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New cutaneous vaccine adjuvant that STING a little

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Generating a strong, long-lasting protective immune response is the goal of vaccination. Skin is one of the most obvious and attractive vaccination site and activation of innate immune cells is a proven strategy in vaccination. Despite the considerable improvement of injection devices, an unmet need for developing efficient vaccine adjuvants that induces little to no skin inflammation remains. While using adjuvants can enhance the immunogenicity of the vaccination formula and reduce the amount of antigen required, adverse reactions have to be considered as they could outweigh its benefits. Many current adjuvants induce severe skin inflammation that dramatically impacts the integrity of skin epithelia. Although there has been great progress in the identification of new adjuvants adjuvant, alum remains the dominant adjuvant for human vaccines. Even though many new adjuvant candidates have been evaluated over the years, most have failed to be successful in humans mainly because of toxicity, stability and cost. Furthermore, each adjuvant induces a characteristic immunological differentiation program such as Th1, Th2 or Th17, independently of the antigen targeted. An improved understanding of innate immune signaling should greatly contribute to the design more precise immunostimulants. The discovery of the STING pathway, a central pathway in antiviral innate immunity opened up several new possibilities in this area. STING agonists would be candidates for clinical testing as adjuvants and as stimulants for immune activity. The most potent natural STING agonist in humans is 2' 3'-cGAMP.

Wang and colleagues demonstrate the great potential of 2' 3'-cyclic GMP-AMP (cGAMP) adjuvant, the natural agonist of STING (Wang et al., 2016). The immune responses generated by cGAMP a string and long-lasting, greatly enhancing immunological protection against pandemic influenza, more efficient in intradermal delivery than intramuscular and not toxic for the skin.

The understanding of innate sensing of nucleic acids pathogen- or danger associated molecular patterns (PAMPs or DAMPs) is a critical step towards the improvement of the efficacy of vaccine formulations. Cytosolic pattern recognition receptors that sense nucleic acids in the cytoplasm have recently been explored. Immune sensing of nucleic acids is involved in both early innate defenses and subsequent bridging with adaptive immune responses (Stetson and Medzhitov, 2006). Viral infection can be sensed by the recognition of nucleic acids of viral origin through structural features that aren't founds in self nucleic acids. By contrast toll-like receptors (TLRs) can sense RNA and DNA molecules of both exogenous and endogenous origin. Recently, a new cytosolic DNA

sensor pathway has been described in dendritic cells to trigger a cell-autonomous antiviral response associated with IFN- $\alpha$  production via cyclic-GMP-AMP (cGAS), stimulator of interferon genes complex (STING) and interferon regulatory 3 (IRF3) (Lahaye et al., 2013; Sun et al., 2013). In regards to the potential cell damage generated by viral infection or cell stress, it has been hypothesized that cGAS sensor is activated by endogenous DNA (Marichal et al., 2011). However, STING is also implicated in sensing RNA as the replication of RNA viruses is enhanced in its absence (Marichal et al., 2011), and in viral restriction as several RNA viruses can antagonize STING (Aguirre et al., 2012). Furthermore, it has been recently suggested that the RNA virus, influenza A H1N1, stimulates the production of interferon through a cGAS-independent STING pathway through interaction with hemagglutinin fusion peptide (Holm et al., 2016).

Vaccine adjuvants are essential to the success of a vaccine by enhancing immunogenicity, reducing the antigen dose and the number of immunizations and potentiating a durable and fast T cell immune response and long lasting antibody production. Currently available influenza vaccines trigger a strain-specific immune response unfortunately obsolete against new influenza viruses or mutated substrains. Aluminium salts and MF59<sup>®</sup> are the major licensed adjuvants used in influenza vaccines. Although it is thought that the induced inflammation represent an important part of the adjuvancity of Aluminium Hydroxyde, its use results in necrosis of muscle fibers and inflammation with edema and infiltration of leukocytes. MF59<sup>®</sup> increases chemokine and inflammatory cytokine production and induces the recruitment of monocytes and neutrophils and the site of injection. Nonetheless, the injection of those adjuvanted vaccines induces local inflammatory reaction associated with clinical experiences of redness, swelling and pain at the injection site.

Several STING agonists vaccine formulations have been recently tested: cyclic dinucleotides adjuvanted formulations have demonstrated great antitumor potential in multiple therapeutic models of established cancer (Fu et al., 2015) and encapsulated dinucleotides with lipid nanoparticles demonstrated potent antigen delivery and stimulation in the draining lymph nodes in models of anti-tumor and anti HIV gp41 vaccination (Hanson et al., 2015).

Skin vaccines, advantages inconvenients, future/ recent developments...

Wang and colleagues demonstrate that the small STING natural agonist cGAMP has a great potential as influenza vaccine adjuvant. Indeed, intradermal vaccination with cGAMP induces a greater IFN- $\gamma$  response by CD4 and CD8 T cells and a higher IgG2a antibody titer when compared to intramuscular immunization with cGAMP or AddaVax™ – the squalene-based oil-in-water emulsion similar to MF59® - influenza vaccine formulations (Wang et al., 2016). Furthermore, they show that cGAMP influenza vaccine formulation induces very little to no inflammation at the site of injection and that neither dermis or epidermis are affected unlike other adjuvants such as resiquimod, a R848 small molecule agonist for TLR7/8 able to induce a strong type I IFN/ Th1 response similarly to single stranded viral RNAs.

#### Conflict of Interest

The authors state no conflict of interest.

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