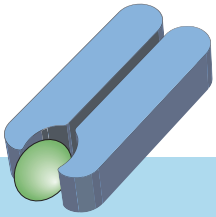
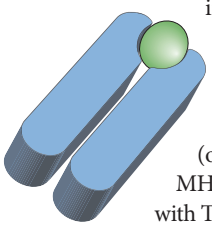
Nature Reviews Immunology | AOP, published online 15 April 2011; doi:10.1038/nri2978



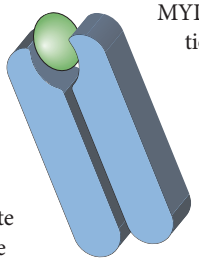
INNATE IMMUNITY

Intracellular MHC class II: not just hiding

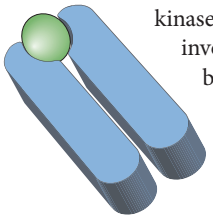
Cell surface expression of MHC class II molecules on antigen-presenting cells (APCs) is essential for the induction of adaptive immune responses. Surface MHC class II molecules present antigenic peptides to $CD4^+$ T cells and, following ligation, mediate reverse signal transduction that regulates cell adhesion, cytokine production and co-stimulation. A study published in *Nature Immunology* now reports a role for intracellular MHC class II molecules in promoting Toll-like receptor (TLR) signalling and thus innate immune responses.



Liu *et al.* were intrigued when they observed that challenge of MHC class II-deficient mice (or chimeric mice with MHC class II-deficient APCs) with TLR ligands resulted in reduced levels of pro-inflammatory cytokines — such as tumour necrosis factor (TNF), interleukin-6 (IL-6) and type I interferons (IFNs). Moreover, these mice survived longer than control mice after induction of bacterial sepsis. Interestingly, *in vitro* experiments revealed that MHC class II-deficient APCs produced low levels of pro-inflammatory cytokines after TLR triggering, although cytokine production in response to stimulation of the IL-1 receptor or nucleotide-binding oligomerization domain protein 2 (NOD2) was normal. These observations led the authors to suggest that MHC class II molecules are selectively involved in TLR signalling events.



So, how can MHC class II molecules regulate TLR-dependent cytokine expression? The authors investigated the TLR signalling events in MHC class II-deficient macrophages following treatment with lipopolysaccharide (LPS). This analysis showed that MHC class II molecules contribute to the activation of mitogen-activated protein kinases and nuclear factor-κB (NF-κB), in a manner that is dependent on myeloid differentiation primary response protein 88 (MYD88) and TIR-domain-containing adaptor protein inducing IFNβ (TRIF). By screening for tyrosine kinases that directly interact with MHC class II molecules following TLR stimulation, Liu *et al.* identified Bruton's tyrosine kinase (BTK; which is known to be involved in TLR signalling) as a binding partner.



Indeed, phosphorylation of BTK was shown to be impaired in MHC class II-deficient macrophages. Furthermore, overexpression of constitutively active BTK enhanced the MYD88- or TRIF-dependent activation of NF-κB and IFN-regulatory factor 3 (IRF3) in TLR-stimulated MHC class II-deficient macrophages, and thus restored the levels of pro-inflammatory cytokines produced by these cells. BTK was found to interact with intracellular but not with plasma membrane MHC class II molecules, and CD40 was required for this interaction. Importantly, immunoprecipitation experiments revealed that MYD88 and TRIF are associated with activated BTK following TLR triggering only in the presence of MHC class II molecules.

Taken together, these results indicate a non-classical role for intracellular MHC class II molecules in promoting TLR signalling and thus in regulating innate immune responses to pathogens.

Maria Papatriantafyllou

ORIGINAL RESEARCH PAPER Liu, X. *et al.* Intracellular MHC class II molecules promote TLR-triggered innate immune responses by maintaining activation of the kinase Btk. *Nature Immunol.* 27 March 2011 (doi:10.1038/ni.2015)