Alerting the immune system's watchmen to improve vaccines

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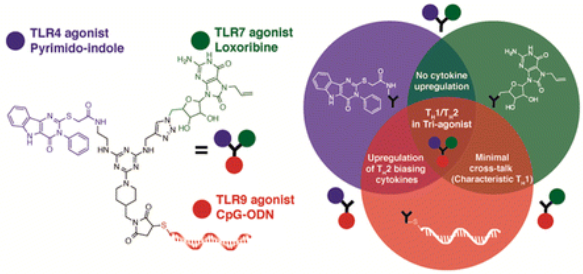

As the days get colder and shorter, we carve jack-o-lanterns and drink pumpkin spice lattes. But one fall tradition can actually keep you healthy: getting your flu shot. Like all vaccines, the flu shot trains the immune system to fend off infection, but some need help to produce the full effect. Today, in *ACS Central Science*, researchers report a new way to help improve vaccines using molecules that more effectively direct the immune system.

Some vaccines, like the flu shot, contain a dead or weakened version of the disease-causing pathogen. Other vaccines, like those for hepatitis b and meningitis, contain just a protein, or other molecule (an "antigen") unique to the microbe. When there is a whole pathogen, the innate immune system is strongly activated, which includes alerting cellular watchmen called the toll-like receptors (TLRs). Antigen-based vaccines do not cause as strong a response, but they produce fewer side effects. Thus, an adjuvant is usually added to antigen-based vaccines to boost their effectiveness. A common adjuvant is a TLR agonist, or activator. In nature, multiple TLR activators work together to effectively direct the immune system. Aaron Esser-Kahn and colleagues investigated whether they could probe this biological machinery and improve the efficacy of antigen-based vaccines.

The researchers suspected that how the TLR agonists were arranged in space could affect their activity. So, they synthesized probes that displayed three different TLR agonists with a defined spatial orientation. The researchers found that their triply-linked activator more effectively raised an immune response than simply mixing the three ingredients together. In addition, by deconstructing the three-way activator into their two component parts, the team studied which components are most important and which arms of the immune response they activate. Esser-Kahn notes that this information will help researchers design better vaccines.

More information: Janine K. Tom et al. Modulation of Innate Immune Responses Covalently Linked TLR Agonists , *ACS Central Science* (2015). DOI: 10.1021/acscentsci.5b00274

Abstract

We present the synthesis of novel adjuvants for vaccine development using multivalent scaffolds and bioconjugation chemistry to spatially manipulate Toll-like receptor (TLR) agonists. TLRs are primary receptors for activation of the innate immune system during vaccination. Vaccines that contain a combination of small and macromolecule TLR agonists elicit more directed immune responses and prolong responses against foreign pathogens. In addition, immune activation is enhanced upon stimulation of two distinct TLRs. Here, we synthesized combinations of TLR agonists as spatially defined tri- and di-agonists to understand how specific TLR agonist combinations contribute to the overall immune response. We covalently conjugated three TLR agonists (TLR4, 7, and 9) to a small molecule core to probe the spatial arrangement of the agonists. Treating immune cells with the linked agonists increased activation of the transcription factor NF-?B and enhanced and directed immune related cytokine production and gene expression beyond cells treated with an unconjugated mixture of the same three agonists. The use of TLR signaling inhibitors and knockout

studies confirmed that the tri-agonist molecule activated multiple signaling pathways leading to the observed higher activity. To validate that the TLR4, 7, and 9 agonist combination would activate the immune response to a greater extent, we performed in vivo studies using a vaccinia vaccination model. Mice vaccinated with the linked TLR agonists showed an increase in antibody depth and breadth compared to mice vaccinated with the unconjugated mixture. These studies demonstrate how activation of multiple TLRs through chemically and spatially defined organization assists in guiding immune responses, providing the potential to use chemical tools to design and develop more effective vaccines.

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