Veterinary Immunology and Immunopathology 148 (2012) 161–167

Contents lists available at ScienceDirect

Veterinary Immunology and Immunopathology

journal homepage: www.elsevier.com/locate/vetimm

Review paper

Bovine γδ T cells: Cells with multiple functions and important roles in immunity

Efrain Guzman[a], Sally Price[b], Hannah Poulsom[a], Jayne Hope[a,*]

[a] Institute for Animal Health, Division of Immunology, Compton, Newbury RG20 7NN, United Kingdom
[b] Health Interactions, Oxford OX2 7LG, United Kingdom

ARTICLE INFO

Keywords:
Bovine gamma delta T cells
Mycobacteria
Antigen presentation
WC1

ABSTRACT

The γδ T-cell receptor (TCR)-positive lymphocytes are a major circulating lymphocyte population in cattle, especially in young calves. In contrast, human and mice have low levels of circulating γδ TCR$^+$ T cells (γδ T cells). The majority of the circulating γδ T cells in ruminants express the workshop cluster 1 (WC1) molecule and are of the phenotype WC1$^+$ CD2$^-$ CD4$^-$ CD8$^-$. WC1 is a 220 000 molecular weight glycoprotein with homology to the scavenger receptor cysteine-rich (SRCR) family, closely related to CD163. The existence of 13 members in the bovine WC1 gene family has recently been demonstrated and although murine and human orthologues to WC1 genes exist, functional gene products have not been identified in species other than ruminants and pigs. Highly diverse TCRδ usage has been reported, with expanded variable genes in cattle compared to humans and mice. Differential γ chain usage is evident between populations of bovine γδ T cells, this may have implications for functionality. There is a growing body of evidence that WC1$^+$ γδ T cells are important in immune responses to mycobacteria and may have important roles in T cell regulation and antigen presentation. In this review, we will summarize recent observations in γδ T cell biology and the importance of γδ T cells in immune responses to mycobacterial infections in cattle.

Contents

* Corresponding author. Tel.: +44 01635 578411; fax: +44 01635 577263.
E-mail address: jayne.hope@bbsrc.ac.uk (J. Hope).

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doi:10.1016/j.vetimm.2011.03.013

1. γδ T-cells in cattle

γδ T cells represent a minor percentage of the peripheral lymphocyte pool in most animals. In contrast, they represent a major lymphocyte subset in cattle and can constitute up to 60% of the circulating T-cells in calves (Davis et al., 1996). As such, γδ T cells are likely to be critical to bovine immunity, perhaps more so than in other animals, and particularly in young calves. A large proportion of bovine γδ T cells express WC1, a transmembrane glycoprotein and member of the scavenger receptor cysteine rich (SRCR) family which is closely related to CD163 (see below). Functionally expressed WC1 molecules have so far only been identified in ruminants (O'Keeffe et al., 1999), pigs and camelids although there is recent molecular evidence of the existence of WC1 orthologues in mice and man (Holm et al., 2009). A number of monoclonal antibodies raised against WC1 (Morrison and Davis, 1991; Wijngaard et al., 1994) have shown specificity for WC1 subpopulations which have been broadly recognized as WC1.1$^+$ and WC1.2$^+$. These two populations have been shown to be mutually exclusive of each other. A third population referred to as WC1.3$^+$ has been shown to be a subset of WC1.1$^+$ γδ T cells (see below).

2. The WC1 receptor

The WC1 receptors have been shown to be transmembrane glycoproteins belonging to the scavenger receptor cysteine rich superfamily (SRCR) (Freeman et al., 1990). Sarrias et al. (2004) showed that WC1 is composed of up to eleven extracellular SRCR domains with interdomain homology, organized in a particular pattern (a–[b–c–d–e–d′]–[b–c–d–e–d′]) (Fig. 1). CD5 and CD6 are also members of the SRCR superfamily, but WC1 is distinguished from the others by having a more complex gene structure made up of at least 13 genes, and by the presence of numerous alternative spliced gene products (O'Keeffe et al., 1994; Herzig and Baldwin, 2009).

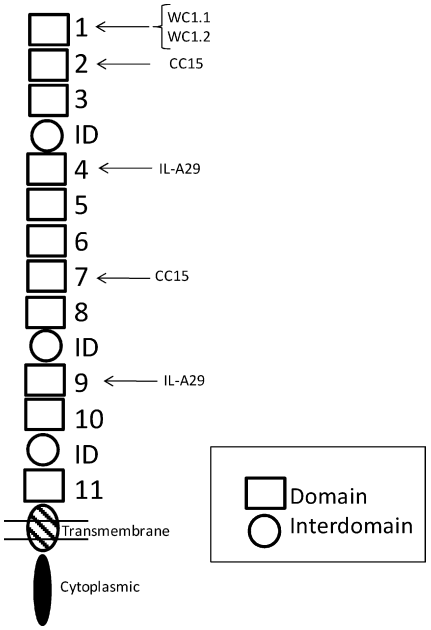

Fig. 1. Schematic representation of WC1 indicating proposed antibody specificity.
Adapted from Herzig and Baldwin (2009).

The monoclonal antibodies CC15 and IL-A29 were originally characterized in 1990 as recognizing a population of cells that were CD4$^-$CD8$^-$ but which expressed the γδ TCR (Clevers et al., 1990). Almost 20 years later Chen et al. (2009) identified the binding characteristics of both of these antibodies in relation to WC1 gene products: CC15 was shown to be a pan-reactive anti-WC1 mAb and IL-A29 was found to recognize most WC1 gene products (Fig. 1). In the same report other anti-WC1 mAbs recognizing subpopulations of WC1$^+$ γδ T cells were also analyzed (Herzig and Baldwin, 2009).

From the molecular evolution point of view, recent data has shown that bovine WC1 is a member of the CD163 family and based on protein alignment, WC1 is most similar to CD163c-α (Herzig et al., 2010b), also known as SCART in mice. However, SCART is not a mouse WC1 orthologue, since cattle also encode for separate SCART genes (Kisielow et al., 2008). It appears that in ruminants, the CD163 family has been greatly expanded to include multiple genes such as various WC1, two SCART, CD163a and b. The functional advantages for this expansion are still unclear. Although birds have been shown to encode for an expanded CD163 gene family (Iwasaki et al., 2001) no functional gene products have been identified.

The importance of WC1 expressed on γδ T cells remains elusive. A role for WC1 as a co-stimulatory molecule for the γδ TCR has been suggested by the presence of several tyrosine-based motifs in the WC1-gene product intracellular domains. Earlier studies suggested that WC1 was involved in IL-2-independent regulation of γδ T cells (Kirkham et al., 1997; Takamatsu et al., 1997) and later studies have shown that WC1 is constitutively phosphorylated and associated with src family tyrosine kinases (Pillai et al., 2007). More recently, a report by Wang et al. (2009) showed that WC1 phosphorylation is required for the WC1-mediated T-cell proliferation, suggesting a role for WC1 as a co-stimulatory molecule similar to CD4 or CD8.

3. TCR gene usage by bovine γδ T cells

Human and murine γδ T cell subsets show a tissue-specific distribution and this is illustrated by the tissue specific distribution of G and D gene segment usage. Human Vδ1$^+$ T cells are found in intestinal tissue and Vδ2$^+$ mainly in blood (Chowers et al., 1994; Holtmeier et al., 1995). Mice have a skin-associated γδ T cell population only expressing Vγ5 and Vδ1 (Asarnow et al., 1988) and a population in the reproductive tract and tongue that preferentially uses Vγ6 and Vδ1 (Itohara et al., 1990). As mentioned above, bovine γδ T cell subsets had largely been identified using mAb against the three distinct WC1-expressing cell subsets (WC1, WC1.1 and WC1.2) or defined by the absence of WC1 (γδ TCR$^+$ WC1$^-$). The TCR δ chain repertoire in cattle has been shown to be highly diverse (Herzig et al., 2006b; Van Rhijn et al., 2007). Herzig et al. (2010a) have sequenced and annotated the loci containing the δ chain of the TCR in