SYK IS INDISPENSABLE FOR CpG-INDUCED ACTIVATION OF HUMAN B CELLS

Mariann Kremlitzka[1,2]

Bernadett Valent[1], Anna Erdei[1,2]

[1]Department of Immunology, Eötvös Loránd University

[2]Research Group of the Hungarian Academy of Sciences, Budapest, Hungary

Background: B cells are efficiently activated by CpG oligodeoxynucleotides (ODNs) resulting in pro-inflammatory cytokine and antibody production mainly via Toll-like receptor 9 (TLR9) and the adaptor molecule myeloid differentiation marker 88 (MyD88). Here we identified a novel, spleen tyrosine kinase (Syk) dependent pathway which is indispensable for CpG induced activation of human B cells.

Methods: Resting tonsillar B cells were stimulated with CpG. Effect of Syk inhibition on various B cells' functions (proliferation, cytokine- and antibody production) were assessed. Activation of Syk dependent pathways was investigated with Western Blot.

Results: Stimulation of B cells resulted in time- and dose-dependent Syk and src kinase phosphorylation, proliferation, cytokine and antibody production. Notably, all these functions were abrogated in the presence of Syk and Src inhibitors. Syk was induced both via TLR9-dependent and –independent manners. Uptake of CpG ODNs was not reduced in the presence of Syk inhibitor, however co-localization of CpG and TLR9 was clearly reduced after it. Expression of TLR9 was significantly elevated after CpG stimulation, which was again abrogated by Syk inhibitors.

Conclusions: These data indicate a new and alternative pathway of CpG induced B cell stimulation through cell surface pattern recognition molecules. CpG-induced Syk activation is a prerequisite for optimal delivery of CpG into TLR9-containing endolysosomes and for induction of its receptor, allowing efficient propagation of TLR9-mediated signaling in human B cells.