REPORT: Immune Responses to Maedi-Visna Infection

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The Maedi-Visna virus (MVV) and the caprine arthritis encephalitis virus (CAEV) are lentiviruses affecting both sheep and goats. Although initially considered as two separate viruses, recent phylogenetic data suggest that CAEV and MVV should more accurately be classified as small ruminant lentiviruses (SRLV) (Pisoni et al., 2005).

The SRLV primarily infect immune cells called monocytes and macrophages, and these cells are involved in clearing pathogens very early in infection. However, SRLV can also infect mammary epithelial and endothelial cells suggesting that the mammary gland is a main reservoir for the virus (Lechat et al., 2005; Milhau et al., 2005). This allows for efficient transmission of the virus through the colostrum and milk and can therefore serve as a direct mode of transmission to newborn lambs. Transmission can also occur between other flock members through prolonged direct contact with bodily secretions, and sexual transmission may also be possible (Ahmed et al., 2012).

Very little is known about how the immune systems responds to SRLV infection, and relatively few studies have investigated how the virus behaves and interacts with the immune system of these animals. However, due to similarities with the human immunodeficiency virus (HIV), HIV research can help improve our understanding of the dynamics of SRLV pathogenesis.

IMMUNE RESPONSES
There are two types of immune responses involved in controlling MVV infection. The first response is the innate immune response and serves as one of the first lines of defense against invading pathogens. The innate immune response involves a variety of non-specific cells and proteins that can target and destroy invading pathogens. The acquired immune response, in contrast, takes time to develop but is responsible for the production of pathogen-specific T and B-cell subsets and contributes to the development of pathogen-specific antibodies. The acquired immune response can further be sub-dived into Th1, or cell mediated immune response (CMIR), and Th2 immune response, or antibody-mediated immune response (AbMIR). These responses serve different functions as the Th1 immune response involves antigen-specific T cell subsets to target intracellular pathogens such as viruses and some bacteria (Kindt et al., 2007). The Th2 immune response however, is characterized by B-cell proliferation and high antibody levels and primarily targets extracellular pathogens such as bacteria and parasites (Kindt et al., 2007).

Innate Immunity
The innate immune response to SRLV infections involves a variety of innate immune effector cells such as macrophages, and Natural Killer (NK) cells, as well as a variety of innate antiviral peptides that can directly interfere with the viral replication cycle. These antiviral proteins include TRIM5α, APOBEC3G (A3G) and tetherin, and are expressed when the cell recognizes a viral component through toll-like receptors. The role of these peptides has not been widely
studied in sheep or goats but TRIM5α has been identified in sheep for its role in restricting SRLV (Jauregui et al., 2012), and the role of tetherin has been investigated for its role in restricting endogenous retroviruses (Arnaud et al., 2010). However, A3G has not yet been identified in sheep or goats, but it has been studied for its role in restricting HIV-1 infection, and therefore due to similarities between SRLV and HIV-1 this peptide may be effective and limiting viral replication in sheep (Blacklaws 2012).

Another important component to the innate immune response in sheep is the role of γδ T cells. γδ T cells are a unique set of T cells that are present in high numbers in sheep, goats, and other ruminants (Kaba et al. 2011). These cells tend to localize to mucosal surfaces and can easily become activated upon antigen exposure. A few studies have investigated the role of γδ T cells in SRLV infection, and animals infected with SRLV tend to have higher levels of γδ T cells compared to healthy animals (Jolly et al. 1997; Ponti et al. 2008; Kaba et al. 2011). This suggests that these cells are being produced in higher number in infected animals to help combat the infection, however further investigation is warranted.

**Acquired Immunity**

The acquired immune response to SRLV infections involves branches, CMIR and AbMIR, but neither is adequate to clear the virus (Reina et al., 2008). Little research has investigated the efficacy of the CMIR to combat SRLV infection, however, there is evidence to suggest that some of the Th1 cytokines may act on infected cells to promote viral replication (Murphy et al., 2012). However, despite the possible Th1 cytokine induced viral activation, the CMIR is better suited to control the disease. For example, animals that mount a CMIR tend to have lower antibody levels and show fewer clinical signs of disease compared to animals that mount an AbMIR (Trujillo et al., 2004). Those animals that mount an AbMIR have high antibody levels, show more clinical signs of disease, and the disease tends to progress rapidly (Trujillo et al., 2004). 

Although in some instances antibodies can help control various diseases because they have the ability to bind to a pathogen and prevent it from infecting other cells, in the case of SRLV, the majority of antibodies produced are ineffective, and may bind to virus particles but will not neutralize it (Bertoni et al., 2000; Trujillo et al., 2004a). Additionally, the virus may mutate in response to this antibody-mediated selection pressure to avoid immune detection (Naryan et al., 1978; Narayan et al., 1981). This is similar to observations made in HIV-1 patients; however it is unclear how exactly this works in sheep and goats.

**GENETICS**

There are a variety of genetic parameters that are associated with susceptibility or resistance to an infection, and in the case of SRLV, there are a few immune molecules that have been identified for their role in slowing SLRV disease progression. The MHC class I and class II molecules, which are molecules found on every cell of the body, and specialized immune cells, respectively, have polymorphisms associated with disease susceptibility or resistance. Additionally, some recent ovine genome-wide association studies (GWAS) have identified the TMEM154, TMEM38A genes associated with resistance, whereas the DPPA2 gene was associated with susceptibility (Heaton et al., 2012, White et al., 2012). The role of the TMEM154 and TMEM38A proteins is currently unknown but DPPA2 is a gene expressed during fetal development and is responsible for embryonic lung development, suggesting that altered fetal lung development may increase the susceptibility to SLRV infection (White et al., 2012).
Given the complex nature of the immune response to SLRV infection and the dynamic host-virus interaction that occurs, it is likely that it is not one or even a few genes are responsible for disease resistance or susceptibility. Instead it is likely a complex interaction between several genes for both the innate and acquired immune systems (Petrovski et al., 2010; Luo et al., 2012). Therefore genomic selection may not be effective for breeding for SRLV resistance, however, it may be possible to breed based on phenotype. For example, helminth resistance in sheep is also a polygenic trait and selecting animals based on low fecal egg counts has allowed for development of helminth resistant sheep (Bishop 2012).

An additional strategy for breeding for SRLV disease resistance would be to breed for overall enhanced immune responses (EIR). This approach involves measuring CMIR and AbMIR in response to various antigens. Research in dairy cattle has identified high immune response cows that may have a lower disease incidence than other cattle (Thompson-Crispi, unpublished data). Upon further investigation, it may be possible to identify and breed high immune response sheep, which may be protected from MVV and other diseases.

CONCLUSION
The immune response to SRLV infection involves a variety of complex interactions between a variety of host immune cells and the virus. However, a great deal is largely unknown about the dynamic host-virus interaction. Evidence taken from HIV-1 research can enhance our understanding of this interaction, however, despite their similarities SRLV and HIV-1 are two distinct viruses and extrapolating knowledge from HIV-1 infection must be approached with caution. Therefore before effective vaccines, and treatment therapies can be developed, understanding how the virus behaves within the host is necessary.

REFERENCES


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