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Research Paper

Advances in swine immunology help move vaccine technology forward

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ABSTRACT

In veterinary animal species, vaccines are the primary tool for disease prevention, a key tool for treatment of infection, and essential for helping maintain animal welfare and productivity. Traditional vaccine development by trial-and-error has achieved many successes. However, effective vaccines that provide solid cross-protective immunity with excellent safety are still needed for many diseases. The path to development of vaccines against difficult pathogens requires recognition of uniquely evolved immunological interactions of individual animal hosts and their specific pathogens. Here, general principles that currently guide veterinary immunology and vaccinology research are reviewed, with an emphasis on examples from swine. Advances in genomics and proteomics now provide the community with powerful tools for elucidation of regulatory and effector mechanisms of protective immunity that provide new opportunities for successful translation of immunological discoveries into safe and effective vaccines.

1. Introduction

For the purpose of protecting animal health, vaccinology is the application of immunology to solve infectious disease problems. Infectious diseases exert a profound burden on animal health and welfare, cause economic injury to farmers and producers, and threaten human populations through zoonotic transmission of endemic and epidemic disease due to established and newly emergent pathogens. More recent non-disease applications of immunology include the use of vaccination to induce immunological castration of boars for elimination of boar taint.

2. Innate immune response to infection

In the case of infectious disease, the immunological principles that guide current thinking on vaccine development and efficacy can be grouped into categories related to antigen detection, stimulation of an appropriate adaptive response, and establishment of memory. Detection of a pathogen is mediated by innate danger signals in cells that sense infection by the presence of molecular structures, including viral double-stranded RNA, CpG motifs of bacterial DNA, bacterial lipopolysaccharide (LPS), and repetitive structures such as viral capsids, that are not present in healthy cells. The danger signals elicit a robust intracellular immune response with sufficient plasticity to guide intracellular immune responses that are appropriate for the invading pathogen (Beutler et al., 2007). A striking demonstration of this plasticity is the varying patterns of gene expression induced in human dendritic cells exposed to *Escherichia coli*, influenza virus, or *Candida albicans* (Huang et al., 2001). In this microarray expression

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profiling experiment, 289 genes were pathogen-regulated. Interestingly, a unique set of 118 genes were specific for *E. coli*, and 58 were specific for influenza, but no genes were specifically induced in response to the fungus (Huang et al., 2001). This result suggests that a multitude of signals are triggered and integrated early in an immune response to finely modulate host responses to infection.

Viral infection of permissive cells induces, most prominently, a mRNA expression profile dominated by type I interferons (α and β) and interferon-responsive genes. These pathways are activated by viral components binding to cell surface and intracellular sentinel proteins including various Toll-like receptors (TLRs), retinoic acid-inducible gene (RIG-I), and melanoma differentiation-associated protein 5 (MDA-5), to initiate signaling cascades through a variety of pathways that trigger type I interferons and interferon-responsive effectors. Similarly, bacterial infection also induces gene expression cascades through interactions of cell wall components, CpG and other conserved bacterial features with TLRs. Signaling cascades through NF-κB and cyclic AMP-dependent protein kinases, in particular, induce inflammatory cytokine production. The molecular sensors and signaling pathways for other common pathogen classes, including fungi, nematodes, cestodes, amoeba, apicomplexa and so on, are less well characterized. It may reflect the fact that rapidly dividing organisms such as viruses and bacteria require rapid responses to overcome the high rates of replication that these pathogens can achieve and which may result in incapacitation or death. Therefore, there is a powerful selective force to evolve efficient innate sensors, response pathways, and effector molecule countermeasures. By contrast, pathogens that do not produce an immediate threat to host well-being may have evoked a lower selective pressure, or the animal hosts may have evolved immunological strategies that tolerate the pathogen at the cost of reduced energy partitioning for growth and reproduction, in which case more time is available to develop physiological and immunological survival mechanisms.

The general molecular features of innate anti-viral and anti-bacterial responses that have been elucidated primarily in murine host–pathogen models provide useful models for investigation of host defense in veterinary species. In swine, for example, respiratory infection by the gram-negative bacteria, *Actinobacillus pleuropneumoniae*, induces an acute, robust lung cytokine response characterized by IL-1, IL-6 and IL-8 production (Baarsch et al., 1995, 2000; Morrison et al., 2000; Myers et al., 2002; Van Reeth et al., 2002). However, despite the presence of bacterial LPS and CpG DNA, there is no induction in vivo of tumor necrosis factor (TNF), the classical inflammatory cytokine molecule and effector product of NF-κB activation, even though in vitro incubation of alveolar macrophages with boiled extracts of *A. pleuropneumoniae* readily induces TNF (Baarsch et al., 1995, 2000). The lesson learned here is that laboratory models provide guidance for hypothesis-driven studies in veterinary animal species, but the details must be verified by experimental analysis.

A contemporary idea in anti-viral immunity is that the plasmacytoid dendritic cell, a rare cell type in blood, produces prodigious amounts of interferon α upon viral stimulation, and thus plays a key role in antiviral immunity (Liu, 2005). Nevertheless, direct evidence in support of this key antiviral role has been difficult to obtain (Reizis et al., 2011). Indeed, an interesting example in swine relates to the role of type I interferon in development of immunity to porcine reproductive and respiratory syndrome virus (PRRSV). An early, influential study concluded that PRRSV does not result in appreciable interferon α production (van Reeth et al., 1999). Since other studies indicated that PRRSV infection was persistent and adaptive immune responses were slow to develop, it was widely assumed that lack of interferon production was the key immunological defect (Murtaugh et al., 2002). However, direct examination of adaptive immune responses to PRRSV infection, in comparison to simultaneous responses to an irrelevant antigen, indicated no delay in the antigen-specific adaptive response (Mulupuri et al., 2008). It was subsequently shown that type I interferon induction is a variable, strain-dependent feature of PRRSV infection (Lee et al., 2004). The role of type I interferons in PRRSV immunity and vaccinology is confusing at present and serves as a cautionary tale against relying on untested assumptions about immunological mechanisms in veterinary species (Murtaugh and Genzow, 2011).

The discovery of TLRs and other innate sensors of microbial infection in the 1990s appeared to present a convenient mechanistic explanation for the activity of adjuvants. It held the promise that development of TLR ligands would provide a rational route to improved adjuvants for subunit and inactivated microbial vaccines. While it is clear that TLR ligands enhance adaptive B-cell and T-cell responsiveness (Khoruts et al., 1998; St Paul et al., 2013), these actions may not be mediated by TLR signaling. A well-known property of adjuvants is the enhancement of antibody responses, but genetic ablation of TLR signaling pathways did not affect the level of antibodies raised to various T-cell dependent antigens administered with a variety of classical adjuvants (Gavin et al., 2006). Likewise, administration of type I interferon or poly ICLC (a synthetic complex of polyinosinic–polycytidylic acid stabilized with poly-L-lysine and carboxymethylcellulose), a TLR-3 agonist, with attenuated PRRSV vaccination did not enhance protection against virulent challenge, and may have exacerbated disease (Charerntantanakul et al., 2006; Murtaugh and Genzow, 2011; Zhu et al., 2007). Although the molecular mechanisms by which adjuvants potentiate antigen-specific immune responses are not completely elucidated, the investigations stimulated by the discoveries of innate sentinels of danger or non-self have firmly established the role of innate responses to infection in initiation of productive antigen-specific B-cell and T-cell responses that are the foundation of vaccination.

3. Antigen-specific adaptive immunity

Prior to the discovery of innate molecules that sensed different classes of pathogens, Coffman and Mosmann and colleagues recognized that individual helper T-cell clones displayed cytokine secretion patterns that fell into two classes based on production of interleukin-2 (IL-2), interferon γ, and IL-4 (Mosmann et al., 1986; Mosmann and