IMMUNE RESPONSES TO PARASITIC INFECTIONS

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Parasites of all types (protozoans, helminths and arthropods) occur commonly in flocks of sheep and can cause severe disease. The economic losses associated with infection, which arise both from lost productivity and the costs of treatment, are large even in temperate countries with good veterinary services, such as the UK, and are correspondingly much greater in countries with warmer climates and less efficient monitoring and control of disease. Control of the majority of these infections is dependent upon chemotherapy and improved stock management, but a number of factors have created pressures for alternative approaches. These factors include economic constraints, the development of extensive drug resistance, and environmental and consumer concerns over the widespread use of chemical control methods. Among the alternatives under consideration are breeding for enhanced resistance to infection, the production of transgenic resistant animals, and the development of effective vaccines. All of these approaches require an understanding of the nature of the response to infection in order, firstly, to identify those components that require selective enhancement to improve resistance and those that need to be down-regulated to prevent interference with resistance and, secondly, to identify and exploit the genes that regulate host resistance. This short review will look at resistance to two of the major groups of parasites affecting sheep in the UK- the protozoa and worms that infect the gastrointestinal (GI) tract

Resistance to Infection

Resistance to parasite infection is a multifaceted phenomenon.. Individual animals, or breeds, may be resistant because their structural, biochemical or physiological characteristics are less suitable for the establishment and survival of parasites than those of others. This form of resistance (*innate resistance* or *innate immunity*) helps to regulate the numbers of parasites that develop in an animal when it is exposed to infection. *Resilience* is a form of resistance that enables an animal to cope with the harmful effects of a parasite burden (eg the ability to sustain reduced PCV when infected with some of the GI nematodes). Both of these aspects of resistance can be selected for, there being significant individual and breed-related variation. They are constitutive - ie are always present, operate each time an animal is infected, but show no enhancement on reinfection. In contrast *acquired*, or *adaptive, immunity*, expressed through the operation of the immune system shows the characteristics of *specificity*, i.e the responses concerned are induced by and operate against particular parasite species, and *memory*, i.e. responses to reinfection operate more rapidly and more effectively. Like innate immunity, the capacity to express acquired immunity is genetically determined and variable between individuals and breeds.

Intestinal Immunity

Immune responses operating in the GI tract differ in many respects from those that operate systemically against parasites in organs such as the skin, blood, and muscles. This reflects both a different organisation of the immune system in the gut, (based on the gut associated lymphoid tissues), distinctive populations of T lymphocytes (e.g. those expressing the γ/δ rather than the α/β T cell receptor), separate

migratory patterns of lymphocytes, and a distinctive repertoire of effector mechanisms. The latter include those capable of operating against organisms in the gut lumen (e.g. secretory IgA) and those that function within the mucosal tissues (e.g. mucosal mast cells). Immune-mediated inflammatory responses can dramatically change the structural and functional environment of the intestine, to the disadvantage of parasites living there. Under normal circumstances the intestinal infection elicits multiple responses operating simultaneously or sequentially; frequently these can be both protective (i.e. defend against infection) and pathological (i.e. cause tissue damage) and the balance between the two can be critical for the host.

Anti-Parasite Responses

The operation of immune responses against intestinal parasites is the subject of intensive research, but progress in understanding these responses has been somewhat slower than progress in the analysis of immunity to systemically located parasites. This is in part a consequence of the difficulty in finding out what is going on in the intestine *in vivo* and the difficulty of modelling this *in vitro.* Key questions that this research addresses are:-

Why are intestinal parasitic infections so prevalent and persistent in domestic animals?
When immunity is effective how does it operate?
Why is immunity frequently ineffective?
How can immunity be improved?

Prevalence and persistence are undoubtedly influenced by factors such as intensive husbandry, nutritional and physiological stress, but must also reflect inefficient or ineffective immune responses. The intestine is certainly capable of mounting effective anti-parasite responses, and most of what is known of these responses has come primarily from research using rodent models, although comparable data from infections in sheep are increasingly available (Miller, 1996). Like all immune responses against biologically meaningful targets, intestinal immune responses are initiated by the presentation of processed antigens to lymphocytes of the T helper (Th) subset, which recognise these antigens through their T cell receptors. These cells then regulate the subsequent response through their release of cytokines - which are essentially short-range hormones that communicate with other lymphocytes, inflammatory cells and a variety of other cell types (Fresno and Rivas,. 1997). Th cells are themselves divisible into subsets, each of which produces a characteristic profile of cytokines; the subsets therefore influence immune responses in different ways. In rodents, and probably in sheep, cells of the Th1 subset liberate cytokines that regulate cell-mediated responses (eg. macrophage activation), control T cell responses and the production of antibody of particular isotypes. Th2 cells liberate cytokines that regulate humoral responses, particularly production of isotypes such as IgA and IgE, and induce inflammatory responses involving eosinophils and mucosal mast cells. In general, Th1 responses are involved in protection against intracellular protozoans, e.g. coccidians such as *Eimeria* and *Cryptosporidium* (Ovington and others, 1995). Here the important cytokines are interleukin -12 (IL-12), released from macrophages, and interferon gamma (IFNγ) from Th1 cells and natural killer cells. IFNγ appears to control intracellular killing mechanisms that are able to destroy invading coccidians. In contrast, Th2 cells are required for protection against intestinal nematodes (Finkelman and others, 1997). Key cytokines include those that regulate mucosal mast cell and eosinophil responses (e.g. IL-3, 4, 5, and 9), those that regulate IgA production (IL-5), and those that are now known to influence the activity of the intestinal musculature to generate expulsive responses (e.g IL-4 , IL-13). Control of intestinal nematodes may be exerted through antibody-mediated effects on their growth, development and reproduction and by inflammatory changes that alter the structure and function of the intestine itself.

Th1 and Th2 cells are mutually interactive and each can down-regulate the activity of the other. Dominance of a response by one Th subset can determine whether the outcome is increased resistance to infection or continuing susceptibility. There is clear evidence from some rodent systems that there is a complex interaction between parasite and host genotype which can bias the Th response to one pole or the other, resulting in the expression or the failure of immunity. Some parasites are clearly able to modulate Th responses in ways that interfere with host immunity and thereby promote their own survival.

Vaccination

The first successful anti-parasite vaccine was that produced in the 1960's against lungworm infection in cattle, later used against lungworm in sheep. This vaccine, which was developed largely empirically, used attenuated (irradiated) infective larvae to stimulate resistance against subsequent infection and gave excellent protection. Subsequent attempts to use similar approaches for vaccines against other parasites were much less successful, and it is only relative recently that effective vaccines against other veterinary parasites have reached the market (Tomley *et al*., 1995). Some still use attenuated organisms (e.g. that against coccidiosis) others have exploited molecular approaches (e.g. those against larval tapeworms and ticks). With the understanding we now have about immune responses to parasites it is possible to adopt a rational approach to vaccine development. The elements of such an approach include identification of the antigens (and epitopes) that elicit good protection and minimal pathology, production of these antigens by recombinant technology or by chemical synthesis, use of presentation routes and modalities that maximise the host's response, activate the correct T cell subsets and release the appropriate cytokines, and (in the case of GI parasites) target protective responses to the intestinal mucosa.

A particular challenge for vaccines is to ensure good immunity in animals or breeds whose responses to infections with the target parasite are genetically poor. To do this requires a detailed knowledge of which components of responses are defective and a good background understanding of the reasons why this may be so. It is encouraging that, from laboratory models and from work in sheep, this knowledge is now becoming available, and should provide a firm basis for future progress in vaccine development.

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