Novel anti-inflammatory adjuvants for vaccines to prevent and/or treat autoimmune diseases

The increase during the last 30 years in the incidence of autoimmune diseases (AD) in the developed countries, points to environmental rather than genetic risk factors. Indeed, studies have shown that ADs are rare in countries where parasites are common, because of the latter's capacity to bias the host to immune tolerance, this way averting pro-inflammatory responses harmful to both the host and parasite. A situation like that occurring during pregnancy, where due to the immunotolerance induced to prevent fetal rejection, ADs can go temporarily into remission. During pregnancy there is an increased production of glycoforms having fucosyl residues, like Lewis^X trisaccharide, which bind to the DC-SIGN lectin receptor on dendritic cells, biasing them to an anti-inflammatory immunity. An immune modulatory mechanism duplicated by the parasitic helminths and some tumor cells, to prevent production of a pro-inflammatory immunity, which would destroy them. Hence, ADs can be treated and/or prevented by modulating the immune system to induce an anti-inflammatory immunity targeting the self-antigens causing the autoimmune response.

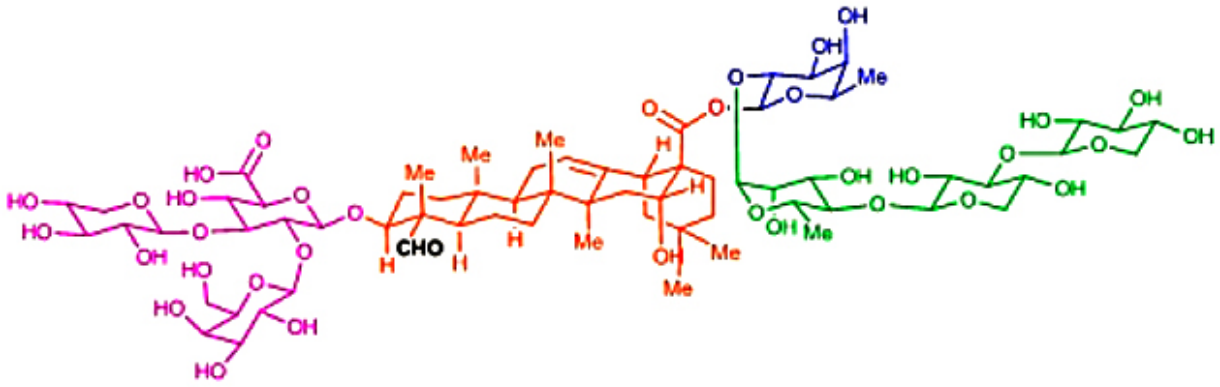

Fig. 1. Structure of QT-0101. The fucosyl residue is shown in blue and the aldehyde group (-CHO) in black. The triterpene nucleus is shown in red and the oligosaccharides in violet and green.

Essentially, ADs are caused by pro-inflammatory T-cell mediated immunity targeting proteins that are normal self-antigens, but, which are mutated or chemically modified after their synthesis to yield neoantigens. This pro-inflammatory immune response can then spread to other regions of normal self-antigens causing organ damage, like in multiple sclerosis (MS) and type 1 diabetes (T1D). Two kinds of vaccines are being developed to treat/prevent ADs, the tolerogenic and immunogenic vaccines, both being quite different from the classic pro-inflammatory vaccines against infectious diseases and cancer. Tolerogenic vaccines are made of fused proteins having a neoantigen and an endogenous immune modulator, like a cytokine or other protein ligand that

controls certain T-cell functions. Binding of these fused proteins to activated T-cells that recognize the self-antigen moiety, results in the T-cells' death and a long-term remission of the AD. Yet, these vaccines apparently work only after autoimmunity has been stablished, i.e. after the T-cells have been activated by a self-antigen, which makes them good candidates for therapeutic purposes. In contrast, the immunogenic vaccines can induce an anti-inflammatory response before the onset of autoimmunity; but, their development has been hindered by the lack of authentic sole anti-inflammatory adjuvants, such as fucosylated compounds.

While in immunogenic vaccines, the adjuvant's fucosyl residue would modulate the immunity type, their antigen upon uptake by endocytosis and processing by dendritic cells, will define the induced antibodies' specificity. An innovative anti-inflammatory adjuvant is the fucosylated glycoside QT-0101 (Fig. 1), composed of deacyated Quillaja saponins like QS-21. Removal of the acyl group from the fucose residue, leaves the hydroxyls at positions 3 and 4 free to interact with the binding site of DC-SIGN and induce an anti-inflammatory immunity. Because QT-0101 also has an aldehyde group that provides T-cells with an alternative co-stimulatory signal, it could prevent T-cell anergy. Hence, QT-0101 works by switching the systemic pro-inflammatory immune response to an anti-inflammatory one against a self-antigen; a response that would favor sialylation of the antibodies' Fc region, blocking their capacity to bind to the Fc receptors on dendritic cells and macrophages and promote inflammation. Because a specific anti-inflammatory antibody response can be induced before autoimmunity develops and without the risk of immunosuppression, the immunogenic vaccines may be used in both preventive and therapeutic modes. Since preventive vaccines against proteopathies like Alzheimer's disease, also require an anti-inflammatory immunity, QT-0101 may be an effective option for these vaccines.

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Publication

Effects of immunomodulators on the response induced by vaccines against autoimmune diseases.
Marciani DJ
Autoimmunity. 2017 Nov