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Inflammatory Th17 responses to infection with *Mycobacterium avium* subspecies *paratuberculosis* (MAP) in cattle and their potential role in development of Johne's disease

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A B S T R A C T

Chronic intestinal inflammation typically associated with late stage Johne's disease (JD) in cattle occurs despite a lack of significant expression of the typical proinflammatory cytokines IFNγ and TNFα derived from Th1- like T cells. In contrast, these cytokines appear to be relatively abundant during early infections with *Mycobacterium* avium subspecies *paratuberculosis* (MAP), the causative agent of JD in cattle. The roles of non-classical immune responses, such as those associated with Th17 cells, in response to MAP infection and development of clinical JD are less clear. In this review, we examine literature suggesting that *Mycobacterial* infections, including *Mycobacterium tuberculosis*, *Mycobacterium bovis*, and MAP, are all associated with expression of Th17 promoting cytokines (IL-23, IL-22, IL-17a). We discuss the possibility that Th17 associated cytokines, particularly IL-23, may act as contributing factors in development and maintenance of inflammation characteristic of clinical JD. An as yet relatively unexplored source of chronic inflammation due to over expression of IL-1α and IL-1β is also presented. We further discuss the fact that, as with the typical Th1-like cytokines IFNγ and TNFα , IL-17a is not significantly expressed in CD4+ T cells from cows with clinical JD, possibly due to T cell exhaustion. Finally, we present the notion that the Th17 driving cytokine IL-23 expressed by infected macrophages and associated epithelial cells may contribute to chronic inflammation during later stages of JD.

1. Introduction

Johne's disease (JD) in cattle is of considerable concern to the dairy industry. JD is caused by *Mycobacterium avium* subspecies *paratuberculosis* (MAP), an intracellular pathogen. Dairy farmers lose an average of $200 million to $1.5 billion each year from increased culling, decreased production and increased testing associated with Johne's disease (Lombard et al., 2013). In 2007, the estimated US national herd infection rate was 68% as determined by the National Animal Health Monitoring System (NAHMS; APHIS, 2007). This rate increased dramatically to about 91% from 2007 to 2013, though some differences in testing methods exist between these time points (Lombard et al., 2013).

MAP primarily affects the ileum of cattle, causing inflammation and disruption of the intestinal lining, leading to incurable diarrhea and subsequently reducing the ability of infected animals to absorb nutrients. Healthy ileal tissue contains continuous villus structures lined with epithelial cells. As MAP infection progresses, inflammation increases, large numbers of infiltrating macrophages are typically found associated with sites of MAP infection, and the apparent number of villus structures decreases (Roussey et al., 2016). Previous studies have outlined some aspects of MAP infection and potential immune responses against MAP using both peripheral blood mononuclear cells (PBMCs) and infected tissues (reviewed in Coussens, 2001; Stabel, 2006). Most of these studies focused on classical Th1-like and Th2-like immune responses, with a few studies addressing γδ T cells and regulatory T cells (Kabara et al., 2010; Roussey et al., 2014; Koets et al., 2015; Ganusov et al., 2015). Many studies have focused on the link between macrophages, the preferred host cell for intracellular MAP infection, and T cells. It has been suggested that immune cells from subclinical MAP infected cows initially respond to MAP antigens with a classical Th1-like immune response, including production of IFNγ. Clinical stages of Johne's disease (JD) appear to coincide with a shift to a classical, humoral Th2-like immune response (Ganusov et al., 2015; Koets et al., 2015), including production of anti-MAP IgG antibodies.

Currently, mechanisms resulting in early inflammatory responses to MAP and those detectable during the sub-clinical stage of infection in the ileum are not well understood. The initial Th1-like response does indeed appear to decline over time as primarily measured by IFNγ production from resident T cells. Mechanisms responsible for this loss in IFNγ production are not clear, but it has been suggested that both regulatory T cells and T cell exhaustion might be contributing factors (Roussey et al., 2014; Ganusov et al., 2015; Roussey et al., 2016). Lack of IFNγ production in MAP infected tissues and in peripheral T cells responding to MAP antigens is not accompanied in a loss of tissue inflammation. Even during this phase of infection (typically referred to as

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late subclinical or early clinical), inflammation of MAP infected tissues is quite profound. Although one might suggest that TNFα could be an important mediator of inflammation within MAP infected tissues, as in some human Crohn's disease tissues, TNFα does not appear to be as important with MAP in cattle (Khalifeh and Stabel, 2004). Thus, at sites of MAP infection, the abundance of both TNFα and IFNγ is not necessarily consistent with the degree of inflammation observed (Roussey et al., 2016; Khalifeh and Stabel, 2004; Coussens et al., 2004). Understanding what factors might be driving inflammation in Johne's disease associated lesions therefore requires us to look beyond the classic Th1-like response mediators often associated with such processes. One possibility for unchecked inflammation may be the presence of large amounts of IL-1α and IL-1β described previously (Aho et al., 2003; Sommer et al., 2009; Chiang et al., 2007). Another possibility is the potential development of a non-classical and highly proinflammatory Th17-like response. In this review we summarize current knowledge of the inflammatory response to Johne's disease caused by MAP infection in cattle. We review evidence that Th17 cells and the cytokines which promote Th17 cell development may be associated with MAP-induced inflammation independent of the role of classical Th1-like cytokines, such as IFNγ and TNFα.

2. The Th17 response

T cells are influenced to differentiate into specific subtypes by secreted proteins (mainly cytokines) from antigen presenting cells (APCs) and epithelial cells. T cells respond to local cytokine combinations and co-stimulatory factors by developing into cytotoxic cells, helper T cells leading to enhanced humoral immunity, regulatory T cells, or into more complex pro-inflammatory mediators, including Th17 cells. Th17 responses are so called due to the production of the cytokine interleukin-17a (IL-17a) by T cells. The Th17 pathway is typically outside the normal pathogen response paradigm, but has been shown to be responsible for clearing extracellular pathogens and inducing inflammation (Zielinski et al., 2012; Santarlasci et al., 2009). Th17 cells originate from a distinct subset of helper T cells and their activity can dampen other T-cell response pathways (Santarlasci et al., 2009; Weaver et al., 2005; Cosmi et al., 2008). In some cases, other cell types may be coerced to adopt a Th17-like phenotype. These include a subset of γδ T cells (Peckham et al., 2014) and even cells that are terminally differentiated, such as activated regulatory T cells (T-reg) (Bhaskaran et al., 2015). T cells may also adopt a Th17 phenotype following direct stimulation of Toll-Like Receptors 2 and 4 (TLR-2, 4) on the T cell surface (Nyirenda et al., 2011; Bhaskaran et al., 2015), which are thought to have involvement with Mycobacterial infection (Mucha et al., 2009; Sánchez et al., 2010). Unlike αβ T cells, γδ T cells do not require antigen presentation via the major histocompatibility complex (MHC) for stimulation to produce IL-17a or other cytokines (Baldwin et al., 2014). The unique T cell receptor (TCR) on γδ T cells allows direct stimulation by many antigens (Zeng et al., 2012; Baldwin et al., 2014). Also, γδ T cells do not require IL-23 for initial production of IL-17a (Lee et al., 2015). However, continued IL-17a secretion by γδ T cells such as those seen by Baldwin (Baldwin et al., 2014) may require IL-23 acting on IL-23R positive cells. Tissue-resident IL-23R+ γδ T cells could thus be a source of IL-17a during early infection with MAP, either with or without IL-23 production. During tissue injury, IL-23R+ γδ T cells have been shown to induce inflammation and limit permeability of intestinal epithelium (Lee et al., 2015). Our own work and that of others has shown that γδ T cells respond to MAP antigen stimulation and are present in MAP infected ileal tissues. Furthermore, the intestinal homing molecule CCR6 is expressed on the surface on the surface of both γδ T cells (Zeng et al., 2012; Lügering et al., 2005; Lyadova and Panteleev, 2015) and CD4+ Th17 cells (Duhen and Campbell, 2014; Lee et al., 2015). Lastly, mRNA encoding lymphocyte chemotactic factor CCL20 is also upregulated in MAP-infected tissues (Khare et al., 2012). Together CCR6 and CCL20 expression would support migration of these Th17-like cells to intestinal tissues, mucosal sites, and Peyer's patches (Duhen and Campbell, 2014; Lim et al., 2008; Lügering et al., 2005; Rout, 2016), the primary sites of MAP infection.

During the initial 18 h of infection with MAP, expression of mRNAs encoding cytokines that could direct T cells to differentiate into a Th17-like phenotype, are upregulated. This has been documented for PBMCs exposed to MAP, as well as in MAP-infected macrophages (IL-6 and IL-23) (Roussey et al., 2014; Dudemaine et al., 2014). In lesions with low MAP burdens (Grade 1), a similar pattern of mRNA expression is observed (primarily IL-17a and IL-6) (Roussey et al., 2016). In tissues that were heavily infected with MAP, a Th17 associated IL-17a response was not detected. This suggests that a non-classical Th17-like response by T cells, could play a role in early stage lesions of MAP-infected tissues from JD + cows, but production of IL-17a declines with advancing disease, much like the decline in classical Th1 responses.

The phenotype of both γδ T cells and αβ T cells depends, in part, on the local mix of cytokines. APCs (Siakavellas and Bamias, 2012; Dudemaine et al., 2014) and epithelial cells (Lee et al., 2017; Seydel et al., 1997; Ghadimi et al., 2012) can all produce Th17 directive cytokines, such as IL-23, IL-6, IL-1β. The presence of IL-23, IL-6, and IL-1β leads to the development of a Th17-like phenotype in naïve T cells and secretion of Th17 cytokines (Neurath, 2007; Siakavellas and Bamias, 2012; Passos et al., 2010). Our recent work has shown that both the Th17 directing cytokine IL-23 and potential Th17 cells expressing the IL-23 receptor (IL-23R) are more abundant in peripheral blood of Johne's disease positive cows than in blood from healthy cows. Further confirmation of MAP's influence on IL-23R expression in T cells was observed after treating PBMCs from healthy cows with MAP *in-vitro*. MAP was capable of stimulating exoression of IL-23R as observed by increases in the mean relative percent of T cells expressing IL-23R following exposure to MAP (DeKuiper and Coussens, 2019a, 2019b).

3. Th17 cytokines

3.1. Cytokines responsible for driving

Th17 immune responses are capable of affecting other pathways in the immune system and can have implications for the surrounding tissues. The primary cytokines involved in Th17 cell differentiation are IL-6, TGFβ, IL-23, and IL-1β (Bettelli et al., 2008; McGeachy et al., 2009; Zollinger et al., 2008), while IL-21 appears to be responsible for amplifying Th17 cells following differentiation (Nurieva et al., 2007). Most Th17 driving cytokines can exert deleterious effects if their expression is not tightly controlled. For example, continuous stimulation by IL-23 can cause inflammation (Lee et al., 2017; Schmidt Paustian et al., 2017) and depletion of type 3 innate leukocyte cells (ILC3) in the proximal small intestines of mice (Schmidt Paustian et al., 2017). While IL-23 expression is associated with long-term control of M. tubercuosis Khader et al. (2011), inhibiting IL-23 promotes an anti-inflammatory gut environment, diminishing symptoms from irritable bowel disorder (IBD) in mice (Maxwell et al., 2015). Thus, in intestinal tissues, IL-23 appears to be predominately a destructive inflammation inducing cytokine. Similarly, IL-1β is important in mounting a proper Th17 response against *M. tuberculosis* but can lead to inflammation and tissue injury. IL-6 exhibits a dual nature, demonstrating anti-inflammatory or regulatory properties in muscle and other tissues, but in intestinal tissues, macrophage associated IL-6 causes disruption in tissue integrity (Gabay et al., 2010; Dinarello, 2011; Sosenko et al., 2006). Clearly, failure to properly limit and control expression of one or more of these Th17-driving cytokines could lead to the type of tissue injury and rampant inflammation observed in clinical Johne's disease. In recent studies, we have observed enhanced serum IL-23 levels and decreased IL-17a levels in blood from cows with Johne's disease relative to serum healthy controls (DeKuiper and Coussens, 2019a, 2019b).

Immune cells responding to Th17 instructive cytokines often secrete both IL-17 and IL-22. Colonic epithelial cells respond to IL-22 by

Table 1
MAP-induced cytokine expression during subclinical and clinical stages of disease.

Cytokines	Activated by	Expressed in Tissue or PBMC?	Found in sub-clinical?	Found in clinical?	Reference
TNFa	MAP	Both	Yes	No	Roussey et al., 2014; Roussey et al., 2016
IFNg	MAP	Both	Yes	No	Roussey et al., 2014; Roussey et al., 2016
IL-1β	MAP	Macrophages/Tissue	Yes	Unknown	Kabara et al., 2010; Coussens et al., 2004
IL-6	MAP	PBMC/Macrophage/Epithelial/ Tissue	Yes	No	Roussey et al., 2014; Murphy et al., 2007; Everman et al., 2015; Roussey et al., 2016
IL-10	MAP	Macrophages/Tissue	Yes	No	Janagama et al., 2006; Roussey et al., 2016
IL-23	MAP	PBMC/Macrophage	Yes	Unknown	Roussey et al., 2014; Dudemaine et al., 2014
IL-22	IL-23	Unknown	Unknown	Unknown	
IL-17a	MAP/IL-23	Both	Yes	No	Roussey et al., 2014; Roussey et al., 2016; DeKuiper and Coussens, 2019a

increasing Claudin-2, thus increasing cell permeability of the tissue (Wang et al., 2017). However, IL-22 is most often found to have a protective role. For example, application of IL-22 to mice with induced colitis caused tissues to revert to a normal phenotype and protects them from irritable bowel disease (Aden et al., 2016; Zenewicz et al., 2008). *M. tuberculosis* studies have shown IL-22 is important for macrophagic phagosomal fusion and *M. tuberculosis* growth inhibition (Dhiman et al., 2009). One possibility for the co-production of IL-17a and Il-22 would be to limit the tissue damage and inflammation produced by IL-17a promoting cytokines such as IL-1β and IL-23.

4. MAP driving Th17

It is clear that, in the initial 18 h, expression of mRNAs encoding cytokines that direct T-cell responsiveness and differentiation to a Th17-like response (IL-6, IL-1, IL-23) are upregulated in PBMCs exposed to MAP and MAP-infected macrophages (Roussey et al., 2014). Enhanced expression of mRNAs encoding IL-17a and IL-6 was also observed in early-stage (Grade 1) lesions from MAP infected cows (Roussey et al., 2016). The initial increase in mRNAs encoding IL-6 and IL-17a in early stage MAP ileal tissue lesions decreases as MAP infection and lesion scores (Grade 2–4) increase (Roussey et al., 2016). This scenario is similar to what is observed with challenge infection of calves with *Mycobacterium bovis* (*M. bovis*). In this model, mRNA encoding IL-17a is upregulated in lung granulomas with low bacterial burden (early stage; Grade 1) compared to granulomas with high bacterial burdens (Grade 3 and 4) (Palmer et al., 2016). In both models, considering the relationship between Th17 promoting cytokines and inflammation, it is possible that continual IL-23 expression promotes tissue injury and inflammation. Eventual loss of IL-17a production as lesion burdens increase could be attributed to T-cell exhaustion from prolonged IL-23 exposure (Schmidt Paustian et al., 2017). To our knowledge, this possibility has not yet been tested in either MAP lesions or in lesions from *M. bovis* infections. However, as noted above, we have observed enhanced IL-23 and reduced IL-17a levels in serum from cows with Johne's disease relative to serum from controls (DeKuiper and Coussens, 2019a, 2019b).

In vitro, monocyte-derived macrophages (MDMs) upregulate IL-23, IL-6, and IL-1β mRNA when exposed to MAP (Dudemaine et al., 2014). MDM expression of both IL-1α and IL-1β mRNA and protein can be quite significant following infection with MAP (Chiang et al., 2007). Monocytes, precursors to macrophages and dendritic cells, can produce IL-23 when exposed to Mtb (Stephen-Victor et al., 2016). Dendritic cells produce IL-23 in the presence of *M. bovis* antigen and Mtb (Szpakowski et al., 2015; Thacker et al., 2009; Stephen-Victor et al., 2016). In addition to antigen presenting cells (APCs), such as macrophages and dendritic cells, IL-23 may originate from epithelial cells (Lee et al., 2017; Seydel et al., 1997) at sites of MAP infection in intestinal tissues. While it has been established that Madin–Darby bovine kidney (MDBK) epithelial cells upregulate IL-6 when infected with MAP (Everman et al., 2015), expression of IL-23 from these model cells has not been explored in the context of MAP exposure.

5. Final thoughts

There is now ample evidence that Th17 cells and IL-17a are important pieces of the immune response to MAP and other mycobacteria. What is not yet clear is the precise role these cells might play in both control of infection and development of disease. On one hand, IL-17a secretion might provide an initial inflammatory response that helps to clear or limit infection. There is evidence that both αβ T cells and γδ T cells might participate in this early response. However, continued expression of IL-17a and the Th17 driving cytokines IL-1β and IL-23 may lead to progressive inflammation and disease symptoms. Importantly, inflammation derived from epithelial or macrophage IL-23 and IL-1β would not be controlled by T cell exhaustion or other T cell regulatory mechanisms that would reduce Il-17a and IFNγ in late stage infection with MAP. Thus, loss of the classic Th1 cytokines IFNγ and TNFα, as observed in advanced Johne's disease, nor loss of IL-17a expression as observed in our recent studies (Table 1), would not reduce IL-23 or IL-1 driven inflammation at sites of infection. Clearly, the role of Th17 associated cytokines in development of clinical Johne's disease warrants further study. In addition, the rapid and regulated expression of IL-17a in early infection as one mechanism that aides in clearance or control of MAP and other mycobacteria in some animals is worthy of additional studies, particularly as a potential marker of vaccine induced protective immune responses.

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