Antibodies and T Cells in Viral Infections

The vertebrate immune system functions to eliminate foreign nucleic acids that invade from infectious pathogens and malignant tumors. DNA/RNA motifs characteristic to microbes and cancer cells are recognized as "non-self" by the host innate immune system, represented by pattern-recognition receptors (PRRs), thereby being classified into microbe-associated molecular patterns (MAMPs). MAMPs participate in immune enhancement, which is a host strategy to eliminate invading cells. That is, a variety of PRRs recognize nucleic acid MAMPs. Of the Toll-like receptors (TLRs), TLR3 recognizes RNA double-stranded (ds) motifs such as viral dsRNA. TLR3 is particular in that 1. It is preferentially expressed in endosomes of antigen-presenting dendritic cells (CD141+ DCs), 2. It can be an exclusive target to induce cross-antigen presentation, 3. Several structured RNAs successfully attain endosomal TLR3 in antigen-presenting (CD141+) DCs. Here the researchers summarize the current status of TLR3 adjuvants designed to enter cells without transfection, minimize inflammatory side effects, and provide optimal immune enhancement.

1. Introduction

The genomic DNA of vertebrates, including humans, mutates over time and thereby evolves. On the other hand, DNA mutates endogenously at a certain frequency during the replication process, regardless of survival advantage or disadvantage. Mutations are often neutral. In general, genetic drift is subject to environmental selection and favorable traits are fixed. On the other hand, genomic DNA can also mutate in response to exogenous factors. Exogenous genetic mutations include cases of infections mediated by foreign agents such as retroviruses and transposons. The invasion of microorganisms and mutated genes threatens the identity of an individual's DNA, and the host immune system defends against this crisis by eliminating non-identical nucleic acids and proteins by inducing cell death and inflammation.

The vertebrate immune system consists of two modes of non-self-identification strategies: innate immunity and acquired immunity. Genetic mutations in vertebrates can lead to evolution if they occur in germ cells, and to cancer if they occur in somatic cells. Innate immunity prevents microbial invasion and specifically recognizes nucleic acids and membrane components, whereas acquired immunity specializes in identifying protein and peptide mutations. Both have surveillance mechanisms and appear to be sophisticated self-preservation mechanisms. Immune enhancement is one strategy to control infectious diseases and cancer [1][2]. Vaccination is an immunoenhancing method that targets specific 'non-self' organisms, usually in combination with antigen and adjuvant, to eliminate 'non-self' patterns [1][2]. Substances that have an immune-enhancing role are called adjuvants. Adjuvants are an important component of vaccines, but their own immunoenhancing effect (without antigen) is difficult to assess ex vivo and in vivo. It has been surmised that host response to the adjuvant usually reflects its inflammatory characteristics rather than its immune-potentiating effect [3]. Therefore, safe (non-inflammatory) vaccine adjuvants are rarely developed universally, and few TLR adjuvants have been established in drug discovery research.

2. TLR3-Specific Adjuvants

Human antigen-presenting dendritic cells (designated as CD141+ DCs) predominantly express TLR3 in endosome [4]. CD141 is an epitope of thrombomodulin. Several TLR3 agonists are currently developed aiming at clinical study, which satisfy the safe criteria and guarantee the specific targeting of DCs [3][5]. The researchers introduce ARNAX [3][5], and PLGA-Riboxxim [6] in this section.

ARNAX is a synthetic dsRNA 5'-capped with DNA [3]. The first report on this designed molecule was published in 2015, and proved that both in vitro-transcribed and chemically-synthesized products work as vaccine adjuvant [3]. Finally, the molecule was engineered so as to adapt GLP studies in animals, and surpassed criteria of safety and relative resistance to nucleases in preclinical studies. ARNAX can directly (s.c. or i.p.) administer to animals without transfection reagents to

evoke protective immunity against cancer or infectious diseases (defined by antigen) [3][5][7]. In vitro studies suggested that it acts on Toll-like receptor 3 (TLR3)-positive cells through endocytosis and the double-stranded RNA portion in ARNAX can activate TLR3 in the endosome [3]. Efficient activation of TLR3 by ARNAX required a double-stranded RNA portion greater than 120 bp [3][8][9]. In target cells, no activation of cytoplasmic RNA sensors such as RIG-I and MDA5 was observed in mouse in vivo studies [3][5]. Spleen CD8a+ dendritic cells exposed to ARNAX and antigen showed increased levels of co-stimulators, interferon (IFN)-message and IL-12p40 [3][5][10]. ARNAX has been used in vaccine to remit implant tumors and viral infections in mouse models [5][7].

Riboxxim is 100bp GI-rich dsRNA [6]. Initial models were Riboxxol or RGIC50 (50bp dsRNA) that contains Inosine. RGC100 was 100bp dsRNA with GC-rich sequence containing no Inosine, published in 2013 [11]. RGC100 was incorporated into JAWS II DC-like cell line (murine) and human CD1c+ DCs, and induced T cell proliferation. High levels of inflammatory cytokines were measured in the supernatant of DCs in response to GC100, suggesting that GC100 works as immune-potentiating adjuvant. Of note, no type I IFN was detected in the supernatant, for the reason unknown [11]. In the subsequent studies using PLGA-Riboxxim [6], Koerner et al., reported that Riboxxim activates the RIG-I/MAVS pathway in addition to the TLR3/TICAM-1 pathway in DCs, resulted in a strong type I IFN response including T cell proliferation. The authors showed efficient uptake of PLGA Roboxxim in murine and human DCs without transfection [6]. PLGA-Riboxxim was described in 2021 as a microparticle (MP)-adsorbed TLR3 agonist. MP enables DCs to take up tumor-associated antigen and TLR3 agonist simultaneously. PLGA-Riboxxim barely induce cytokinemia when administered by s.c. in mice. In tumor (OVA-loaded)-implant mice, tumor regression was observed in response to PLGA-Riboxxim + OVA antigen. Authors insisted that the combined activation of TLR3/TICAM-1 and RIG-IMAVS pathways is of great advantage for Riboxxim [6]. Since it activates both TLR3 and RIG-I, it appears to mediate a dsRNA transfer from endosome to cytoplasm in DCs.

The properties of ARNAX and PLGA-Riboxxim are more rational in terms of cytokine toxicity than the dsRNA adjuvants polyI:C and polyI:C (12U) reported earlier as TLR3 agonists [12]. Thus, these compounds appear to be a candidate for safe Th1 skewering adjuvant that could overcome regulatory approval. This research reviews the characteristics of designed TLR3 agonists in comparison with current Th1 adjuvants [11][12] and the advantages in vaccine development.

3. Innate and Acquired Immunity to Protect against Cancer and Infectious Diseases

Defensive immunity requires activation of innate and acquired immunity. Innate immunity recognizes microbial components (microbe-associated molecular patterns, MAMPs; pathogen-associated molecular patterns, PAMPs) and regulates cells through receptor signaling; MAMPs/PAMPs are characteristic motifs present in microbes but not in humans and are recognized by host pattern recognition receptors (PRRs) [13]. Innate immune PRRs, represented by Toll-like receptors (TLRs), are conserved in almost all multicellular organisms [14][15]. PRRs recognize "non-self" nucleic acids and signal the exclusion of foreign organisms even in plants [16], especially those that are infectious pathogens, to protect the host from infections. Thus, MAMPs are potential candidates for vaccine adjuvants, some of which have been investigated in clinical trials. However, a series of innate immune signals induced by administration of MAMPs, accompanied with severe inflammatory toxicity and signs of disease, forced the discontinuation of clinical trials. Insofar as vaccine side effects are representative of an innate immune response, administration of MAMPs would mimic the symptoms of an infectious disease. In other words, the genomic and nucleic acid identity of multicellular organisms is maintained by acute inflammation caused by the host's innate immunity. This highlights the need to ensure the safety of the use of MAMPs as vaccine adjuvants by making some adjustments prior to their clinical use.

In humans, the innate immune response of the host varies widely from individual to individual. In addition to genetic factors such as single nucleotide polymorphisms, epigenetics plays a major role in orchestrating the biological response to pathogens, including changes (or activation) of cells responsible for immune and cytokine responses [17][18]. That is, infectious diseases are systematized as syndromes caused by host responses triggered by innate and acquired immunity in addition to pathogenicity of the pathogen [19]. Therefore, the challenge is to design adjuvants that harmlessly evoke the immune system rather than induce pathogenicity resembling infectious diseases.

Innate immunity can be triggered by all cells in the body after exposure to microorganisms and is not limited to immune cells. Typical type I transmembrane receptors that sense infection by foreign pathogens are TLRs, and cytoplasmic receptors that sense infectious pathogens within cells are RIG-I-like receptors (RLRs) and Nod-like receptors (NLRs) [15]. Collectively referred to as PRRs [9], they are distributed in cytoplasm of cells throughout the body, resulting in a systemic response to infection; PRRs simultaneously function as adjuvant receptors. Thus, microbial adjuvants are presumed to be involved in the etiology and pathogenesis of infectious diseases. For this reason, many attenuated vaccines that imitate infectious diseases and signs should reach a high threshold in terms of safety.

Activation of acquired immunity is achieved by mechanisms involving antibody production or activation of T lymphocytes [1][2][19]. The current consensus regarding the origin of the immune system is that innate and acquired immunity are separate but hierarchically linked systems in vertebrates [20]. Acquired immunity is essentially a mechanism by which protists selectively produce a variety of surface proteins through genetic recombination or transformation, as indicated by the presence of rearrangement activating genes (Rag) and transposase activity in protists in the surface protein change mechanism [21]. Protists evade attack by host immune cells by exchanging surface proteins. Human acquired immunity is derived from a gene rearrangement mechanism incorporated into lymphocytes, the activation of which has multiple triggers independent of infection. Although the complement system is classified as innate immunity, complement receptors do not show the same close link to acquired immunity as PRRs. An array of PRR-acquired immunity is triggered by type I interferons and followed by an induced response with inflammation [22], which are inextricably linked to DC activation. Thus, DC activation by PRRs triggers acquired immune response in humans [13][15][20][23]. This sequence of immune activation is conserved from lamprey to humans.

Activation of acquired immunity is characterized by the proliferation of specific lymphocyte clones triggered by signals from cell adhesion clusters known as antigen-presenting complexes [24]. Dendritic cells select specific T lymphocytes and subsets to be responsible for antigen presentation [6]. Thus, activation of acquired immunity can be monitored by the proliferation of T cells and subsets with receptors that match the specific antigens presented by the major histocompatibility complex (MHC) of dendritic cells [6][25]. Activation of T lymphocytes reflects the binding of dendritic cells to the molecular cluster of T cells. Molecules and cytokines clustered on dendritic cells tend to be upregulated in response to adjuvants, amplifying T cell activation [13][15][24].

B lymphocytes are responsible for antibody production; B lymphocytes have antigen receptors that recognize antigens and activate specific B cell clones [26]. Through dendritic cell-dependent or -independent pathways, B cells are potently activated (antibody production) [27]. Activation-induced cytidine deaminase (AID) governs B lymphocyte class switching (switch recombination), and humoral factors and CD4+ helper T cells are involved in B lymphocyte activation [27][28]. Adjuvants are thought to be important in enhancing the production of subclass-specific immunoglobulins by promoting class switch recombination [26][29].

Natural killer (NK) cells belong to innate lymphocytes and are activated in response to adjuvants [3][30][31]; NK cell activation involves dendritic cell-dependent and -independent pathways, and the Rae-1 molecule in stimulating cells is thought to be involved in activating NK receptors [30][31]. Adjuvants may be associated with activation of other innate lymphocytes, NKT cells, and γδ T cells, but this has not yet been determined [32][33][34]. Vaccines can be designed to selectively reproduce this sequence of events, and adjuvants may help to achieve these cascades.

4. Antibodies and T Cells in Viral Infections

DC activation orchestrates the acquired immune response. Which of T cells and B cells play a major role in virus elimination is case-dependent, but both work for protection of host genes from mutation. Dendritic cells bind T cells displaying the MHC complex (CD4/8, MHC (peptide)–T cell receptor, TCR)) and other co-stimulatory molecules [35][36]. The dissociation constant (Kd) of the MHC (peptide)–TCR complex is weak, about 10^{-6}(depending on the sequence), and requires other molecules for strong adhesion [19]. Furthermore, a large number of TCRs must be assembled to allow sufficient proliferative T-cell signaling [19]. CD8+ T cells activate proliferation pathways, such as Src, protein kinase C (PKC) and PI3-kinase, through dendritic cell–T-cell adhesion. Neutralizing antibodies recognize antigen structures with four planes in the variable region and thus have high affinity, with the Kd of an antibody–antigen complex usually greater than 10^{-9} [19]. In chimeric antigen receptor T (CAR-T) cells, antibody F (ab) have been shown to bind well to CD19 and other molecules on target cells by external cross-linking [37]. Antibodies are often effective in recognizing not only antigens on cells but also free antigens in the liquid phase [38][39]. The multifaced recognition shows the advantage of neutralizing antibodies.

The advantage of cytotoxic T lymphocytes (CTLs) lies in recognition of intracellularly processed short-chain peptides. Short-chain peptides were conceived as candidates for universal vaccines against cancer and infectious diseases. Mutant antigens, testis-specific antigens, and pan-cancer antigens, such as WT1, have been selected as cancer vaccines. However, exogenous administration of short-chain antigen peptides is usually unsuccessful because neither phagocytosis nor antigen cross-presentation occurs in DCs [40]. Furthermore, the diversity of the human MHC creates additional challenges. Because humans are hybrids, it can be difficult to extrapolate results from inbred strains of mice to human clinical trials [40].

In this context, the efficacy of vaccine-induced antiviral immunity depends on the type of virus, even when the vaccine-associated enhanced disease is excluded [41]. For certain viruses, such as respiratory syncytial virus (RSV) and SARS-CoV, vaccine efficacy cannot be predicted from the antibody titer of vaccines [7][42]. In such cases, evaluation of "antiviral effectors" (represented by T cells) other than antibody titers is necessary for prevention [43][44], and fever and inflammatory signs are not necessarily reliable markers for assessing vaccine efficacy.

What is needed for the SARS vaccine is not an increase in neutralizing antibody titers but activation of dendritic cells by Th1 adjuvants [42][43]. This includes combined effects consisting of antigen-specific CTL induction, CD4+ T cell activation, and antibody production. In addition, other inducers for dendritic cell activation may exist. Where vaccines have proven to be effective, for example, against measles, mumps, and rubella viruses, a distinction must be made because neutralizing antibodies are effective against these viral infections [19]. In addition, antibody titers alone may not be sufficient to determine vaccine efficacy in some virus species [44][45][46]. For this reason, viral vaccines require the quantification of CTLs as well as antibodies.

5. Safeguarding of the Vaccine

Vaccines are one method of deliberately activating immunity to protect against infection. A vaccine consists of an antigen and an adjuvant. Peptide vaccines for cancer immunity have proven that peptides alone do not exert immuno-potentiating functions. Immune enhancement usually results from the addition of an adjuvant. However, attenuated/inactivated vaccines of viruses and bacteria contain live adjuvants, which inevitably induce side effects indicative of infectious diseases. Such side effects often result in candidate vaccines failing toxicity tests, and therefore not gaining approval. Many of the licensed routine and optional vaccines use Alum as an adjuvant, purportedly from a conventional point of view. The advantages of Alum are that it barely promotes serious fever and inflammation, and does not affect the impurity of the antigen preparation (including the PAMP components). However, despite its long-term use, the molecular response to Alum has not been always defined, making it impossible to define and standardize adjuvant function [47][48].

The immune response to vaccines varies from individual to individual and also between infectious strains and mutant strains. Vaccines can also induce adverse events, such as an over-amplified immune response, which may be damaging to the host [49][50]. In general, vaccines require immune enhancement by the inclusion of a safe adjuvant. It is essential to establish a non-toxic and versatile adjuvant that can be used with a wide range of antigens in all patients. Next-generation vaccines that are superior to mRNA need to be supported by the development of adjuvants that meet safety standards.

6. Perspective Remarks

Adjuvants include a wide range of compounds recognized by PRRs. TLR signals (with the exception of TLR3) converge onto MyD88 and are classified as 'inflammatory' adjuvants leading to cytokinemia in patients with infectious diseases. Only TLR3 can induce selective activation of antigen-presenting (CD141+) dendritic cells through its adaptor TICAM-1 alone and is thereby considered a safe dendritic cell adjuvant. Thus, adjuvants should be categorized into inflammatory adjuvants and dendritic cell adjuvants by clear definitions, and the current categorization based on identified and unidentified receptors is merely a historical convenience. In this context, ARNAX and PLGA-Riboxxim initiate a new era for adjuvant; both are defined based on their innate immune receptors, and evaluated by their functional properties, efficacy and safety. Although whether or not their functional differences are significant in vaccination remains to be tested, these issues including DC subset and DC's RIG-I activation are rather peripheral: it is crucial to establish a strategy of DC-targeting for safely evoking cross-antigen presentation. Generally, designed adjuvants appear to work better in safety and efficacy in vaccination according to comprehensive studies [51][52]. Activation of DCs followed by acquired immunity is the pivotal aim of vaccine adjuvant, and inflammation and cytokinemia are rather separate responses for development of new vaccines.

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