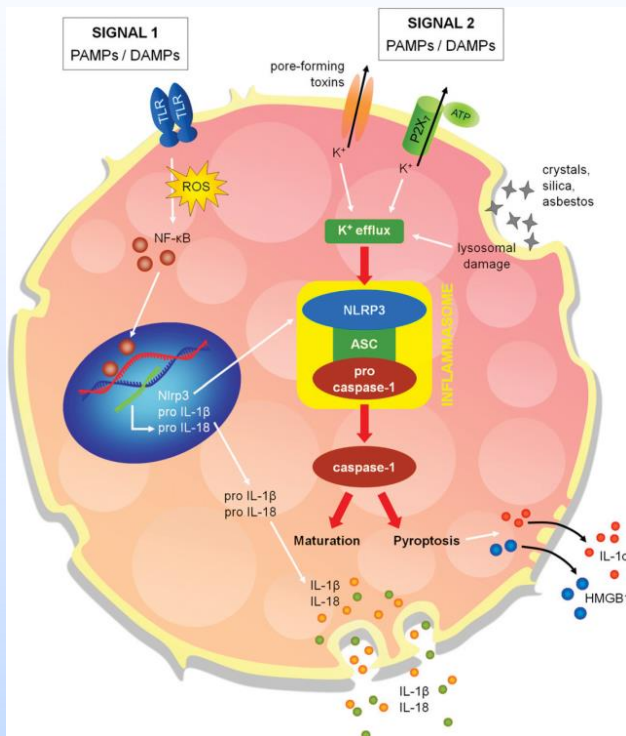
Inflammasome



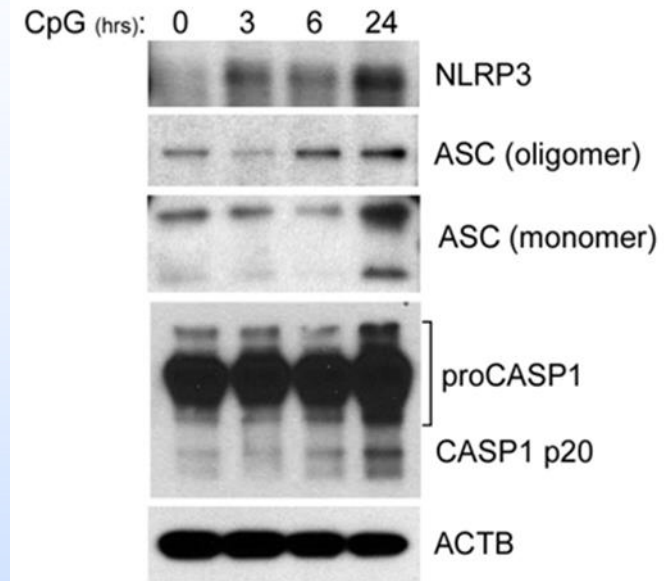
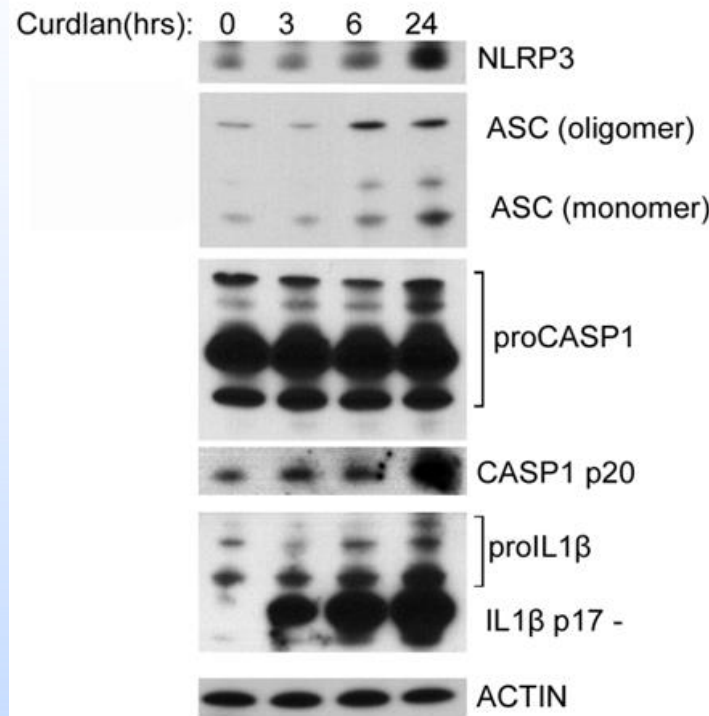
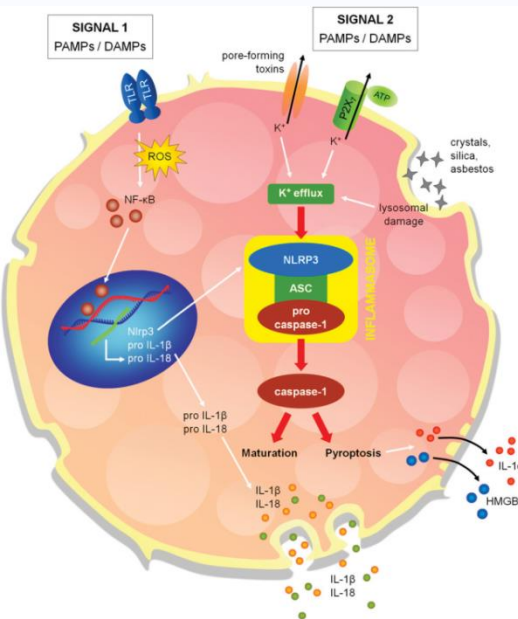
IL-1 β after 1,3 β -glucan stimulation



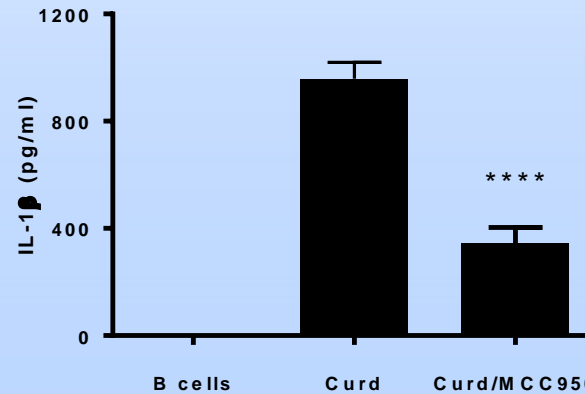
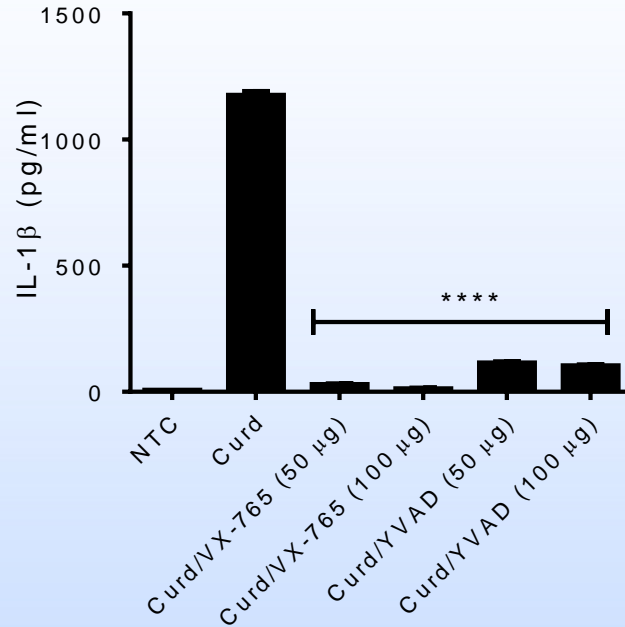
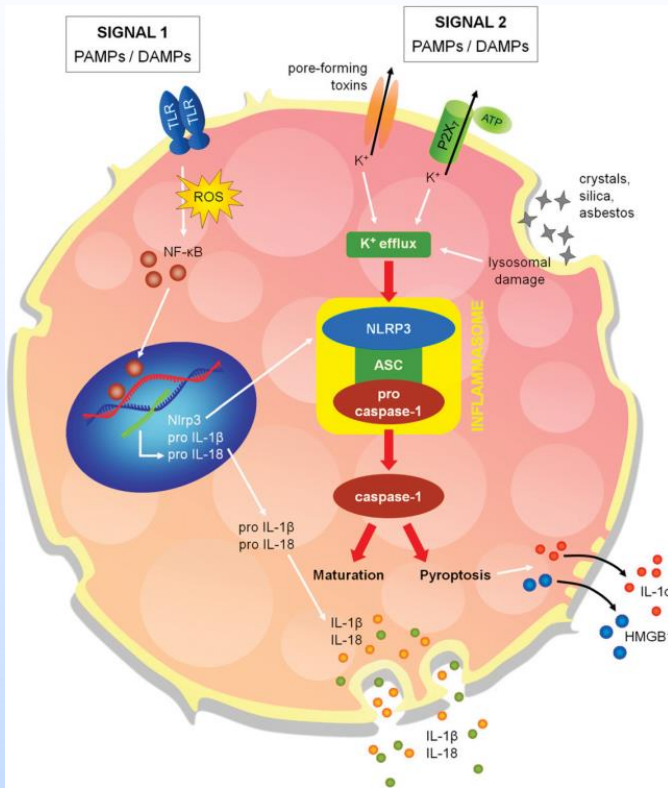
IL-1 β secretion after β -Glucan but not CpG stimulation



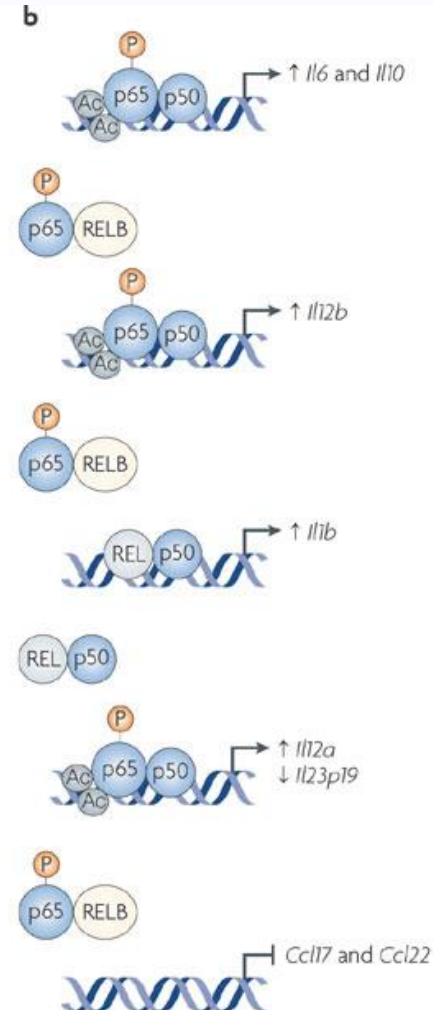
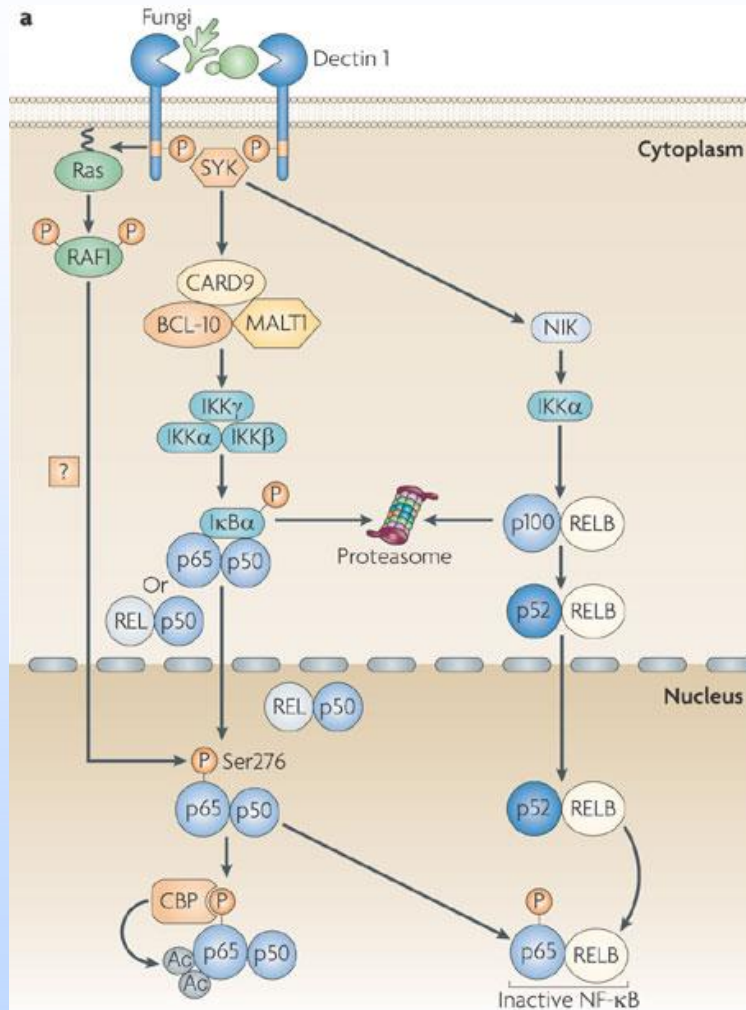
β -Glucan and CpG stimulate the NLRP3 Inflammasome



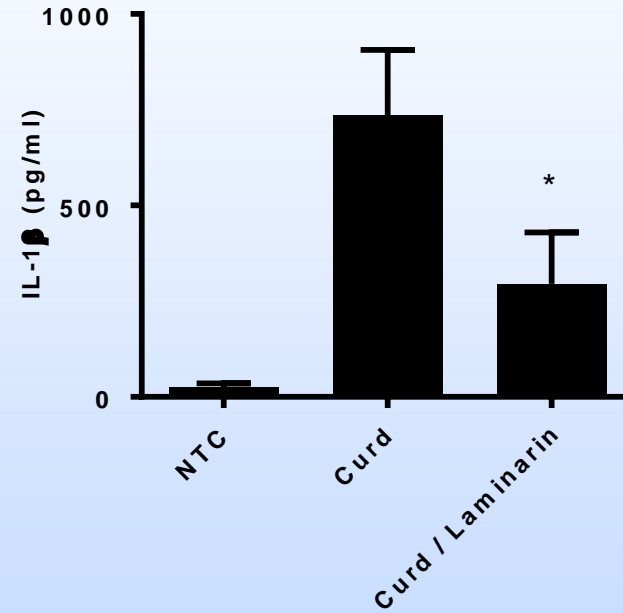
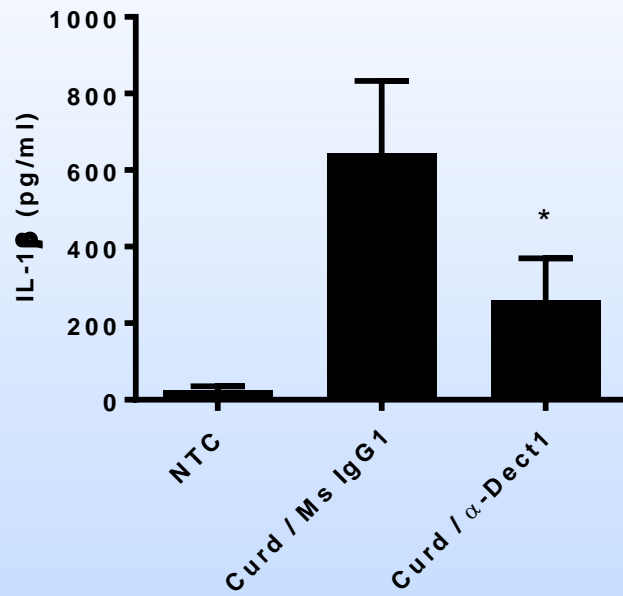
IL-1 β Secretion is Dependent on NLRP3 and Caspase-1



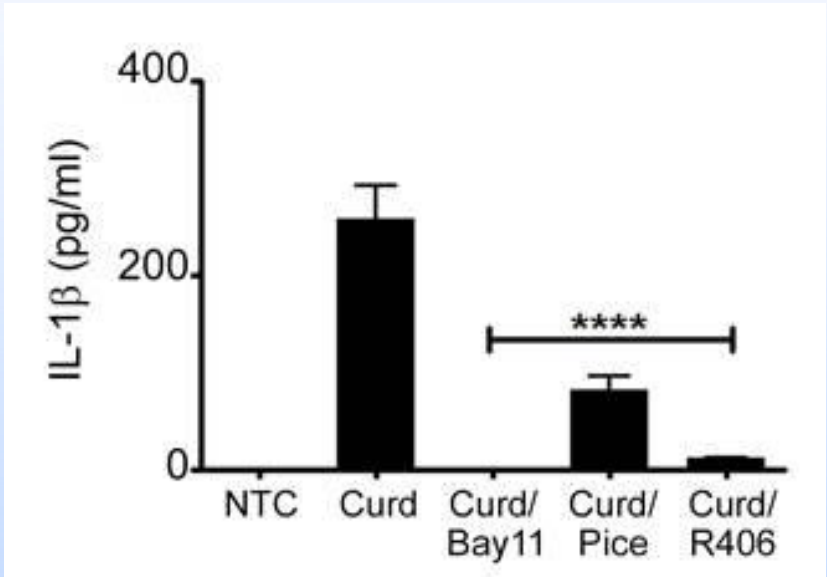
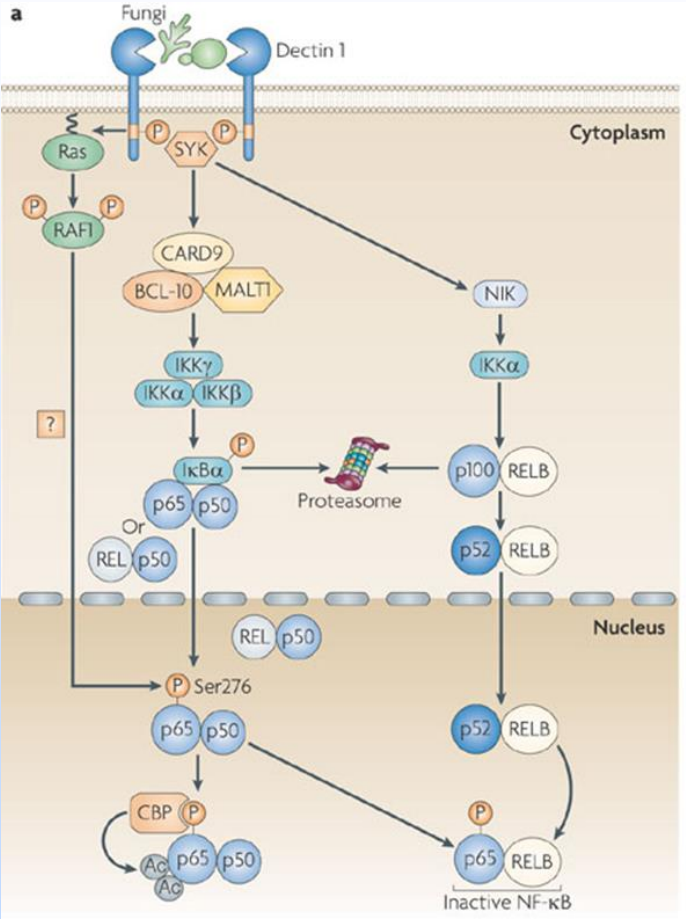
β-glucan signaling



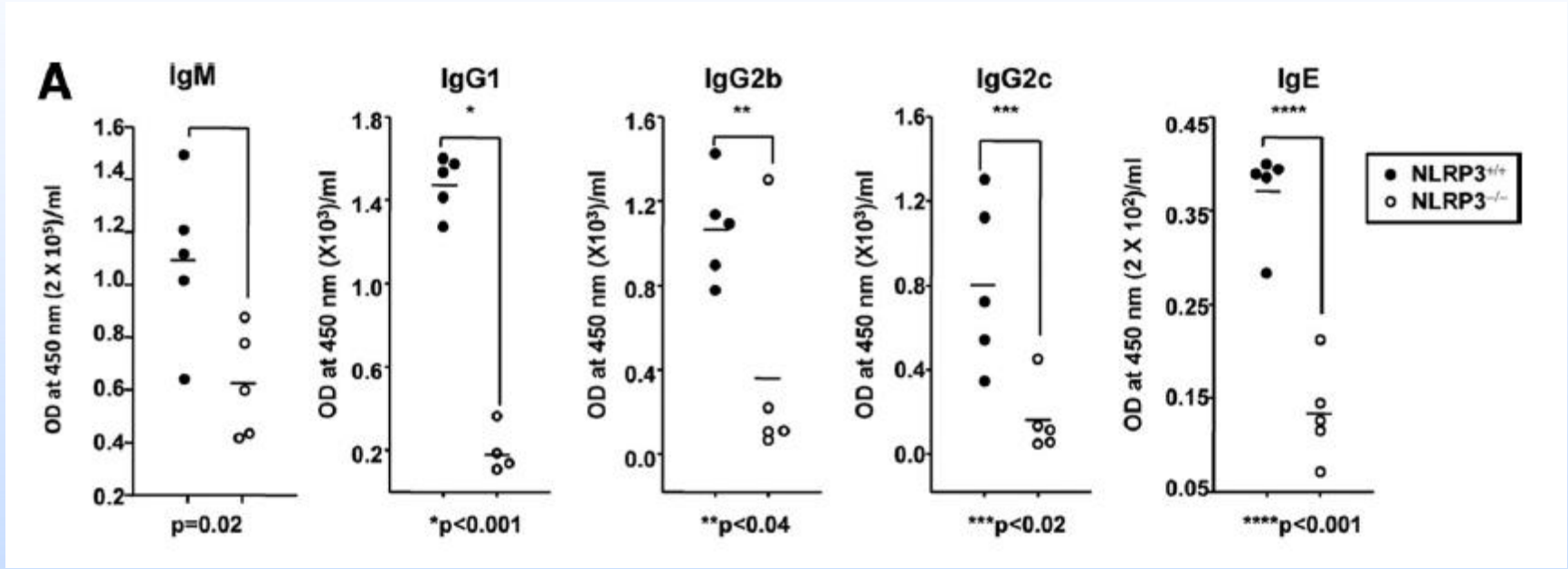
Dectin-1 is Required for β -glucan-Induced IL-1 β Secretion



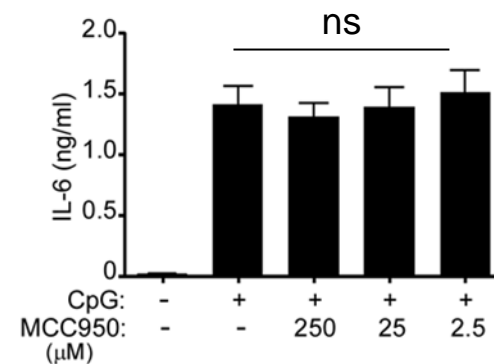
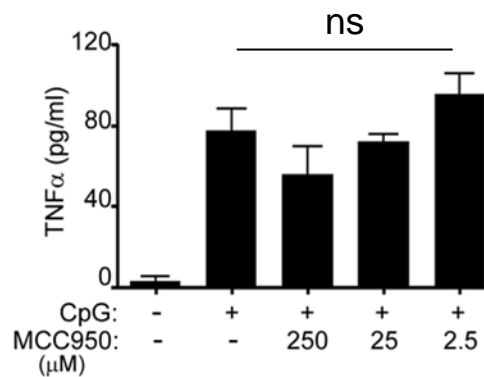
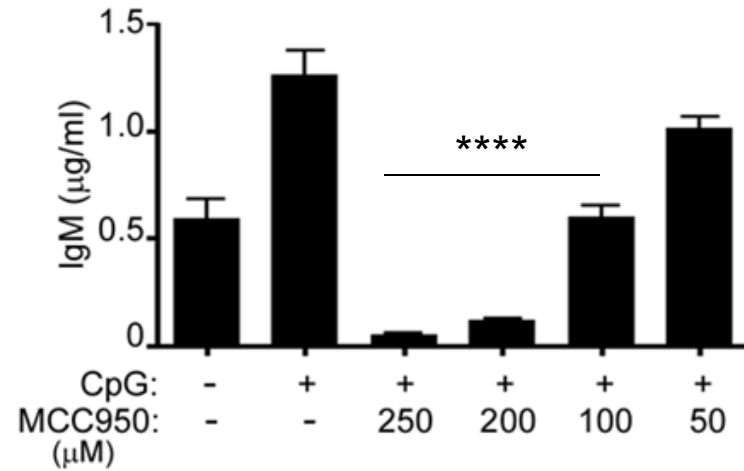
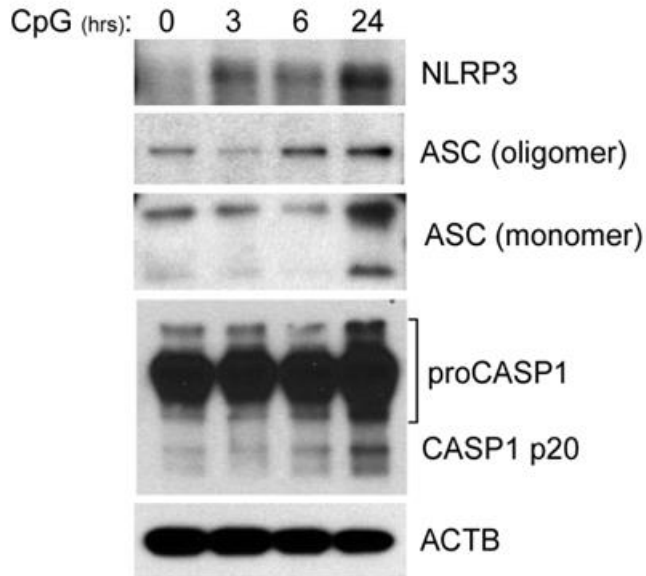
SYK and NF-κB are Required in β-glucan-Induced IL-1β Secretion



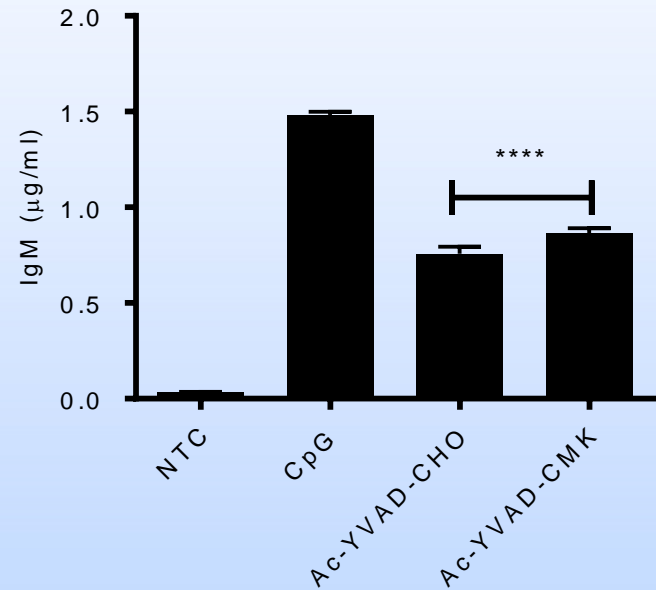
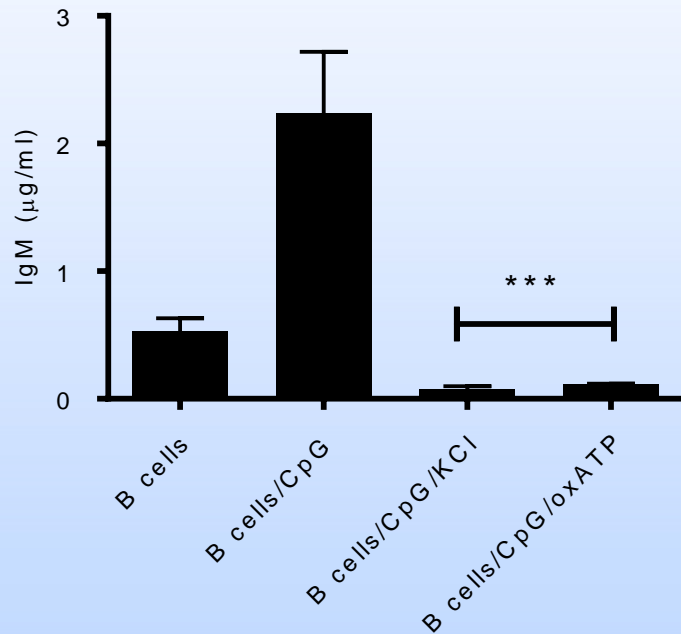
Decreased IgM levels in NLRP3 deficient mice



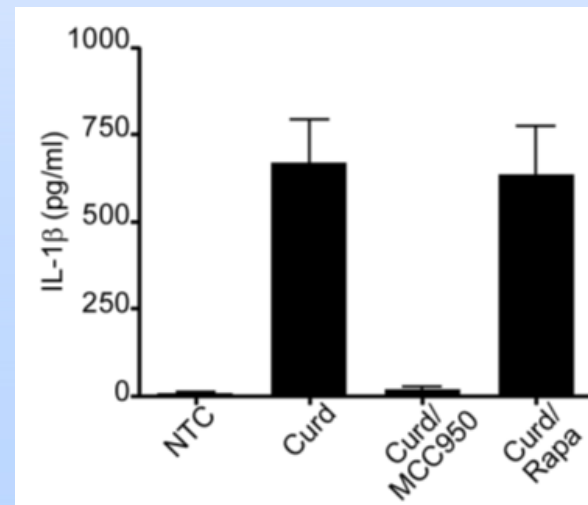
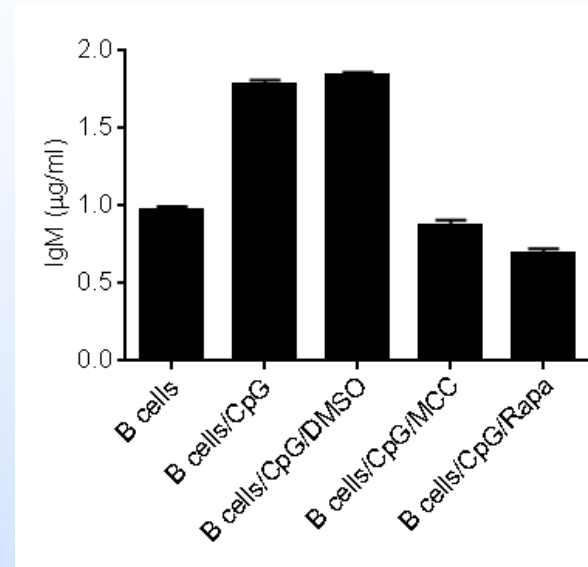
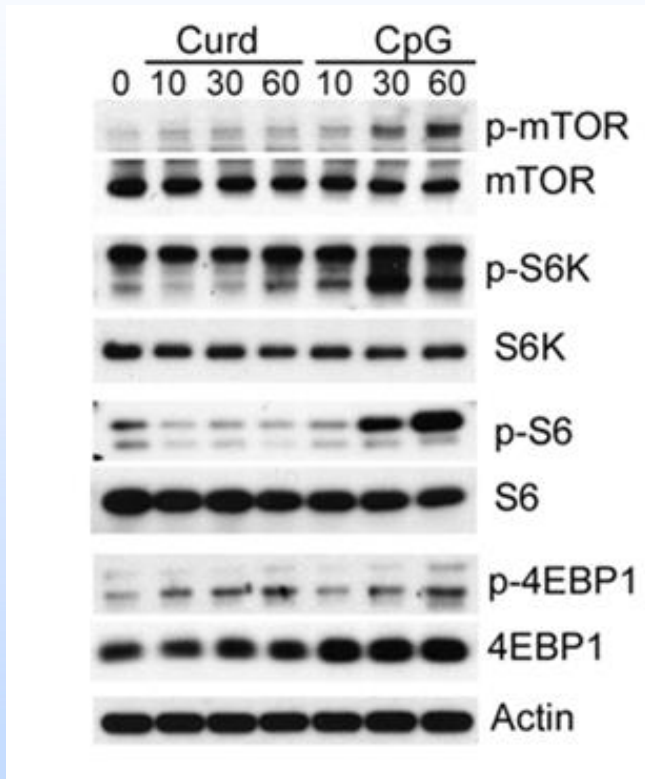
NLRP3-mediated IgM Production



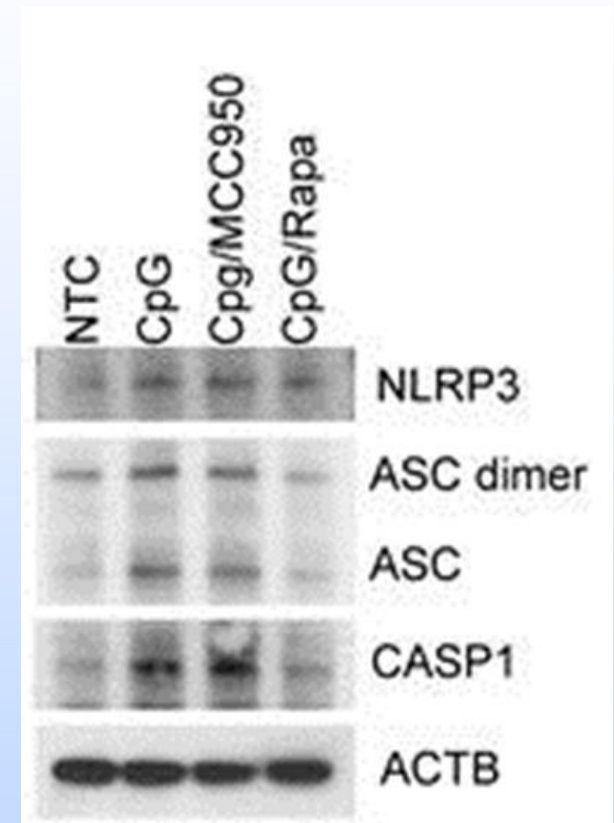
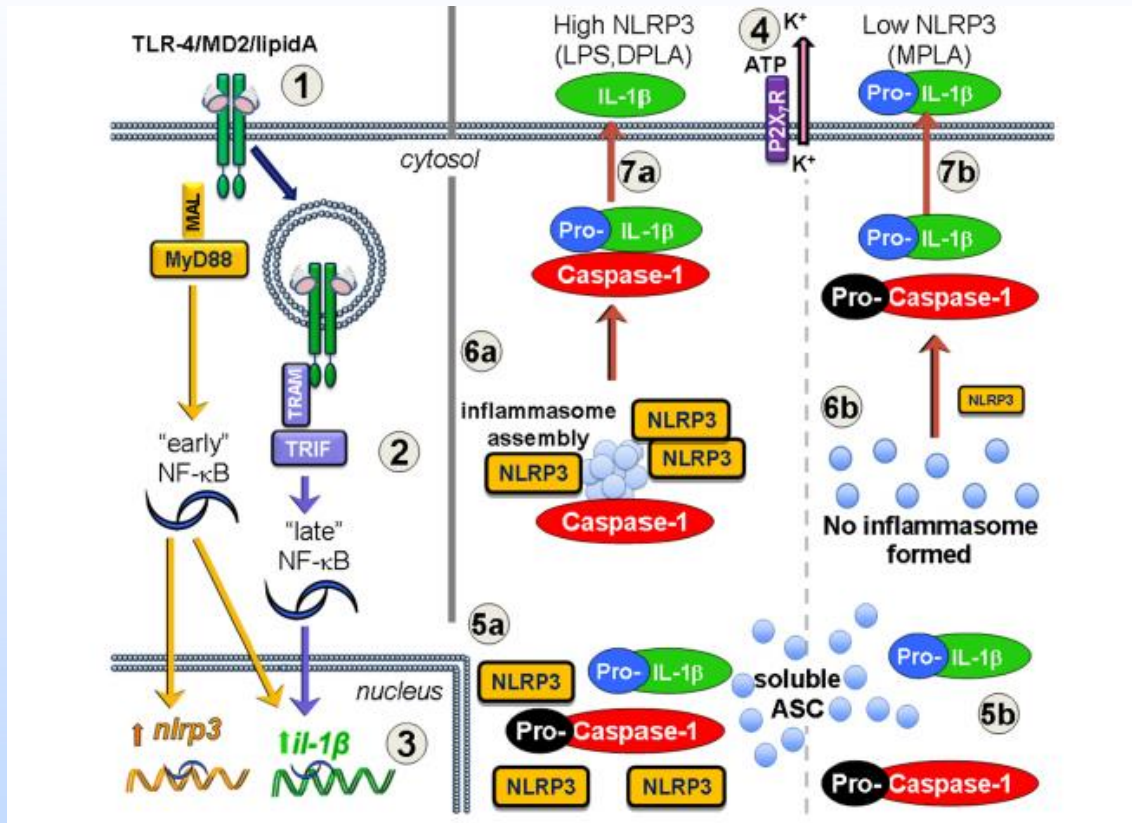
IgM induction by CpG is Mediated by ATP, K⁺ Depletion and CASP1



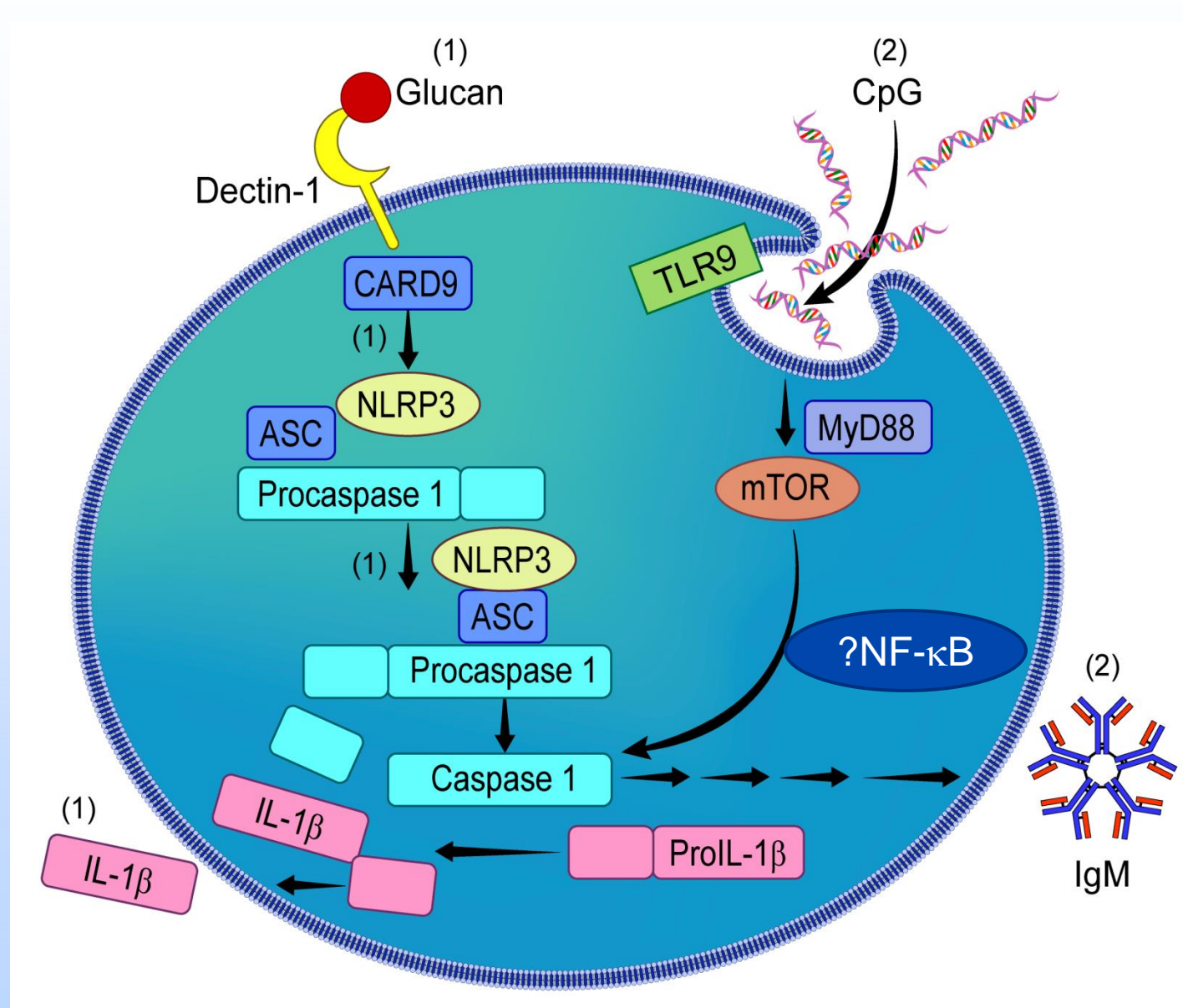
mTOR is Required for IgM Production in CpG Stimulated B-Lymphocytes



How does mTOR regulate IgM?



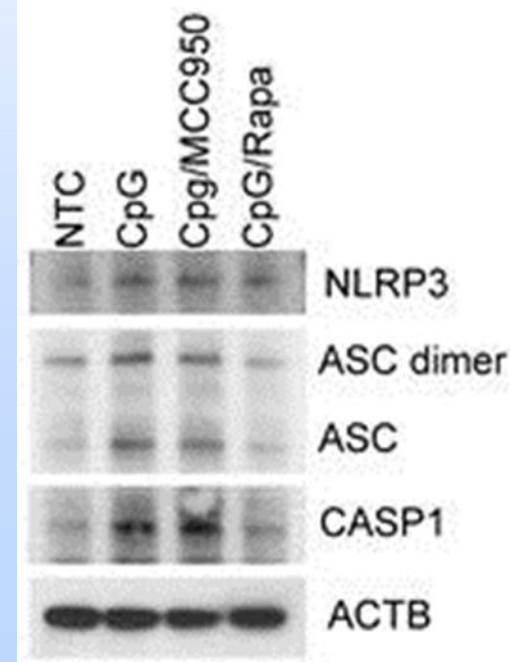
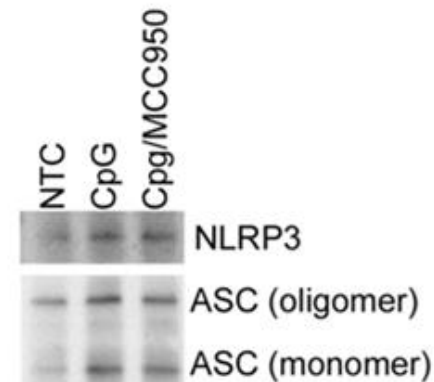
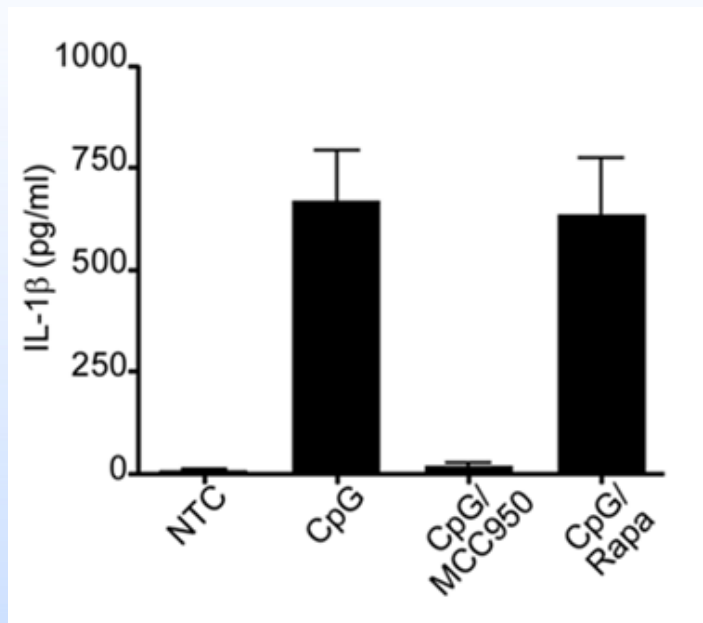
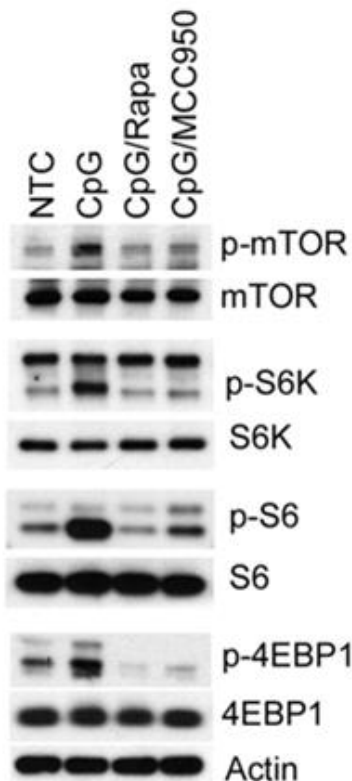
Proposed Mechanism





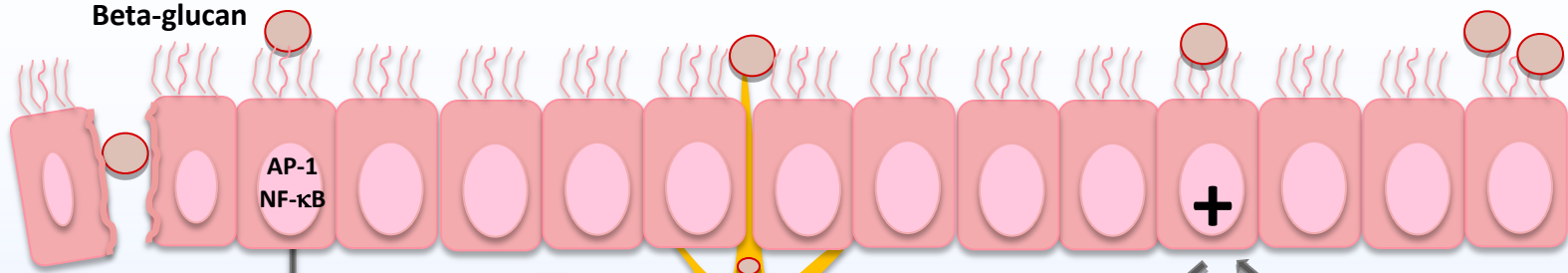
Questions & Discussion

mTOR is Required for IgM Production in CpG Stimulated B-Lymphocytes



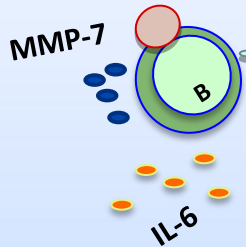
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EM Carmona et al. Respir Res. 2010.

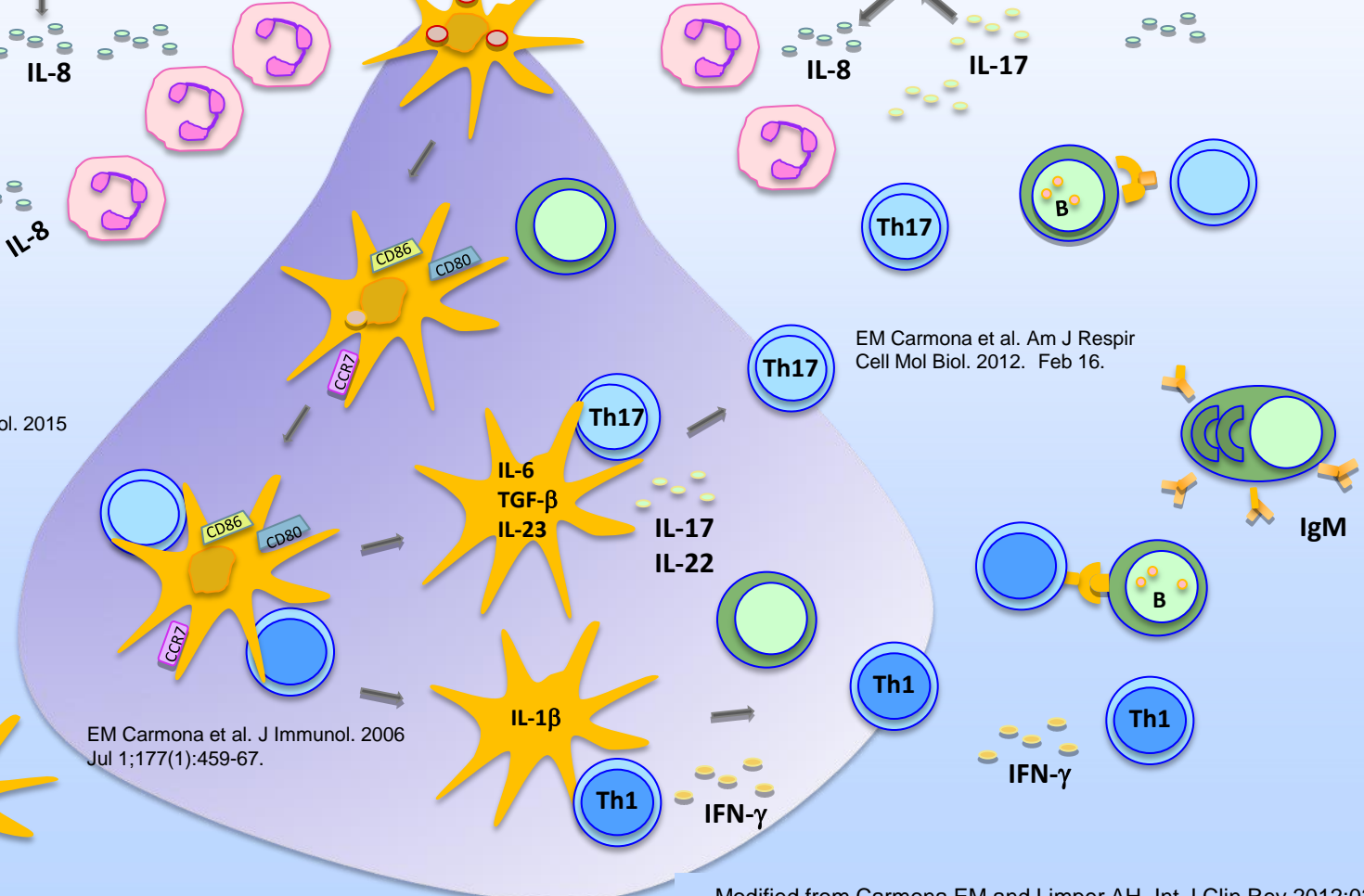
MF Ali. et al. Sci Rep. 2017



MF Ali. et al. J.Immunol. 2015



EM Carmona et al. J Immunol. 2006 Jul 1;177(1):459-67.



EM Carmona et al. Am J Respir Cell Mol Biol. 2012. Feb 16.