Genetics of Helminth Resistance in Sheep

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Gastrointestional (GI) parasites or helminths are a major source of economic loss to sheep producers worldwide (Halliday et al., 2012). These production losses include reduced meat, milk and wool production as well as the costs associated with treatment. However, losses may also arise due to the interactions between helminths and other pathogens such as *Mycobacterium avium sbsp. paratuberculosis*, the causative agent of Johne's disease (Whittington et al., 2001), and helminth infection may also influence severity and detection of other diseases (Lass et al., 2012; Claridge et al., 2012). Currently, the sheep industry relies heavily on the use of anthelmintic drugs to control parasite load, however, increasing anthelmintic resistance has caused researchers to explore alternate control methods (Kaplan and Vidyashankar, 2012). Some of these alternate strategies include, enhanced nutrition, pasture management, vaccine development, and genetic selection for enhanced helminth resistance. Although a sustainable disease control program will require implementation of many of these strategies, it is highly unlikely that complete helminth eradication is achievable or desirable given the long co-evolutionary history of GI parasites with sheep. This article will discuss the potential of using genetic selection for enhancing parasite resistance. For the purpose of this paper 'resistance' refers to the ability of the sheep to control the helminth life cycle (Bishop, 2012).

Sheep become infected with helminths when they ingest larvae from contaminated pastures. The larvae then burrow into epithelial lining of the gut where they feed on blood from the host and mature into egg producing adults. Their eggs are shed in the feces where they hatch into larvae that feed on fecal bacteria. As the larvae grow, they molt several times, and during their L3 stage of development they rely solely on stored nutrients. Due to this reliance on stored energy, larvae can only survive on pasture for weeks-to-months and will travel up grass blades in search of their host to complete the life cycle.

In order to improve helminth control, researchers have explored the possibility of breeding for enhanced helminth resistance. This strategy is based on the premise that sheep and helminths have co-evolved for millions of years allowing for the survival of both species (Stear et al, 2011). In support of this, a delicate balance is established during infection between the sheep's immune response and the secretion of helminth proteins that modulate the host immune system (Bai et al. 2012). Also, it has been proposed that sheep evolved selective grazing strategies to help reduce parasite load (Karlsson and Greeff, 2012). These strategies, however, have been disrupted by selectively breeding for enhanced meat, milk and wool production and by the intensive farming practices of today. Despite this altered host-parasite relationship, there are breeds around the world that have developed helminth resistance through natural selection. For example, in some remote areas off the Scottish coast, a high parasite load appears to have induced breed-specific selection pressure resulting in breeds that are more resistant than others (Karlsson and Greeff, 2012). Other breeds such as Barbados Blackbelly, U.S. St. Croix, Florida Native and Gulf Coast Native breeds, Indonesian Thin tail, Indian Garole, and African Red Maasai also appear to have enhanced helminth resistance and are being used in genetic studies that aim to identify genes that confer helminth resistance (Bishop, 2012).

The process of breeding for enhanced helminth resistance firstly involves being able to reliably quantify a desirable phenotype, and there must be variation in the phenotype that is attributed to genetic variation. For sheep, fecal egg counts (FEC) are generally used as a tool to quantify the parasite load. This method however, may not be ideal, since fecal egg counts can vary depending on the season and stage of production and they may not represent the actual parasite load (Singleton et al., 2011). Packed cell volume (PCV) is also used as an indirect indicator of parasite load, since it measures the number of red blood cells present and thus is an indicator for anemia. However, this method is also variable and can't be used for helminth species that don't cause anemia (Bishop et al., 2012). Other indirect indicators that have been used to monitor parasite load include measuring blood eosinophil count and helminth-specific antibody titers; however, these immunological parameters change over time and depend on the previous exposure to the parasite (Bishop, 2012). Despite these challenges, the scientific community has agreed that helminth resistance is a moderately heritable trait (Bishop, 2012), suggesting that there is potential to enhance helminth resistance through selective breeding or by introducing resistance alleles into susceptible breeds (Koudande et al., 2005; Yazdi et al., 2010).

With increasing availability of genomic tools, it may be possible to use marker-assisted or genomic selection to improve helminth resistance. Early research in this area has revealed that helminth resistance as a polygenic trait, meaning that resistance is attributed to the combined effects of DNA sequence variants within many genes. More recently, single nucleotide polymorphisms (SNP) have been identified in several immune related candidate genes that are associated with helminth resistance, however, a recent genome-wide association study failed to validate these associations, and these authors raised the possibility that there may be hundreds-to-thousands of genetic variants that contribute to helminth resistance (Kemper et al., 2011).

Although breeding for enhanced helminth resistance using genomic methods may prove to be difficult in the immediate future, it may be possible to enhance resistance to helminths using phenotypes rather than genotypes. Researchers in Australia, New Zealand and the UK for example, have pursued this approach by selecting animals based on FEC, growth rates, and anemia scores. Consequently, semen is now available to producers around the world that want to introduce resistance genes into their flock. However, it is unclear how these resistance genes will affect North American breeds under current pasture and management conditions. Additionally, it is possible that breeding for enhanced parasite resistance may compromise the immune response to other infections. For example, helminths are extracellular pathogens, and the host relies on an antibody-mediated immunity (AbMI) for protection. If animals are selected for enhanced AbMI, this may compromise their cell-mediated immune response that combats intracellular pathogens such as viruses, intracellular bacteria such as *Mycobacterium avium sbsp. paratuberculosis* and *Corynebacterium pseudotuberculosis*, and intracellular parasites such as *Toxoplasma gondii* that survive and thrive inside the host cells. Breeding for enhanced helminth resistance may also place selection pressure on the worms to adapt to their new hosts over time. Additionally, it is possible that breeding based on a helminth resistance phenotype may also reduce the genetic merit of other desirable traits.

Despite the potential drawbacks, there are substantial benefits to breeding for enhanced helminth resistance. For instance, genetic change is permanent and resistance will last throughout the sheep's lifetime, and once established, little additional input is required. This approach also adds diversity to the anthelmintic management strategies and reduces dependence on anthelmintic drugs. Non-resistant sheep will potentially also benefit from the introduction of helminth resistance, as pasture parasite loads will be lower. However, before large scale helminth resistance breeding programs are initiated, further research is required to assess the efficacy of such a strategy under Canadian environmental and management conditions. Genomic tools can be used in these studies to monitor and minimize potential impacts on other health and production traits to ensure a productive healthy flock.

References

Bai, X., Wu, X., Wang, X., Guan, Z., Gao, F., Yu, J., Yu, L., Tang, B., Liu, X., Song, Y., Wang, X., Radu, B., Boireau, P., Wang, F., Liu, M. 2012. Regulation of cytokine expression in murine macrophages stimulated by excretory/secretory products from Trichinella spiralis in vitro. Mol. Cell. Biochem. 360: 79-88.

Bishop, S. C. 2012. Possibilities to breed for resistance to nematode parasite infections in small ruminants in tropical production systems. Anim. 6:5 741-747.

Claridge, J., Diggle, P., McCann, C. M., Mulcahy, G., Flynn, R., McNair, J., Strain, S., Welsh, M., Baylis, M., Williams, D. J. L. 2012. *Fasciola hepatica* is associated with the failure to detect bovine tuberculosis in dairy cattle. Nat. Commun. 3: 853.

Halliday, A. M., Lainson, F. A., Yaga, R., Inglis, N. F., Bridgett, S., Nath, M., Knox, D.P. 2012. Transcriptional changes in Teladorsagia circumcincta upon encountering host tissue of differing immune status. Parasitology 139: 387-405.

Kaplan, R. M. and Vidyashankar, A.N. 2012. An inconvenient truth: global worming and anthelmintic resistance. Vet. Parasitol. 186: 70-78.

Karlsson, L. J. E. and Greeff, J.C. 2012. Genetic aspects of sheep parasitic diseases. Vet. Parasitol. 189: 104-12.

Kemper, K.E., Emery, D.L., Bishop, S.C., Oddy, H., Hayes, B.J., Dominik, S., Henshall, J.M., and Goddar, M.E. 2011. The distribution of SNP marker effects for faecal worm egg count in sheep, and the feasibility of using these markers to predict genetic merit for resistance to worm infections. Gen. Res. 93: 203-219.

Koudandé, O.D., van Arendonk, J.A., Iraqi, F. 2005. Marker-assisted introgression of

trypanotolerance QTL in mice. Mamm. Genome. 16: 112-9.
Lass, S., Hudson, P. J., Thakar, J., Saric, J., Harvill, E., Albert, R., and Perkins, S. E. 2012. Generating super-shedders: co-infection increases bacterial load and egg production of a gastrointestinal helminth. J. R. Soc. Interface 10: 20120588.
Singleton, D. R., Stear, M. J., Matthews, L. 2011. A mechanistic model of developing immunity to *Teladorsagia circumcincta* infection in lambs. Parasitol. 138:3 322-332.
Stear, M. J., Singleton, D., Mathews, L. 2011. An evolutionary perspective on gastrointestinal nematodes in sheep. J. Helminthol. 85: 113-120.
Whittington, R. J., Lloyd, J. B., Reddacliff, L. A. 2001. Recovery of Mycobacterium aviumsubsp. paratuberculosis from nematode larvae cultured from the faeces of sheep with Johne's disease. Vet. Microbiol. 81: 273-9.
Yazdi, M. H., Sonesson, A. K., Woolliams, J. A., Meuwissen, H. E. 2010. Combined detection and introgression of QTL in outbred populations. Gen. Sel. Evol. 42: 16-26.