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Review

Gastrointestinal Nematodes in Sheep: Looking Back for Building Up Future

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Abstract: Gastrointestinal nematodes (GINs) are common parasites in grazing sheep. They have been traditionally controlled through the strategic administration of anthelmintics, but the increasing emergence of resistance, makes it necessary to identify new control alternatives. Vaccines and the selection of resistant animals are strategies based on the development of an effective immune response. For the development of these strategies, a detailed understanding of the effective immune response is essential. Some local breeds, such as the Canaria Hair Breed (CHB) sheep, are particularly resistant to GINs infection. This review presents some previous studies conducted in the CHB that have confirmed its ability to develop an immune response oriented toward the adult stage rather than the larval stage in single infection, and the contribution of Tgd+ cells, eosinophils, and local IgA in these mechanisms. The response capacity of very young lambs of this breed to vaccination against *Teladorsagia circumcincta* and the possible role of Treg lymphocytes compared to other more susceptible breeds are also discussed, as well as the possible biotechnological implications that these findings may have on vaccine design and the identification of genetic resistance markers.

Keywords: gastrointestinal nematode; breed resistance; Canaria Hair Breed; immunity; local breed

1. Introduction

Parasites play a critical role in preserving ecosystem health, affecting not only individuals, but also the global community [1]. In fact, having parasites is the rule instead of the exception in wildlife [2]. Human beings in western society have been able to reduce parasite exposure to a minimum. Clearly, it is a great health advance. However, there is a theory that considers the loss of these "*old friends*" as a potential cause of the increased incidence of several immune diseases that are more prevalent in developed countries [3,4]. As anecdotal data, it is curious that the increasing prevalence on allergic diseases in pets [5] matches with a greater investment on anti-parasitic drugs for them [6].

The almost "parasite sterile" human and pet is possible because we live in "isolation" from parasite sources. The use of proper effluent disposal, food control or hygiene, amongst many other factors, are key measures. A similar goal can be reached rearing domestic animals indoors. However, when grazing ruminants such as sheep it is inevitable that, as well as wild ruminants, they can be infected by gastrointestinal nematodes (GINs) [7,8]. *Haemonchus contortus*, *Teladorsagia circumcincta* and *Trichostrongylus* spp. are the main genera/species parasitizing sheep, attending to their prevalence and pathogenicity. Globally, they can cause diarrhea, anaemia, weight loss and, occasionally, death. This leads to substantial losses in meat, milk and wool production [9]. Gastrointestinal nematodes are responsible for 80% of direct total economic losses, representing approximately

1.8 billion euros per year. The other 20% loss is attributed to the acquisition of anthelmintic drugs for worm treatment and control [7,8].

Possibly, livestock rearing conditions have influenced the negative impact of internal parasites. For example, high grazing density increases pasture contamination with helminth eggs [10]. In order to maintain high levels of performance in favorable conditions for worm transmission and alleviate the consequences of parasitic diseases, the development of antiparasitic drugs and vaccines has been essential. Over time, chemical and immunological control methods allowed for the selection of animals with high performance [11] but, unintendedly, they shielded them from the metabolic costs associated with the development of immune responses, especially in terms of energy and protein allocation. Although there is controversy in the literature about the metabolic cost of developing natural resistance to pathogens in productive terms [11–13], this could partly explain the greater susceptibility of commercial breeds to pathogens in comparison to their indigenous counterparts [11].

Even though the chemoprophylactic approach has been unarguably efficient for worm control, its use as a single control strategy is unsustainable in the long term [10]. Gastrointestinal nematodes can develop resistance to drug, even to multiple chemical actives [14], in a very short span of time. Drugs aim at one or a few parasitic targets and, as soon as some worms overcome it, this trait is fixed in the next generations very quickly, immediately spreading the resistance [15]. Hence, it is becoming increasingly difficult to maintain drug efficacy or to generate new chemical actives [11], making control a real challenge. In order to delay the onset of resistance, several alternative/complementary methods have been promoted, such as rotational grazing, targeted selective treatment, biological control, vaccines and breeding for worm resistance [8]. So far, none of them have reached the efficacy of drugs, but their implementation could be useful for reducing the dependency on chemical control of the farming sector.

The use of vaccines and the selection of resistant animals are GINs control strategies based on the development of an effective immune response [16]. In the first option, this response is achieved through an external stimulation with antigens. Repeated exposure to GINs larvae develops a protective immune response in sheep. Several native natural antigens have been successfully tested in animals; however, recombinant version of these molecules has not been able to reproduce this protection. This is a clear limitation for commercialization [16]. There is one commercially available vaccine against *H. contortus* based on "hidden" natural antigens: Barbervax® (www.barbervax.com). However, there are some limitations for its commercial expansion such as large-scale production, safety regulations and the need to use multiple booster doses [17]. On the other hand, some animals within the flock are particularly resistant to these parasites, being able to control their worm burden and generally being more resilient [18,19]. In Australia, farmers can use the Australian Sheep Breeding Values estimated through faecal egg count (FECs) as a trait for breeding for resistance to GINs [20,21]. Although in New Zealand also uses FEC as estimated breeding values, they have developed a saliva IgA ELISA against a larval carbohydrate antigen (CARLA® Saliva test) [22]. Although farmers are currently using these methods in their flocks for improving the health and productivity of their farms, it is also true that they have some setbacks. For instance, samples should be collected at the farm and taken to a laboratory for an analysis which should also be performed by a trained technician. Faecal egg counts need a minimum threshold for being useful, therefore farmers assume productive losses, and they also need worm-infected paddocks for their flocks and adequate environmental condition for parasite development. Possibly, the efficacy of the selection could be improved if new, pen-side and more reliable markers were identified [13,22,23]. In summary, stimulating natural immunity is an attractive alternative, but, although main key "actors" of this response are very well known [24], we still need to understand in depth the finer details of the protective mechanisms to improve both, vaccines and selective breeding.

2. Immune Response to Gastrointestinal Nematodes

The capacity of sheep to respond to GINs in natural infections is generally a consequence of the repeated exposure to parasites, developing a non-sterilizing acquired immune response. Broadly speaking, macrophages and dendritic cells capture parasite antigens, and they will process and present them to lymphocytes. The antigens will be presented through the major histocompatibility complex (MHC-II) class II molecules to CD4+ lymphocytes that will be stimulated thus producing a predominantly Type 2 immune response. This response is characterized by the release of cytokines such as IL-4, IL5, IL10 and IL13. Globally, they will promote the recruitment and activation of eosinophils, mast cells and globule leukocytes (GLs) as effector cells. Several immunoglobulins like IgA, IgE and IgG1 will be produced by B cells [25].

The target of these responses are infective larval stages. Eosinophils are key cells in a resistant mechanism called "delayed rejection". In this case, eosinophils can attach to larval cuticle and degranulate over it. It can produce damage that probably reduces larval viability and its establishment in the abomasum in presence of complement and specific immunoglobulins [26–28].

Intraepithelial mast cells, called globule leukocytes (GLs) in ruminants, are another effector cell that affects GINs [29]. There are receptors on this cell's surface of high affinity to Fc region of the IgE (FceRI). The IgE binds to this receptor, and this triggers the degranulation of the cell close to the worms [25]. These mediators will induce an increase in the gastrointestinal peristalsis and the secretion of mucus with high viscosity, inducing a "rapid rejection" of larvae [29].

Mucosal IgA is produced by plasmatic cells, and it is secreted to the abomasal lumen [24,25]. The recognition of L4 specific antigens by IgA [30] is one of the main mechanisms implicated in the control of worm length and fecundity, at least in *T. circumcincta* infection [24].

3. A Local Sheep Breed as a Biotechnological Resource

Most of the studies about the sheep immune response against GINs have been carried out in commercial breeds of sheep. However, as pointed out above, they have been breed for productive traits with high use of anthelmintic interventions. Generally, they are more susceptible to GINs than indigenous breeds. In 2010, a review proposed a detailed analysis of the immune response of native breeds of sheep that are naturally more resistant to GINs in order to explore and potentially unravel mechanisms underlying such resistance. [11]. In the present paper, we aim to present and discuss some of our results that highlight the potential of using local breeds of sheep as a biotechnological resource. While several excellent studies have focused on other native sheep breeds [31–39] in this manuscript will concentrate on the Canaria Hair Breed sheep (CHB). The CHB is a pre Hispanic hair breed of sheep that was found by the conquest in the fifteen century. Possibly, the ancestor of this breed was from Africa, and arrive to the islands with the pre-Hispanic human population. The Canaries were a common stop for the explorers of the New World and probably sheep of this breed arrive to the Caribbean Islands. Current CHB sheep has been recovery through the introduction of wool-less sheep from Venezuela [40].

4. Can the Local Sheep Breed Develop "Singular" Mechanisms of Protection?

It was shown that the CHB was more resistant to single infection with *H. contortus* than the Canaria Sheep (CS), another native breed from the Canary Islands. The target of this protective immune response was the adult instead of larval parasitic stages, in contrast with previous studies [41]. Interestingly, no statistical differences in immune cell recruitment at the abomasal wall were observed between breeds. However, negative associations with worm length and fecundity with Tgd+ cells and eosinophils were only detected in resistant CHB lambs [42]. Similarly, mucus IgA specific to adult stage was also negatively associated with worm length in CHB while in the CS, a similar association was observed between mucus IgA against larval antigens and parasite length. These data are in agreement with the targeting of the adult stage in the resistant breed [43]. It is fascinating to note that the resistant CHB were able to recognize a wider variety of antigens than the susceptible CS. Similarly, antibody-secreting cells from local or abomasal lymph nodes from these animals showed greater recognition of somatic adult *H. contortus* antigens in the CHB than in the CS (Figure 1). However, it was not possible to identify a common protein in the resistant animals [44]. Similar heterogeneous pattern of antigen recognition was also observed in Scottish Blackface lambs naturally exposed to a predominantly *T. circumcincta* infection [30]. Possibly, these heterogeneous patterns of recognition, among other reasons, may explain why there is no record of loss of genetic resistance to parasites in sheep [45].

It was also possible to show with several experiments that gd T+ cells and eosinophil associations are critical to resistance. For example, one-year-old CHB male lambs were single infected with 10,000 L3 of *H. contortus* and the infection was allowed to progress until day 6 pi to determine whether protection of gd T cells was established at later parasitic stages in this breed. On day 6 pi and subsequence days (days 8, 10, 14, 17 and 21 pi) a monoclonal antibody against a gd T cell subpopulation -WC1- was intravenously administered to these lambs and, as a consequence, gd T cells-WC1+ were successfully depleted. In animals where gd T+ cells were depleted worms were significantly longer and harbored more eggs in their uterus. These data confirm that the target of the immune response in this mechanism of resistance was not the early parasitic stages and that gd T cells are a key cell in the control of worm length in single *H. contortus* infection [46].

Eosinophils are classically associated with protection against L3, and several interesting experiments have been carried out that seem to attribute to them a critical role [27,28]. Although there were no statistical differences in eosinophil counts in the abomasal wall between single infected with *H. contortus* CHB and CS lambs, susceptible lambs showed an eosinophil peak only at early stages of the infection, and their number dropped by day 28 pi. On the contrary, in the resistant breed, the eosinophil counts were very similar between 7 and 28 dpi [47]. To check whether eosinophils had any effect on the singular protection directed against the adult stage, recombinant IL5 (rIL5) was administered subcutaneously with the adjuvant Quil A. It was injected before a single infection with

H. contortus, reproducing the inoculation protocol followed in the previous gd T cells depletion trial. In this way, it was possible to reproduce the mechanism of adult stage protection. The IL-5 is a cytokine involved in eosinophilia and in eosinophil functionality [16]. The animals in which the rIL5 was administered had lower blood eosinophil counts and harbored more worms, and they were longer and more prolific [48]. These two experiments showed that the CHB had as immune target the adult stage instead the larvae, that gd T cells may coordinate this singular immune response and that eosinophils also have a role in this mechanism of protection (Figure 2).

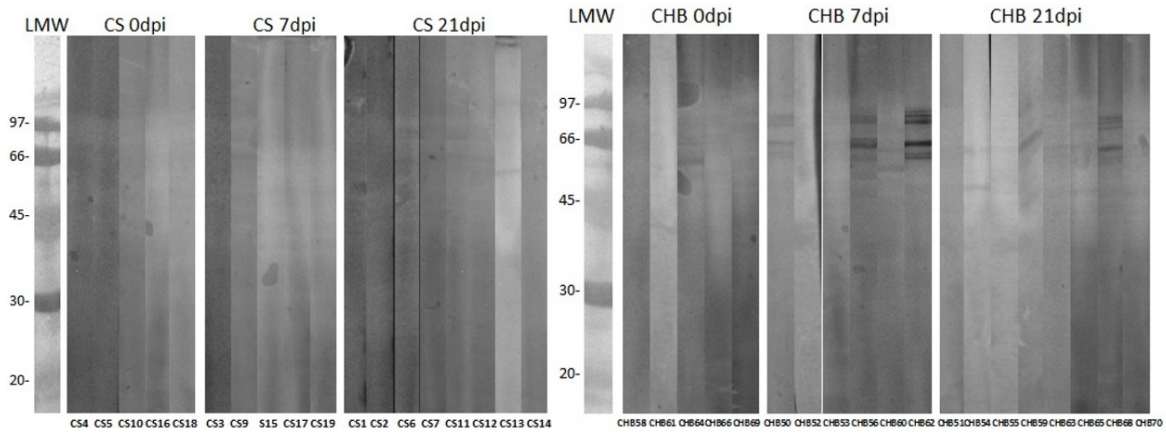

Figure 1. Western blot of somatic adult antigen and IgA produced by antibody-secreting cells obtained from abomasal lymph node of Canaria Hair Breed (CHB) or Canary Sheep (CS) lambs infected with 20,000 L3 of *H. contortus* at 7- and 21-days post infection (dpi). LMW: low molecular marker. Individual animal numbers are represented under each lane. Reprinted with permission from Hernández, 2015.Copyright 2015, Julia Natividad Hernández.

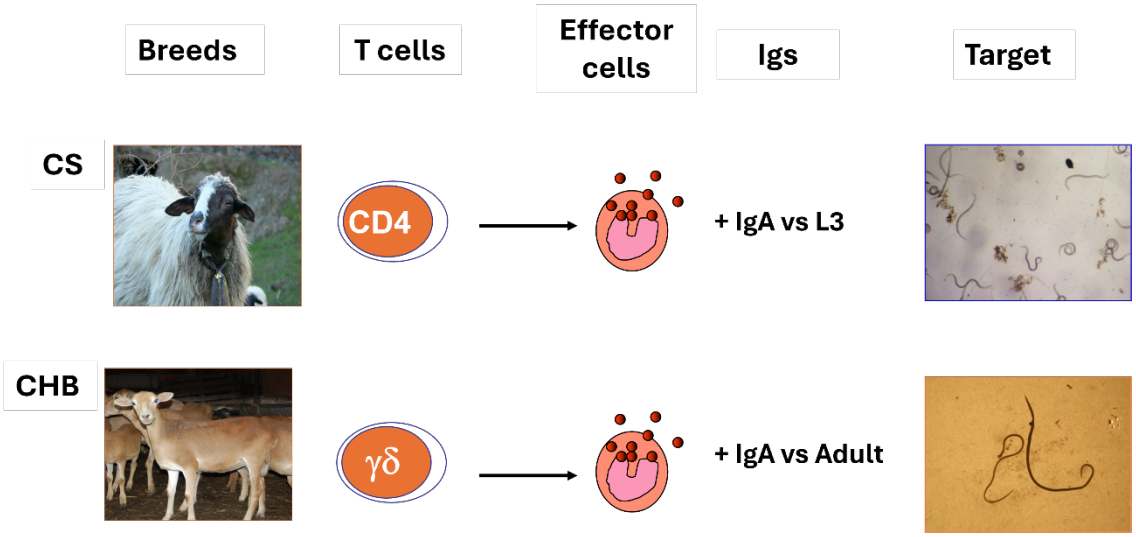

Figure 2. schematic representation of the immune response developed by Canarian breeds of sheep in animals single infected with L3 of *H. contortus*. The Canaria Sheep (CS) follows a classical response whilst the Canaria Hair Breed has gd T cells instead of CD4+ as key T cells, both breeds share eosinophils as critical cells for protection and produce mucus IgA that is associated with larval length and adult length in CS and CHB sheep respectively.

The analysis of the gene expression in the abomasal tissue from CHB and CS lambs single infected with 10,000 *H. contortus L3* showed 711 differentially expressed genes (DEG) in the resistant breed and only 50 in the susceptible breed compared to their control counterparts. Not only were immune pathways implicated, but other pathways such as acute inflammation response, complement activation, accelerated cell proliferation, amongst others, were also up regulated in the resistant breed. Furthermore, several relevant immune genes were also up-regulated in the CHB, such as the IL-5 (cytokine involved in eosinophil proliferation, recruitment and activation) [16] and galectin-11 [49]. This galectin is produced and released by epithelial cells, and it may be implicated in the control of worm length, targeting the L4 [50]. Recently, galectin-11 has been identified in resistant Australian Merino sheep [51] It was also clearly observed in histological samples from abomasum of both indigenous canarian breeds (Figure 3) [47].

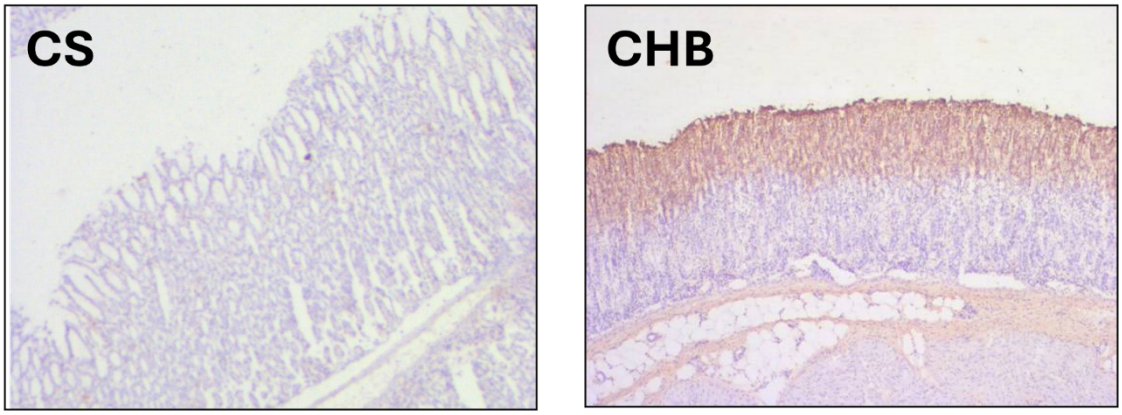

Figure 3. Immunohistochemical staining with antibodies against galectin-11(brown staining) in Canaria Sheep (CS) and Canaria Hair Breed (CHB) lambs experimentally infected with 20,000 L3 of *H. contortus*. Both pictures are representative of both breeds at 28 dpi. Reprinted with permission from Hernández, 2011. Copyright 2011, Álvaro Hernández.

5. Why Do Local Breeds of Sheep Develop This Defensive Mechanism?

It is possible that epidemiological and historical context can explain why this breed needs this powerful unique mechanism of resistance to *H. contortus*. The CHB and its ancestors have been reared in tropical or subtropical areas. As the Canary Islands' grazing area has always been very limited and GINs are present during the whole year [44], these sheep have been traditionally exposed to high *H. contortus* contaminated pastures. Until recently, they have been reared without the use of anthelmintic drugs, which means that these animals must survive in the presence of internal parasites.

May be the mechanisms of protection described above allow the lambs to control worm length even after the first contact with the larvae. Shorter worms ingest lower amounts of blood and harbor fewer eggs in their utero, therefore reducing worm pathogenicity and pasture contamination. Interestingly, the larval stages –usual targets of the acquired immune response- would not have been affected, giving lambs the possibility of naturally boosting their immune system, meanwhile pathogenicity and fecundity are reduced for preserving their lives. This "particular" innate mechanisms of protection could be nicely explored through organoids studies.

Interestingly, no single molecule was identified by all animals, and this may explain why, contrary to what happens with drugs, resistant animals or breeds do not lose this condition [45]. This situation should be considered both in future vaccine and biomarkers of diseases resistance studies.

6. Local Breeds and Acquired Immune Response against Gastrointestinal Nematodes

An experimental infection with *T. circumcincta* was carried out in 6-month-old CHB and CS lambs through oral inoculation of 2000 L3 three times per week for four weeks, mimicking the regular frequency of contact with infective larvae under natural conditions. Canaria Hair Breed lambs had lower FEC and shorter worms that harboured fewer eggs in their utero than CS, showing that CHB lambs were also more resistant to *T. circumcincta* than CS lambs. Although a 50% reduction in worm burden was also observed, this difference was not statistically significant [52].

A detailed analysis of the immune response of these animals showed that animals from both breeds developed a rapid rejection mechanism of protection [16]. CD4+ T cells, GLs and IL-4 production were associated with this protective response. Interestingly, although it was mainly a classical Type 2 response, in both native breeds it was observed an increase in IFN-g, suggesting that a balanced type 1/type 2 immune response may be critical for a successful control of GINs. However, in the local lymph node, CHB had greater proportion of CD4+ and CD8+ than CS, which could be a relevant difference in order to induce a major activation of T cells in the mucosa [53].

7. What about Young Lambs?

Young lambs are more susceptible to GINs than older lambs at early ages, possibly, they may not be immunocompetent enough to control worms [54–59]. An experimental trickle infection of *T. circumcincta* was carried out in 3-month-old CHB and CS lambs. Although no differences in worm susceptibility were observed between breeds, the immune response developed by the resistant sheep was more complex. In CS lambs, only gd

T cells and mast cells were negatively associated with some parasitological variables, whilst the CHB lambs also showed negative association with parasitological variables with GLs, B cells and IgG_1 production [60].

Although the immune response of the CHB was not enough to protect lambs compared to the CS one, its more complex mechanism of response suggested that lambs of this breed may develop protection more quickly than CS, as has been shown in other local breeds [61–63]. In agreement with this hypothesis, 3-month-old CHB lambs responded successfully to a recombinant *T. circumcincta* vaccine whilst their CS counterparts did not. Perhaps it reflected the breed's predisposition to respond at an earlier age [64]. It is also noticeable that young lambs of cross-Texel breed were not protected by this vaccine at this early age either [65].

Despite there were no statistical differences in parasitology between breeds, there was great individual variability in the animal response independently of breed. Some weaned lambs were clearly more resistant than others. It is a great finding, because it means that we can get "*superior-lambs*" from breeds with differences in their resistance-susceptibility to GIN even at this young age. The mechanisms underpinning this response may offer new markers for disease resistance. In this study, it was shown that abomasal MHC-II, GLs counts and *T. circumcincta* specific IgA in mucus were correlated with protective mechanisms. A detailed transcriptomic analysis of the local lymph node showed up-regulated genes involved in several pathways such as inflammation, migration and cell adhesion, haematopoiesis, mononuclear cell proliferation, signal and cell activation, etc. in resistant lambs compared to the susceptible ones. All of them may be key components of this protection. The study of individual genes also suggests some potentially relevant elements of this resistance mechanism, such as dendritic cell activation and antigen presentation, both through MHC-I and MHC-II molecules. All these data are in agreement with the expected type 2 protective immune response [60].

8. Can Vaccine Efficacy Condition Host-Immunity?

Several protective molecules have been identified in sheep, however, most of them failed to protect young lambs. The vaccines that target humoral response, such as Barbervax®, work better in young animals. Nonetheless, the molecules that tried to induce natural immunity generally fail [16]. In the study of the 3-month-old CHB lambs, as described above, responded well to a *T. circumcincta* vaccine prototype that did not protect 3-month-old CS [64] nor young Texel crossbred lambs [65]. This result would suggest that the combination of genetic resistance and vaccination using antigens recognize by animal naturally infected may be complementary control methods. However, vaccination with Barbervax® that used hidden antigens fail to protect resistant Australian Merino lambs [66]

As suggested before, it is possible that the success of the young CHB lambs' response to the vaccine may be explained, at least partially, by their capability to develop a more complex immune response at this age. Data obtained suggested better antigen recognition and a better attempt to coordinate the immune response [64]. The transcriptomic study of the abomasal lymph node of this breed showed a general up regulation of genes involved in a type-2 immune response in comparison to their CS counterparts. Interestingly, in susceptible lambs, genes related to regulatory T cells activation (Tregs) were up regulated [67]. It could partly be explained by the poor response of these animals to the vaccine or because these susceptible animals were unable to combat worms secreting molecules to increase T reg response early. We wonder whether this might reflect human influence, because selection of the most productive animals within flocks has been done on the basis of productive traits, but in a context where bacteria, virus and parasites have been controlled by human beings through the routine use of vaccines, antibiotics and anthelmintics. Maybe the response to these agents entails a metabolic cost for the animals, in which humans have reduced the impact of these pathogens on their growth. It may be interesting to modulate the Tregs response of 3-month-old lambs in combination with the vaccination. In neonatal kids, it has been recently pointed out that these cells may represent a limitation of their response to several vaccines against malaria, AIDS or hepatitis [68]. Some cancer studies have also considered the possibility of reducing the negative influence of these Tregs with some promising results for consideration in cancer therapy [69,70]. Some assays have also been conducted on vaccines against human infections [71] such as malaria [72] or retrovirus [73]. Exploring the effect of partially suppressing the regulatory action of this T cell on vaccination against worms in young lambs would be intriguing.

In conclusion, the relationship between sheep and GINs is atavistic and practically universal in flocks with access to pasture. This ancestral relationship has influenced the evolution of both the agent and the host. Humans have interfered this interaction through the systematic and strategic administration of drugs. This may explain the greater susceptibility of commercial sheep breeds compared to indigenous sheep. Studies conducted in these breeds have shown new targets of protection (adults) and confirm the main "actors" (cells, immunoglobulins, mediators…) implicated in protective responses, previously identified in more commercial breeds. However, the use of new tools such as transcriptomics, proteomics, organoids, or single-cell flow cytometry can be powerful

tools that can detect nuances in immune responses that may be critical in the mechanisms of protection against GINs. Elucidating these aspects, with the help of these breeds, can be decisive in vaccine design, the identification of new drugs, and the selection of resistant animals.

Author Contributions

J.F.G: conceptualization, methodology, data curation, writing-original draft preparation, visualization, investigation, supervision; C.M.: methodology, data curation, investigation, writing-reviewing and editing; T.P.-H.: methodology, data curation, investigation, writing-reviewing and editing; J.N.H.: conceptualization, methodology, data curation, investigation, supervision, writing-reviewing and editing. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

The author original data that supports this manuscript are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflict of interest.

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