

The inflammasome and alum-mediated adjuvanticity

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Abstract

Recent reports have implicated the NLRP3-associated inflammasome in the adjuvanticity of alum. Here, we summarize the major findings and ask what this may mean for improving human vaccination.

Introduction and context

Since the first report by Glenny *et al.* [1] that diphtheria toxoid precipitated with aluminum salt generated significantly better immune responses, aluminum-containing adjuvants (alum, aluminum hydroxide) have become the most widely used in human vaccines. Although safe and efficacious, the mechanism of action has remained obscure. Models have shifted from the capacity of adjuvants to establish depots promoting the slow and sustained release of antigen from the injection site, to current hypotheses acknowledging the key role of the innate immune system in providing cytokines and co-stimulatory pathways important for overcoming activation thresholds for adaptive immunity. In this model, adjuvants mimic signals from microbes whose recognition has been hardwired into innate immune recognition structures, as best exemplified by the Toll-like receptors. Alum provokes an antibody response, characterized by a predominance of immunoglobulin G 1 (IgG1) and immunoglobulin E (IgE), that is associated with Th2-mediated immunity [2], however, and host recognition elements associated with such responses remain incompletely defined.

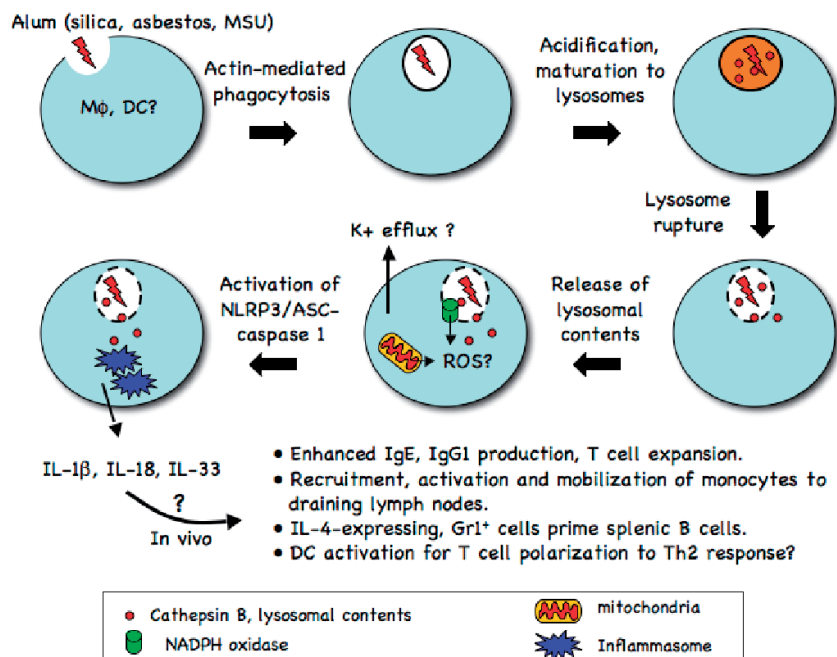
Major recent advances

Recently, several papers have implicated components of the inflammasome in the adjuvant activity of alum. The inflammasome is a cytosolic intermolecular platform assembled in response to a variety of cellular perturbations and leads to the activation of caspase-1 from its inactive procaspase form. In turn, active caspase-1

processes the proforms of several interleukin (IL)-1-family cytokines, including IL-1 β , IL-18 and IL-33 [3], and mediates cell death. Each of the reports investigating alum implicate the inflammasome containing NLRP3 (NALP3, cryopyrin, CIAS1), a member of the nucleotide-binding domain-and leucine-rich repeat-containing family of proteins, and an adaptor protein, ASC [apoptosis-associated speck-like protein containing a caspase recruitment domain (CARD)], raising questions of how alum is sensed by the host. Although different approaches and experimental detail preclude complete assessment, several [4–6], but not all [7], of the groups show that the alum-induced IgE and/or IgG1 response requires NLRP3, although all seem to agree that alum induces IL-1 family members through the NLRP3-mediated activation of caspase-1.

The NLRP3-associated inflammasome can be activated by structurally diverse molecules, including ATP [8–10], gout-associated crystals [monosodium urate (MSU) or calcium pyrophosphate dehydrate] [11], pore-forming toxins (nigericin, maitotoxin, aerolysin, streptolysin O) [8,9,12], bacterial RNA, antiviral imidazoquinoline compounds R837 and R848 [13], skin sensitizers [10,14], fibrillar amyloid β [15] and particulate molecules, including asbestos, silica and, as recently shown, alum [4–7,16–18]. Confirmation of a few of these effects is lacking, but it still remains an enigma how NLRP3 can recognize such heterogeneous structures. Pore-forming toxins or ATP activation of P2X7 receptors trigger potassium ion (K⁺) efflux from the cell [19]. Conversely,

Figure 1. Alum-induced NLRP3 inflammasome activation



Phagocytosed alum-containing lysosomes rupture and release their components to the cytosol by an unknown mechanism. The released contents and molecules generated during this process contribute to NLRP3/ASC/caspase-1 inflammasome activation, which in turn processes the proforms of IL-1 family members to active forms. Either IL-1 family member cytokines or the products from NLRP3 inflammasome activation may elicit various immunostimulatory effects *in vivo*. When and how potassium efflux and reactive oxygen species (ROS) play a role awaits further investigation. DC, dendritic cell; MSU, monosodium urate.

blocking K⁺ depletion inhibits activation of the NLRP3-inflammasome by these agents, as well as by crystal-like particulates, including alum [4,6,12,16,17,20,21]. Recombinant ASC forms oligomeric complexes at sub-physiological K⁺ concentrations, suggesting an important role for K⁺ efflux in promoting inflammasome assembly [21]. The finding that ATP and uric acid crystals released from damaged or dying cells activated the NLRP3 inflammasome raised the possibility that the inflammasome responded to endogenous signals of tissue injury [so-called danger-associated molecular patterns (DAMPs)] as originally proposed by Matzinger [22], rather than to specific microbial ligands [pathogen-associated molecular patterns (PAMPs)] as recognized by the Toll-like receptors. Importantly, however, only the crystalline forms of uric acid (MSU) and alum activate dendritic cells *in vitro*; the soluble forms are inactive [23]. Uric acid does not appear to be an intermediary during activation of the NLRP3 inflammasome pathway by silica, asbestos or alum, however, since uricase does not block inflammasome activation [4–6,16,18]. Thus, the commonality for inflammasome activation by these substances is their physical form as crystals, consistent

with the longstanding observation that particulates work as adjuvants.

Recently, Hornung *et al.* [18] showed that silica, MSU crystals and alum taken up by actin-dependent phagocytosis ultimately cause destabilization of lysosomes, with swelling, increasing pH and eventual rupture of lysosomal contents into the cytosol. Further, the induction of lysosomal rupture activated the NLRP3 inflammasome, even in the absence of other stimuli. Cathepsin B released from the lysosome into the cytosol was critical for activation of caspase-1 under these conditions (Figure 1). Cathepsin B has been previously associated with necrosis-like cell death. The pore-forming toxin, nigericin, induces rapid lysosomal leakage and re-location of cathepsin B into the cytosol [24], leading to caspase-1-independent, but cathepsin B-dependent, death, called pyronecrosis [25]; blocking cathepsin B activity impaired lysosomal leakage [26]. Moreover, NLRP3 mutations associated with human inflammatory syndromes induce a similar cathepsin B-dependent death pathway [26,27]. It is still not clear whether cathepsin B acts upstream or downstream of inflammasome activation, whether cathepsin B is directly sensed or plays a role in generating

a ligand for NLRP3 or whether its cytosolic localization and induction of pyro necrosis is a necessary step for activation of NLRP3. In addition, reactive oxygen species play a role in ATP or crystal-induced inflammasome activation [6,16,17], but the details of the inter-relationship between K^+ efflux, reactive oxygen species, lysosomal disruption, and, finally, their physiological significance in generating enhanced antibody responses remain unknown. Finally, the mechanism by which particulates result in lysosomal destabilization remains unclear, although the possibility exists that physical rupture of the membrane due to the irregularities of the crystalline substances is itself the common underlying pathway.

Future directions

An important question is whether the IL-1 family cytokines generated by the alum-activated NLRP3 inflammasome are critical for isotype switching to IgG1 and IgE. Alum induces neutrophil-rich granulomas at the injection site [28]. When injected into the peritoneum or trachea, alum or silica elicited neutrophil and monocyte recruitment by an IL-1/IL-1 receptor/MyD88 pathway [18,29]. Monocytes recruited by alum process co-injected antigens, mature, migrate to the draining lymph nodes and expand antigen-specific T cells through a process in part dependent on NLRP3 [6,29]. Whether these monocytes are required for enhanced antibody responses remains unanswered. Although IL-1 has been shown to increase antigen-specific T cells [30], IL-1R1-deficient mice generated normal antigen-specific antibody responses following intraperitoneal immunization in models using trinitrophenol-keyhole limpet hemocyanin and asthma [31,32]. IL-18 can increase IgE production and Th2 cytokines [33,34], but IgG1 and IgE production was not affected by IL-18 deficiency [35]. IL-33 stimulates production of IL-4, IL-5 and IL-13 [36]. However, deletion of the IL-33 receptor, T1/ST2, did not impair the alum-induced asthma response [37]. The lack of defects in the individual knockout mice may be due to redundant functions among IL-1 family members. All three of these IL-1 family members share MyD88 for signaling [38], however, and IgG1 production was normal in MyD88-deficient mice immunized with ovalbumin and alum [4,39] and no defect in antibody production was seen using mice genetically deficient in both MyD88 and TRIF (*Myd88*^{-/-}; *Trif*^{*Aps2*/*LpsS2*} mice) challenged with trinitrophenol-hemocyanin [40]. Therefore, until the possibility of a MyD88-independent signaling pathway is shown, the involvement of IL-1 family members in the alum response remains inconclusive.

Most of the *in vitro* experiments in these various reports used macrophages and/or human monocytic cell lines. Since dendritic cells (DCs) play a critical role in T cell activation and differentiation, an important question remains whether alum programs DCs to enhance a Th2-mediated immune response through activation of the NLRP3 inflammasome. Alum induced *in vitro* DC differentiation, as measured by upregulation of costimulatory molecules, in one [41], but not other studies [23,42]. Alum generated uric acid *in vivo* [29], which could lead to crystalline MSU particles able to induce DC maturation. Indeed, the alum-induced recruitment of monocytes to the draining lymph nodes was abrogated by uricase treatment [29]. DC activation may be regulated at the level of caspase-1 or ASC, and not by IL-1 family members. Caspase-1 has been shown to cleave many substrates that can regulate cell survival and tissue repair [43]. Toxin-mediated K^+ depletion induces sterol regulatory element binding protein (SREBP) activation via caspase-1, potentially leading to activation of membrane repair pathways [12]. It is also possible that alum facilitates Th2-associated immune responses independent of DCs. Alum recruits IL-4-expressing Gr1⁺ cells to the spleen where these cells could prime B cells [44–46] and suppress Th1-associated antibody responses [46]. Further study of the alum (or crystal)-induced inflammasome may provide insights into the integration of signals by the inflammasome and the molecular pathways that trigger Th2-associated immune responses, even beyond the antibody-enhancing effects of adjuvants, and greatly improve our capacity to design rational vaccine adjuvants for use in humans as well.

Abbreviations

ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain (CARD); DC, dendritic cell; IgG1, immunoglobulin G1; IgE, immunoglobulin E; IL, interleukin; MSU, monosodium urate.

Competing interests

The authors declare that they have no competing interests.

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