Development of New Toll-Like Receptor 4-directed Adjuvants and Clarification of their Mechanism of Action

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Abstract:

Vaccines are one of the most cost-efficient approaches to tackle infectious diseases. They aim to provide a specific protection to a certain pathogen by inducing a long-lasting immune response.[1] Nowadays, subunit vaccines are a very attractive approach but, despite having clear advantages in respect to the conventional vaccines, are less immunogenic since they are developed using an antigen or a combination of antigens and do not contain the entire pathogen.[1] Therefore, they can be formulated with an adjuvant to enhance the immune response of the antigen as well as its durability.[1] TLR4-targetting adjuvants such as clinically approved 3-*O*-desacyl-4'-monophophoryl lipid A (MPLA), are promising compounds since they are able to trigger innate immunity mechanisms and stimulate the production of pro-inflammatory cytokines and T and B-cell antigen specific responses.[2]

Our aim is to develop new glycolipid-based TLR4 agonists that can be used as vaccine adjuvants and clarify their mechanism of action using different cell-biology techniques. In our group, new TLR4 agonists have been synthesised based on the structure of lipid X, a monosaccharide precursor of the LPS's Lipid A, which is the minimal portion required to activate TLR4.[3] TLR4 signaling. A small library of triacylated monosaccharide FP derivatives was obtained by means of a six-step synthesis. Furthermore, C6 functionalization of the sugar moiety was achieved yielding new promising derivatives. Their biological characterization was performed on a human macrophage cell line (THP-1 X-Blue) using ELISA and western blot techniques to measure cytokine production, namely TNF-α, IL-6 and IL-1β and protein expression. Confocal imaging techniques followed by high content analysis were also used to follow the activation of intracellular inflammatory pathways. Preliminary data shows that FP compounds are immunostimulants and that C6 functionalization of FP derivatives results in an increased TLR4 activation.

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