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Toll Like Receptors: Role in Immunity and Vaccine Production

A. Jayasri[1*] and C.H. Priyadarshini[2]

[1]Assistant Professor and Head, Department of Veterinary Biochemistry, College of Veterinary Science, Rajendranagar, PVNRTVU, Hyderabad-500030.
[2]Assistant Professor, Animal Husbandry Polytechnic, Mahaboobnagar.
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Introduction

Given the growing global concerns about the growing potential of antibiotic resistance, vaccination is now the most effective method of managing infectious illnesses, particularly in low- and middle-income nations with inadequate pharmaceutical regulatory frameworks. However, the resurgence of numerous infectious illnesses and the introduction of novel pathogen strains are raising new public health issues. It's still difficult to create vaccinations that effectively prevent infectious diseases, particularly those caused by newly developing viruses. Understanding host-pathogen immune responses and creating new vaccines based on this information are necessary to increase the immunological potency of currently available vaccinations.

PAMPs are conserved highly expressed functional microbial components, recognized by receptors in humans and animals. Pattern Recognition Receptors (PRRs), which are receptors that bind to PAMPs, identify these conserved microbial components and start immunological cascades that result in chemotactic factors, proinflammatory and antimicrobial responses, and other responses when an infection occurs. Toll-like receptors (TLRs), a type PRRs, are located on both the cell surface and within the endosomes.

Toll-like receptors (TLRs) are a family of type I transmembrane proteins which recognize microbe-associated molecular patterns (MAMPs) such as LPS, peptidoglycan, lipoproteins, flagellin, single-stranded RNA, viral and bacterial DNA. Most cells, including epithelial cells, fibroblasts and immune cells express TLRs on their surface or intracellularly. Ligand binding by TLRs activates a complex network of signal transduction proteins, which induce the secretion of pro inflammatory cytokines and antimicrobial peptides, resulting in the recruitment and activation of neutrophils, macrophages and dendritic cells, and ultimately the activation of the adaptive immune response. TLRs are evolutionary conserved and ten and twelve functional TLRs were identified in humans and mice, respectively. Similarly, in dogs the expression of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8 and TLR9 has been described (Novak et al., 2022).

To date, 10 TLRs (TLR1–TLR10) have been identified in humans, and 13 in mice, and different studies have revealed their respective TLR ligands (Takeda and Akira, 2005). Respective TLR agonist can activate specific TLR signaling, and following recognition of ligands, TLRs recruit adapter molecules such as myeloid differentiation primary response protein 88 (MyD88), TIR domain containing adapter protein (TIRAP)/MyD88 adaptor–like protein (MAL), Toll–IL-1–resistance (TIR) domain-containing adapter inducing IFN-β (TRIF; also known as TICAM1) and TRIF-related adapter molecule (TRAM; also known as TICAM2) culminate in the activation of nuclear factor (NF)-κB or interferon (IFN) regulatory factor (IRF),

regulating immunomodulation. MyD88 is the common downstream adaptor recruited by all TLRs, except for TLR3. TLRs activate multiple steps in the induction of inflammatory reactions toward eliminating the invading pathogens and help in the systemic defense. A strong activation of the innate immune system is important for maturation and activation of immune cells as well as production of cytokines and chemokines to induce a potent adaptive immune response. Moreover, TLRs play role in multiple dendritic cell functions and induce signals that are critical for initiation of the adaptive immune responses.

Numerous investigations are currently underway to develop an effective adjuvant system using TLR agonists to enhance vaccine efficacy (Kayesh et al., 2021; Pulendran and O'hagan, 2021).

Agonists come from a variety of sources, both natural and synthetic, and specific natural ligands have been identified for different TLRs. Examples include lipoproteins and peptidoglycans for TLR2, double-stranded RNA of viral origin for TLR3, bacterial lipopolysaccharide (LPS) and lipoteichoic acid for TLR4, bacterial flagellin for TLR5, single-stranded RNA for TLR7 and TLR8, unmethylated CpG motifs found in bacterial DNA or viruses for TLR9, and viral protein/viral RNP complexes for TLR10 (Bezemer and Garssen, 2021). Synthetic TLR agonists, developed by mimicking the molecular patterns and the immunostimulatory activities of their natural ligands, have been investigated for specific applications (Yang et al., 2022). Synthetic TLR agonists, such as Pam3CSK3 for TLR2 and TLR6, Poly I:C for TLR3, monophosphoryl lipid A (MPLA) for TLR4, imidazoquinoline-like molecules, imiquimod (R-837), resiquimod (R-848), S-27609, and guanosine analogs (e.g., loxoribine) for TLR7/8, as well as unmethylated CpG DNA for TLR9, have been reported (Kaczanowska et al., 2013).

Toll-like receptors (TLRs) play a critical role in the immune response and are increasingly recognized as important components in the development and enhancement of animal vaccines. TLRs are a class of pattern recognition receptors (PRRs) that detect pathogen-associated molecular patterns (PAMPs) and initiate immune responses. Here's how TLRs influence animal vaccinations:

1. Adjuvant Development

- **Enhancing Vaccine Efficacy:** TLR agonists are commonly used as adjuvants in vaccines to boost the immune response. For example:
    - **TLR4 agonists** like monophosphoryl lipid A (MPLA) are used to enhance both innate and adaptive immunity.
    - **TLR7/8 agonists** (e.g., imiquimod) can stimulate antiviral responses by promoting the production of interferons and cytokines.
- **Direction of Immune Responses:** TLR stimulation can bias the immune response toward a Th1, Th2, or Th17 profile, depending on the TLR and context. This is critical for tailoring vaccines against different pathogens.

2. Priming the Innate Immune System

- TLRs rapidly activate the innate immune system, producing cytokines and chemokines that recruit and activate antigen-presenting cells (APCs) like dendritic cells and macrophages.
- This activation creates a robust environment for presenting antigens to T and B cells, thereby improving the generation of adaptive immune responses.

3. Enhancing Mucosal Immunity

- TLRs are expressed in mucosal tissues, and their activation is critical for developing vaccines targeting mucosal pathogens. For example, intranasal vaccines often use TLR ligands to enhance localized immunity in respiratory tracts.

4. Improving Safety and Reducing Side Effects

- Using specific TLR agonists can improve vaccine safety by eliminating the need for

whole-pathogen adjuvants, which can cause adverse effects.

- By modulating immune activation precisely, TLR-targeted adjuvants minimize the risk of overactivation or autoimmune responses.

5. Applications in Novel Vaccine Platforms

- **mRNA Vaccines:** These rely on the innate immune activation of TLRs, particularly TLR7/8, recognizing RNA molecules.
- **Recombinant and Subunit Vaccines:** TLR agonists compensate for the low immunogenicity of purified antigens, making these vaccines more effective.

Examples of Animal Vaccines Utilizing TLR-Based Approaches:

- **Feline and Canine Vaccines:** Adjuvants targeting TLR4 improve responses to rabies and other viral vaccines.
- **Livestock Vaccines:** TLR agonists are used in vaccines for bovine respiratory diseases and porcine infections to enhance immune responses and reduce disease prevalence.
- **Aquaculture Vaccines:** TLR ligands are employed to stimulate immune responses in fish, which have unique immune system features.

Research and Challenges

- Identifying TLR ligands specific to different species is critical because TLR expression and function vary between animals.
- Overactivation or inappropriate activation of TLRs can lead to immunopathology, so precision in adjuvant design is crucial.

In summary, TLRs are central to the design of modern animal vaccines, enhancing immunogenicity, directing immune responses, and improving overall vaccine efficacy and safety.

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