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Review

The bovine model for elucidating the role of γδ T cells in controlling infectious diseases of importance to cattle and humans☆

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ABSTRACT

There are several instances of co-investigation and related discoveries and achievements in bovine and human immunology; perhaps most interesting is the development of the BCG vaccine, the tuberculin skin test and the more recent interferon-gamma test that were developed first in cattle to prevent and diagnosis bovine tuberculosis and then applied to humans. There are also a number of immune-physiological traits that ruminant share with humans including the development of their immune systems in utero which increases the utility of cattle as a model for human immunology. These are reviewed here with a particular focus on the use of cattle to unravel γδ T cell biology. Based on the sheer number of γδ T cells in this γδ T cell high species, it is reasonable to expect γδ T cells to play an important role in protective immune responses. For that reason alone cattle may provide good models for elucidating at least some of the roles γδ T cells play in protective immunity in all species. This includes fundamental research on γδ T cells as well as the responses of ruminant γδ T cells to a variety of infectious disease situations including to protozoan and bacterial pathogens. The role that pattern recognition receptors (PRR) play in the activation of γδ T cells may be unique relative to αβ T cells. Here we focus on that of the γδ T cell specific family of molecules known as WC1 or T19 in ruminants, which are part of the CD163 scavenger receptor cysteine rich (SRCR) family that includes SCART1 and SCART2 expressed on murine γδ T cells. We review the evidence for WC1 being a PRR as well as an activating co-receptor and the role that γδ T cells bearing these receptors play in immunity to leptospirosis and tuberculosis. This includes the generation of memory responses to vaccines, thereby continuing the tradition of co-discovery between cattle and humans.

1. Setting the stage: vaccine has its root in "vacca", meaning cow in Latin

Since this issue of Molecular Immunology is about the potential for using animals other than lab animals as a model for studying human immunology by way of introduction we indicate a number of key immunological observations that were made initially in ruminants, or specifically cattle, prior to the analogous observation in humans. These include the discovery by Roy Owen showing that non-identical twin cattle that exchanged blood due to a shared bovine placenta were tolerized to skin grafts exchanged between the two twins (Owen, 1945); this was later expanded upon by Medawar using mice for which he received a Nobel Prize. The use of gene conversion to diversify antibody repertoires was described in cattle (and sheep) prior to being described for humans (Parng et al., 1996; Reynaud et al., 1985). The ability of γδ T cells to present antigens was also first observed using bovine cells (Collins et al., 1998), followed many years later by a similar demonstration using human cells (Brandes et al., 2005). Cattle also played a significant, if indirect, role in the development of the first vaccine whose root is the Latin word "vacca" for cow. This of course is the story of Edward Jenner who in the late 1790s observed that milk maids exposed to cowpox (caused by the vaccinia virus) were resistant to infection with the smallpox virus. As nice parallels, nearly 200 years later one of the first recombinant vaccines was designed for use in cattle using vaccinia virus as a vector for expressing the hemagglutinin (HA) and F genes of the rinderpest virus (Yilma et al., 1988). Bovine rinderpest

Abbreviations: AMLR, autologous mixed lymphocyte reaction; DAMP, damage-associated molecular pattern; DC, dendritic cell; IFN, interferon; IPP, isopyroprenyl phosphate; KIR, killer inhibitory receptor; mAb, monoclonal antibody; MHC, major histocompatibility complex; PAMP, pathogen-associated molecular pattern; PBMC, peripheral blood mononuclear cell; PRR, pattern recognition receptor; SRCR, scavenger receptor cysteine rich; TCR, T cell receptor; BCR, B cell receptor; TLR, toll-like receptor; WC1, workshop cluster 1.

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was eradicated in 2011 using a thermostable vaccine (Mariner et al., 1990), being only the second infectious disease to be eradicated on earth (the first being smallpox). Rinderpest was known as "cattle plague" because of its devastating effects on livestock and associated widespread famine (Barrett and Rossiter, 1999). Finally, the BCG vaccine for tuberculosis was first developed for and used in cattle (Waters et al., 2012) and was followed by development of the tuberculin skin test in cattle that was subsequently adopted by human medicine and most recently the interferon-γ (IFNγ) test that was also initially developed as a tuberculosis diagnostic tool for cattle (Wood et al., 1990) and is now used for human diagnosis.

These stories of investigation, and related discoveries and achievements in bovine immunology, and the impact on human health are interesting, but it is important to note that ruminant also have greater similarity to humans than do the often-used mouse model with regard to several aspects of immunophysiology, increasing the utility of cattle as a model (Hein and Griebel, 2003). Such aspects include development of the fetus and its immune system. Humans and cattle have similar fetal placentation and gestation time as well as the timing of their immune system development. During fetal life, both ruminants and humans have their lymph tissues populated with T and B cells and these cells have matured and can be found in the periphery prior to birth including in the mucosal-associated lymphoid tissue that develops in utero (Griebel and Hein, 1996). As a result both cattle and humans respond to antigens in utero (Rossi et al., 1978; Tierney and Simpson-Morgan, 1997) and thus studies of immune tolerance pre- and immediately post-birth are more relevant between these two species than between humans and mice. The bovine immune system also has some similarities to humans that mice do not share with regard to pathogen recognition receptors (PRR). This includes the presence of a multigeneic array of killer inhibitory receptors (KIR), making cattle unique outside of primates with both activating and inhibitory KIR within these families. Albeit, the bovine KIR gene subfamily that expanded is related to the single primate KIR3DX1 gene while cattle have only one functional KIR3DL-lineage gene but primates have a variable number (Guethlein et al., 2007). Cattle also have a single functional Ly49 gene as do humans but not mice. It is polymorphic in cattle providing a model to investigate the consequences of this (Dobromylskyj and Ellis, 2007; McQueen et al., 2002; Storset et al., 2003). Cattle and humans both have 10 toll-like receptor genes (Werling and Coffey, 2007); the 10 bovine TLR genes are each homologous to one in humans with 83–90% at the nucleotide level (Menzies and Ingham, 2006). Interestingly, there have been reports of polymorphisms in TLR genes in cattle that contribute to disease susceptibility and resistance for *Mycobacterium avium paratuberculosis* (Fisher et al., 2011) and *M. bovis* (Sun et al., 2012), diseases important in both humans and cattle.

2. Cattle as study species of γδ T cell biology

γδ T cells are found in especially large proportions in a number of species of livestock including ruminants, pigs and poultry (Mackay and Hein, 1989; Mackay et al., 1986; Pieper et al., 2011; Sinkora and Butler, 2009; Walker et al., 1994). Such animals are known colloquially as γδ T cell high species. That is γδ T cells may comprise up to 60% of circulating blood mononuclear cells in the young of cattle (Mackay and Hein, 1989), sheep (Mackay et al., 1986) and pigs (Takamatsu et al., 2006) and while the γδ T cells decrease in representation as the animals age, they still are 'high' into adulthood. For example, 8–18% of adult bovine peripheral blood mononuclear cell (PBMC) populations were γδ T cells (Mackay and Hein, 1989; Rogers et al., 2005), similar in abundance to some other lymphocyte populations in bovine PBMC: CD8T cells (10–26%) (Ellis et al., 1986),

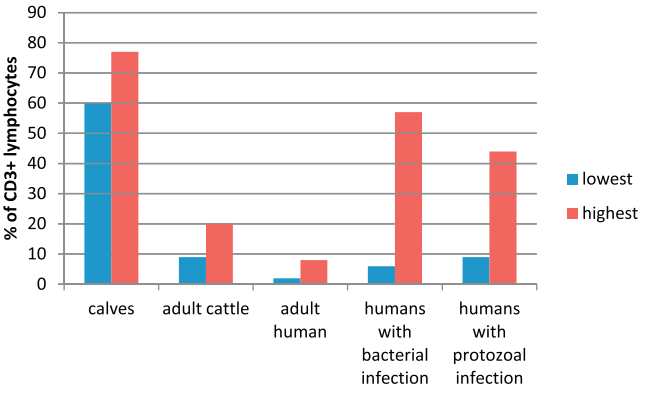

Fig. 1. Relative percentage of γδ T cells in human and bovine CD3⁺ populations. Proportion of γδ T cells among CD3⁺ T cells in humans and cattle at different ages or disease conditions. The minimum and maximal observed ranges are shown. Data for human infectious diseases adapted from (Morita et al., 2007).

CD4T cells (23–35%) (Baldwin et al., 1986), and B cells (20–22%) (Naessens et al., 1990). While the representation of those latter mentioned populations is also similar to those found in human PBMC, the proportion of human γδ T cells is generally decreased to 2–5% by adulthood (Morita et al., 2007). However there can be an increased representation of γδ T cells in human PBMC in response to infectious diseases with the mean percentages associated with various bacterial infections ranging up to 57% of CD3+ cells and in one case of ehrlichiosis the γδ T cells comprised 97% of the CD3+ population (Morita et al., 2007) (Fig. 1).

Based on the sheer number of γδ T cells in the γδ T cell high species it is reasonable to expect them to play an important role in protective immune responses and for that reason alone they may provide good models for elucidating at least some of the roles γδ T cells play in protective immunity. From that viewpoint of undertaking fundamental research on γδ T cells, cattle make good subjects because of the oft-cited advantage of obtaining large numbers of γδ T cells not only because of the higher proportions but because large volumes of blood can be obtained from which to isolate the cells for in vitro assessment and experimentation without harming the animal. Moreover the γδ T cells can be repeatedly sampled from the same animal for longitudinal studies. In addition, in vivo manipulation is possible through the use of monoclonal antibody (mAb) deletions of populations (Kennedy et al., 2002) and even thymectomy can be combined with mAb deletion (Valdez et al., 2001) to prevent development of new γδ T cells. Finally ruminants have also lent themselves to studies on lymphocyte recirculation by using lymph cannulation. These studies provided seminal knowledge early in the scientific history of T cells (Miyasaka and Trnka, 1986). Such studies have been continued and recent studies have shown that the bovine γδ T cells that home to the skin express CCR4 and CCR10 while recirculation of those cells through the afferent lymph is CCR7-independent but may involve CD62L (Vrieling et al., 2012). Using this technique it was shown by Van Rhijn et al. (2007a) that this pattern of bovine γδ T cell migration into and out of the skin occurred at massively greater levels than occurs for other T cell populations. Cattle also provide a model to study the role of γδ T cells in the mucosa of the intestine (Hein and Mackay, 1991; Wyatt et al., 1996); here it has been shown that the bovine γδ T cells that express CD8 accumulate and migrate in response to CCR7 ligands (Wilson et al., 2002). Finally, they are associated with both pharyngeal and palatine tonsil epithelium (Palmer et al., 2011) and the mammary gland (Park et al., 1992), other portals of entry.

Responses of ruminant γδ T cells have been shown in a variety of infectious disease situations in ruminants including to protozoan and bacterial pathogens of cattle: *Theileria parva*

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