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Genomic and Transcriptomic Analysis of Disease Resistance in Sheep

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Abstract This study identified several key genes and pathways linked to disease resistance. Notably, genes involved in the humoral immune response, protein synthesis, inflammatory response, and hematological system development were found to be critical. Central genes such as IL4, IL5, IL13RA2, and IL13 were highlighted for their role in Th2 polarized responses, which are crucial for resistance to nematode infections. Additionally, pathways related to cytokine-mediated immune response and the PPARG signaling pathway were enriched in resistant sheep. The study also identified polymorphisms in immune pathway genes on sheep chromosome 3, which were associated with resistance traits. Furthermore, genomic regions containing candidate genes like ABCB1, IL6, WNT5A, and IRF5 were proposed as potential biomarkers for selecting resilient sheep. The findings of this study provide significant insights into the genetic and molecular mechanisms underlying disease resistance in sheep. The identification of key genes and pathways not only enhances our understanding of host-pathogen interactions but also offers potential genetic markers for breeding programs hoped at improving disease resistance in sheep populations.

Keywords Sheep (*Ovis aries*); Disease resistance; Genomic analysis; Transcriptomic analysis; Gastrointestinal nematodes; Immune response; Genetic markers

1 Introduction

Disease resistance in sheep, particularly against gastrointestinal nematodes (GINs), is a critical trait for maintaining animal health and productivity. GIN infections, such as those caused by *Haemonchus contortus* and *Teladorsagia circumcincta*, can lead to significant economic losses in the sheep industry due to reduced weight gain, lower wool production, and increased mortality rates (Stear et al., 1997; Gossner et al., 2013; Zhang et al., 2019). Understanding the genetic and immunological mechanisms underlying resistance to these parasites is essential for developing effective breeding programs aimed at enhancing disease resistance in sheep populations.

Genomic and transcriptomic analyses have emerged as powerful tools to unravel the complex biological processes involved in disease resistance (Xuan, 2024). These approaches allow researchers to identify genetic markers and differentially expressed genes associated with resistance traits, providing insights into the molecular pathways that confer immunity (Benavides et al., 2016; Chitneedi et al., 2018; Zhang et al., 2019). For instance, transcriptome analysis of abomasal tissues and lymph nodes has revealed key genes and pathways, such as those involved in the Th2 immune response and cytokine signaling, that are crucial for resistance to GIN infections (Gossner et al., 2013; Wilkie et al., 2016; Chitneedi et al., 2018). Additionally, genome-wide association studies (GWAS) have identified specific single nucleotide polymorphisms (SNPs) linked to resistance, which can be used to select and breed more resilient sheep (Haehling et al., 2020; Ahbara et al., 2021).

This research aims to provide a comprehensive overview of the current state of research on the genomic and transcriptomic aspects of disease resistance in sheep. The objectives are to summarize the key findings from recent studies on the genetic and transcriptomic mechanisms of resistance to GIN infections in sheep, highlight the importance of specific genes, pathways, and genetic markers identified through these studies, discuss the potential applications of these findings in breeding programs to enhance disease resistance in sheep populations. By synthesizing the latest research, the study hopes to advance our understanding of the genetic basis of disease resistance in sheep and to inform future strategies for improving animal health.

2 Background and Importance

2.1 Sheep production and global significance

Sheep (*Ovis aries*) are one of the most economically, culturally, and socially important domestic animals globally. They are primarily reared for meat, milk, wool, and fur production, making them a vital component of the agricultural sector in many countries (Clark et al., 2017; Gebreselassie et al., 2019). The UK, for instance, has developed numerous native breeds with unique phenotypic features and excellent productivity, which are utilized worldwide (Romanov et al., 2021). The genetic and genomic information available for sheep has significantly advanced, aiding in the improvement of production traits and overall productivity (Jiang et al., 2014; Rupp et al., 2016).

2.2 Common diseases affecting sheep populations

Sheep populations are susceptible to various diseases, with mastitis being one of the most prevalent and impactful. Mastitis affects milk yield and quality, animal welfare, and incurs substantial economic costs (Banos et al., 2019; Mohammadi et al., 2022). Other common diseases include those affecting the respiratory and digestive systems, which can also have significant economic and welfare implications. The genetic basis of disease resistance is a critical area of research, with studies identifying specific genomic regions and candidate genes associated with resistance to diseases like mastitis (Banos et al., 2017; 2019).

2.3 Economic and welfare impacts of disease resistance

The economic and welfare impacts of disease resistance in sheep are profound. Diseases like mastitis not only reduce milk yield and quality but also increase veterinary costs and labor associated with managing sick animals. Enhancing disease resistance through genetic improvement can lead to better animal welfare, reduced economic losses, and increased productivity. For instance, genomic studies have identified candidate genes and genomic regions associated with milk production traits and somatic cell scores, which are indicators of mastitis resistance (Banos et al., 2019; Mohammadi et al., 2022). The absence of genetic antagonism between milk yield and mastitis resistance suggests that simultaneous genetic improvement of both traits is achievable, further underscoring the economic and welfare benefits of such advancements (Banos et al., 2019).

3 Genomic Analysis of Disease Resistance

3.1 Overview of sheep genomic research

Sheep genomic research has made significant strides in understanding the genetic basis of disease resistance. The application of genetic and genomic techniques has been pivotal in identifying genes and markers associated with resistance to various diseases. Studies have focused on both major and minor genes, utilizing genome-wide association studies (GWAS) and other genomic selection models to enhance breeding programs aimed at improving disease resistance (Bishop and Woolliams, 2014; Merrick et al., 2021).

3.2 Key genes associated with disease resistance

Several key genes have been identified as playing crucial roles in disease resistance in sheep. For instance, a genome-wide scan identified genes such as *SEMA3*, *CD109*, *PCP4*, *PRDM2*, and *ITFG2*, which are associated with disease resistance or cell-mediated immune response (Moioli et al., 2016). Additionally, genes located on sheep chromosome 3 have been linked to resistance against gastro-intestinal nematodes, with significant variations observed in immune pathway genes (Periasamy et al., 2014). In Brazilian Morada Nova sheep, specific single nucleotide polymorphisms (SNPs) such as OAR2_14765360 and OAR12_69606944 have shown associations with resistance traits (Haehling et al., 2020).

3.3 Genetic markers and their role in breeding programs

Genetic markers, particularly SNPs, play a crucial role in breeding programs aimed at enhancing disease resistance. The identification of SNPs associated with resistance traits allows for the selection of animals with favorable genotypes, thereby accelerating genetic progress. For example, SNPs identified in the Morada Nova sheep breed have been linked to resistance and resilience to *Haemonchus contortus*, a major gastrointestinal nematode (Haehling et al., 2020). The use of genomic selection models, which incorporate these markers, has been shown to improve prediction accuracy and breeding outcomes (Merrick et al., 2021).

3.4 Case study: identification of major histocompatibility complex (MHC) genes in sheep

The Major Histocompatibility Complex (MHC) genes are critical for immune response and disease resistance. Although much of the detailed research on MHC genes has been conducted in other species, such as chickens, where MHC molecules are involved in antigen presentation and cytokine stimulation (Gul et al., 2022), similar principles apply to sheep. Identifying and understanding the role of MHC genes in sheep can provide insights into their immune mechanisms and aid in the development of disease-resistant breeds.

3.5 Advances in genomic selection techniques

Advances in genomic selection techniques have revolutionized the breeding of disease-resistant sheep. Techniques such as whole genome sequencing, high-density SNP genotyping, and CRISPR/Cas9 have enabled more precise identification and manipulation of resistance genes (Gul et al., 2022). Genomic selection models that incorporate both major and minor gene markers have shown higher prediction accuracies compared to traditional marker-assisted selection, making them valuable tools in breeding programs (Merrick et al., 2021). These advancements not only enhance the efficiency of breeding for disease resistance but also reduce the reliance on antibiotics and vaccinations, promoting sustainable livestock production.

4 Transcriptomic Analysis in Sheep

4.1 Introduction to transcriptomics and its relevance

Transcriptomics is the comprehensive study of the complete set of RNA transcripts produced by the genome under specific circumstances or in a specific cell. This field provides a snapshot of gene expression at a given moment, reflecting both genetic and environmental influences (Futschik et al., 2020; Jong and Bosco, 2021). In sheep, transcriptomic analysis is particularly relevant for understanding the molecular mechanisms underlying disease resistance, as it allows researchers to identify differentially expressed genes (DEGs) in response to various pathogens and stressors (Chitneedi et al., 2018; Li et al., 2021).

4.2 Techniques used in transcriptomic studies

The primary techniques used in transcriptomic studies include microarrays and RNA sequencing (RNA-Seq). Microarrays quantify a set of predetermined sequences, while RNA-Seq uses high-throughput sequencing to capture all RNA sequences present in a sample (Lowe et al., 2017; Lamas et al., 2019). RNA-Seq has become the preferred method due to its ability to provide a more comprehensive and unbiased view of the transcriptome, including the detection of novel transcripts and alternative splicing events (McGettigan, 2013; Tsimberidou et al., 2020). This technique has been instrumental in advancing our understanding of gene expression regulation and the functional implications of genetic variations (Ozurumba-Dwight, 2022).

4.3 Differential gene expression in response to disease

Differential gene expression analysis involves comparing the transcriptomes of diseased and healthy tissues to identify genes that are up- or down-regulated in response to disease. This approach has been used to uncover the molecular pathways involved in disease resistance and susceptibility in sheep. For instance, studies have identified DEGs associated with immune response, protein glycosylation, and gene regulation in sheep infected with *Mycoplasma ovipneumonia*e (Li et al., 2021). Similarly, genes related to cytokine-mediated immune response and inflammation have been linked to resistance against gastrointestinal nematode infections (Chitneedi et al., 2018).

4.4 Case study: transcriptomic responses to parasite infection in sheep

A notable case study involves the transcriptomic analysis of sheep infected with the gastrointestinal nematode *Teladorsagia circumcincta*. Researchers used RNA-Seq to compare the transcriptomes of resistant and susceptible sheep, identifying 106 DEGs in the lymph node tissues of infected animals. These genes were associated with immune responses and inflammation, highlighting the molecular mechanisms that contribute to resistance against this parasite (Chitneedi et al., 2018). Another study compared the lung transcriptomes of Bashbay sheep, which are resistant to *Mycoplasma ovipneumoniae*, and Argali hybrid sheep, which are susceptible (Figure 1). The analysis revealed significant differences in gene expression related to immune response and protein glycosylation, providing insights into the genetic basis of disease resistance (Li et al., 2021).

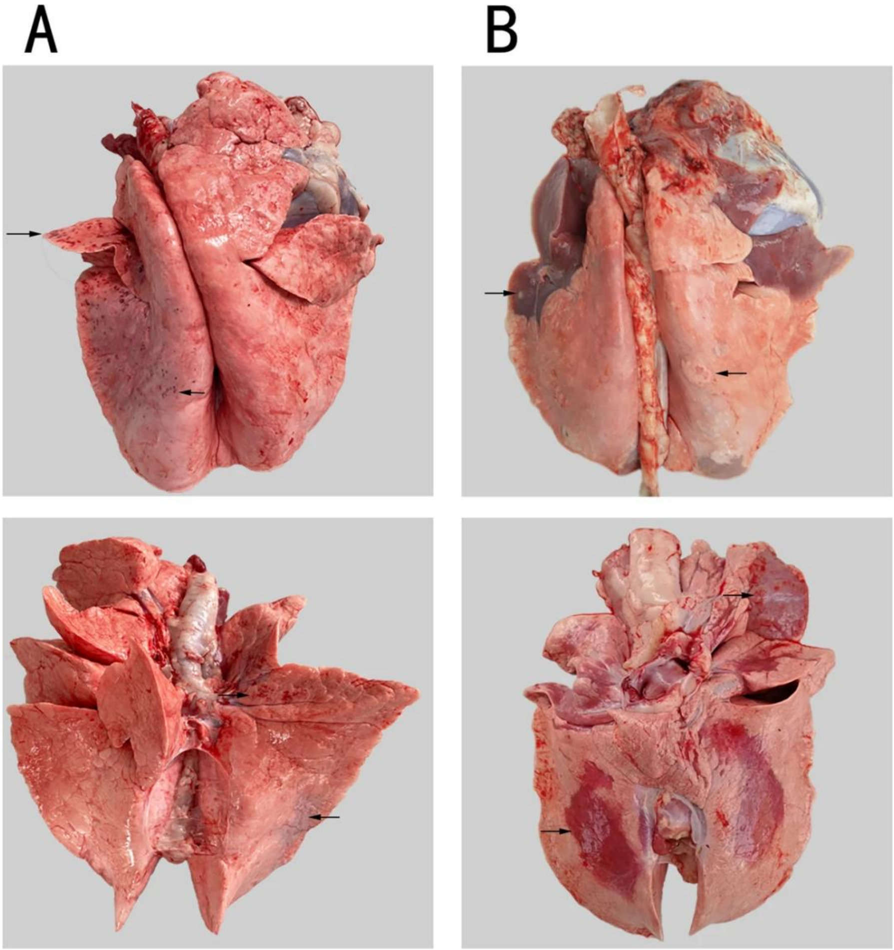

Figure 1 Gross lesions of lungs from Bbs and Ahs at 14th dpi. A The lungs isolated from the thoracic cavity of Bashbay sheep, only a small amount of hemorrhagic spots were observed on the face of lungs; B The lungs isolated from the thoracic cavity of Argali hybrid sheep, there were much severer inflammatory lesions in lungs of Ahs than Bbs, including large-scale red and gray hepatization and bulge nodules. Typical lesions are pointed out by the black arrows in the above figures (Adopted from Li et al., 2021)

4.5 Integrating transcriptomic data with genomic information

Integrating transcriptomic data with genomic information enhances our understanding of the functional consequences of genetic variations. This approach allows researchers to link specific genetic variants to changes in gene expression and to identify potential biomarkers for disease resistance. For example, combining transcriptomic and genomic data has been used to identify genes involved in drug resistance and to understand the impact of genomic alterations on RNA expression in cancer studies (Adashek et al., 2020; Tsimberidou et al., 2020). In sheep, such integrative analyses can help elucidate the genetic basis of disease resistance and inform breeding programs aimed at enhancing disease resilience (Chitneedi et al., 2018). By leveraging the power of transcriptomics, researchers can gain a deeper understanding of the complex molecular interactions that underpin disease resistance in sheep, ultimately leading to improved animal health and productivity.

5 Comparative Genomic and Transcriptomic Approaches

5.1 Cross-species comparisons for disease resistance

Cross-species comparisons are essential for understanding the genetic basis of disease resistance in sheep. By comparing sheep with other livestock and model organisms, researchers can identify conserved genetic elements and pathways that contribute to disease resistance. For instance, studies have shown that certain genes, such as those involved in the immune response, are under selection in both sheep and goats exposed to gastrointestinal nematodes like *Haemonchus contortus* (Estrada-Reyes et al., 2019). These shared genetic signatures can provide valuable insights into the mechanisms of disease resistance and inform breeding programs aimed at enhancing resistance in sheep.

5.2 Lessons from other livestock and model organisms

Research on other livestock species and model organisms has provided significant insights into disease resistance mechanisms that can be applied to sheep. For example, gene-editing technologies like CRISPR/Cas9 have been used to develop tuberculosis-resistant cattle and pigs resistant to porcine reproductive and respiratory syndrome (Pal and Chakravarty, 2019). These advancements highlight the potential of genomic technologies to enhance disease resistance in sheep. Additionally, the study of immune response genes in goats and their response to *Haemonchus contortus* infection has revealed important genetic markers that could be targeted in sheep breeding programs (Aboshady et al., 2020; Shabana and Al-Enazi, 2020).

5.3 Case study: comparative analysis between sheep and goats

A comparative analysis between sheep and goats has revealed both common and unique genetic responses to disease challenges. For instance, both species show genetic variation in response to *Haemonchus contortus* infection, with specific genes like NOS2 and TGFB2 being under selection in both sheep and goats (Estrada-Reyes et al., 2019a) (Figure 2). However, there are also species-specific differences; for example, certain immune response genes are differentially expressed in sheep compared to goats when infected with gastrointestinal nematodes (Aboshady et al., 2020). These findings underscore the importance of species-specific studies while also highlighting the potential for cross-species genetic insights.

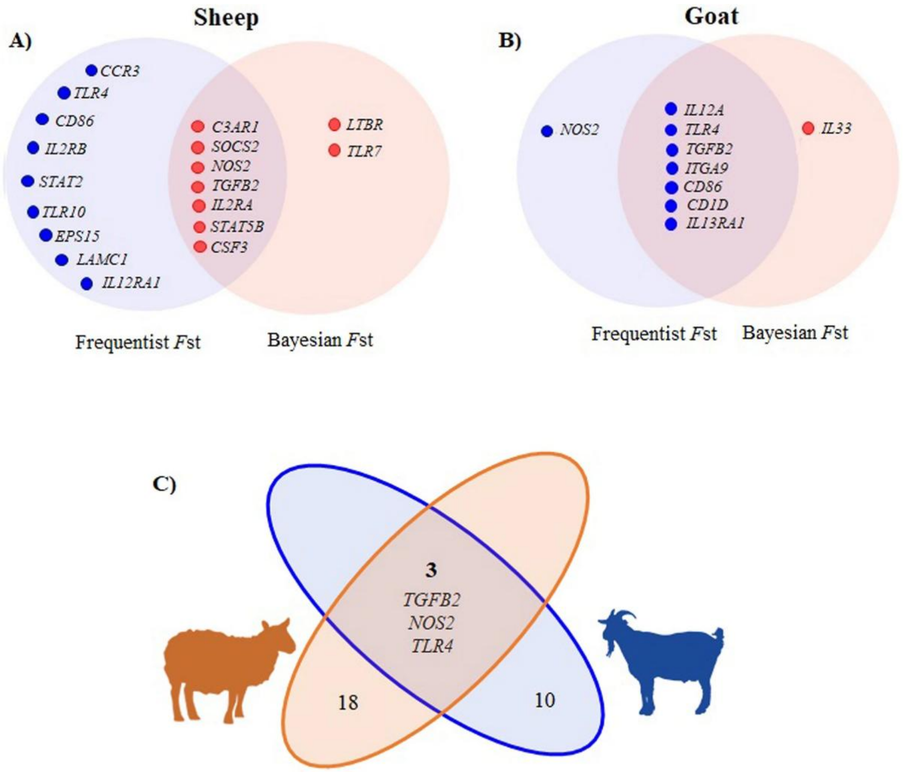

Figure 2 Venn diagram of the shared signatures of selection between frequentist and Bayesian Fst for sheep (a) and goats (b) and the common signatures of selection in both species (c) (Adopted from Estrada-Reyes et al., 2019a)

5.4 Challenges and opportunities in comparative approaches

While comparative genomic and transcriptomic approaches offer valuable insights, they also present several challenges. One major challenge is the complexity of genetic interactions and the influence of environmental factors on disease resistance. Additionally, the genetic diversity within and between species can complicate the identification of universal genetic markers for disease resistance. However, these challenges also present opportunities for developing more targeted and effective breeding programs. By leveraging advanced genomic technologies and cross-species comparisons, researchers can identify robust genetic markers and pathways that contribute to disease resistance, ultimately leading to healthier and more resilient sheep populations (Estrada-Reyes et al., 2019a; Pal and Chakravarty, 2019; Aboshady et al., 2020).

6 Applications in Breeding Programs

6.1 Incorporating genomic and transcriptomic data into breeding

Incorporating genomic and transcriptomic data into sheep breeding programs can significantly enhance the accuracy of selecting for disease resistance traits. Genomic selection (GS) models, which utilize dense marker data, have been shown to outperform traditional marker-assisted selection (MAS) by providing higher prediction accuracies for disease resistance traits (Huang et al., 2019; Merrick et al., 2021). For instance, the use of single nucleotide polymorphism (SNP) markers in GS models has demonstrated improved prediction accuracy for disease resistance in various species, including aquaculture and plants, suggesting similar benefits could be realized in sheep (Carpenter et al., 2018; Luo et al., 2021). Additionally, integrating transcriptomic data can help identify gene expression patterns associated with disease resistance, further refining selection criteria.

6.2 Strategies for enhancing disease resistance in sheep populations

Several strategies can be employed to enhance disease resistance in sheep populations using genomic and transcriptomic data. One effective approach is the use of genomic selection, which involves genotyping large populations and using this data to predict breeding values for disease resistance traits (Miedaner et al., 2020; Granado-Tajada et al., 2021). This method allows for the selection of individuals with superior genetic profiles for disease resistance, even in the absence of phenotypic data. Another strategy is the identification and utilization of quantitative trait loci (QTL) associated with disease resistance, which can be targeted in breeding programs to accumulate favorable alleles (Eydivandi et al., 2021; Zubby, 2023). Additionally, genome editing technologies offer the potential to directly modify genes associated with disease resistance, providing a powerful tool for enhancing resistance traits (Proudfoot et al., 2019).

6.3 Case study: implementation of genomic selection for disease resistance

A case study on the implementation of genomic selection for disease resistance can be seen in the breeding programs for rice blast resistance in rice. Researchers evaluated the utility of GS in improving resistance to rice blast by genotyping populations with SNP markers and assessing the accuracy of various GS models (Huang et al., 2019). The study found that GS models, particularly those incorporating fixed effects, provided high prediction accuracies for disease resistance traits. This approach can be adapted to sheep breeding programs by genotyping sheep populations and using GS models to predict and select for disease resistance traits, thereby improving the overall health and productivity of the flock.

6.4 Future prospects in breeding for disease resistance

The future of breeding for disease resistance in sheep looks promising with the continued advancements in genomic and transcriptomic technologies. The integration of multi-omics data, including genomics, transcriptomics, and proteomics, will provide a more comprehensive understanding of the genetic basis of disease resistance, enabling more precise selection strategies (Granado-Tajada et al., 2021; Zubby, 2023). Additionally, the development of cost-effective genotyping methods and the increasing availability of high-throughput sequencing technologies will make genomic selection more accessible to breeders. Furthermore, advancements in genome editing techniques, such as CRISPR/Cas9, hold the potential to directly introduce disease resistance traits into sheep populations, revolutionizing breeding programs (Proudfoot et al., 2019). As these technologies continue to evolve, they will play a crucial role in enhancing disease resistance and improving the sustainability of sheep farming.

7 Challenges and Limitations

7.1 Technical and methodological challenges

One of the primary technical challenges in genomic and transcriptomic analysis of disease resistance in sheep is the high dimensionality of the data, which can hinder generalization and scalability of machine learning algorithms used for genotype-to-phenotype predictions (Drouin et al., 2018). Additionally, the integration of various genomic data types, such as SNPs, haplotypes, CNVs, and ROH, requires sophisticated computational approaches and network analysis to identify significant genomic regions and candidate genes (Berton et al., 2022). The use of RNA-seq technology to analyze transcriptomes also presents challenges, such as the need for high-quality RNA samples and the complexity of differential expression analysis (Chitneedi et al., 2018). Furthermore, the retrospective genetic analysis using cell-free DNA from archived samples, although innovative, may face limitations in the quality and quantity of DNA that can be extracted from older samples (Hanks et al., 2020).

7.2 Data integration and interpretation issues

Integrating data from multiple sources, such as GWAS, transcriptomics, and metagenomics, poses significant challenges in terms of data harmonization and interpretation. For instance, the integration of GWAS and structural variants to identify molecular biomarkers requires careful consideration of overlapping genomic regions and the biological relevance of identified genes (Berton et al., 2022). Similarly, the use of whole-genome sequencing (WGS) data in quantitative risk assessment models for antimicrobial resistance involves challenges in determining the thresholds of genetic similarity and correlating genotypic profiles with phenotypic outcomes (Collineau et al., 2019). The complexity of interpreting metagenomic data, especially in the context of antimicrobial resistance, further complicates the analysis due to the need to understand horizontal gene transfer and the resistome (Abreu et al., 2021).

7.3 Ethical considerations in genomic and transcriptomic research

Ethical considerations in genomic and transcriptomic research are paramount, particularly concerning the use of genetic information for breeding and disease resistance. The identification of genetic markers and candidate genes for disease resistance must be handled with care to avoid potential misuse or discrimination based on genetic traits (Haehling et al., 2020). Additionally, the use of archived samples for retrospective genetic analysis raises ethical questions about consent and the use of genetic material collected for different purposes (Hanks et al., 2020). Ensuring the privacy and confidentiality of genetic data is also crucial, especially when integrating data from multiple sources and sharing findings within the scientific community (Drouin et al., 2018; Collineau et al., 2019).

8 Future Directions and Research Gaps

8.1 Emerging technologies and their potential

The rapid advancement of genomic and transcriptomic technologies offers promising avenues for enhancing our understanding of disease resistance in sheep. High-throughput RNA sequencing has already provided valuable insights into the molecular mechanisms underlying resistance to various pathogens, such as *Haemonchus contortus* and *Mycoplasma ovipneumoniae* (Zhang et al., 2019; Li et al., 2021). Future research should focus on integrating these technologies with other omics approaches, such as proteomics and metabolomics, to develop a more comprehensive understanding of host-pathogen interactions. Additionally, the application of CRISPR-Cas9 and other gene-editing technologies could pave the way for functional validation of candidate resistance genes identified through genomic studies (Chitneedi et al., 2018; Berton et al., 2022).

8.2 Gaps in current knowledge and research needs

Despite significant progress, several gaps remain in our understanding of disease resistance in sheep. One major gap is the limited knowledge of the genetic basis of resistance to a broader range of pathogens beyond gastrointestinal nematodes. While studies have identified specific genes and pathways associated with resistance to *Haemonchus contortus* and *Teladorsagia circumcincta*, the genetic mechanisms underlying resistance to other pathogens, such as bacteria and viruses, are less well understood (Chitneedi et al., 2018; Kyselová et al., 2023). Furthermore, the role of epigenetic modifications and non-coding RNAs in regulating immune responses in sheep remains largely unexplored. Addressing these gaps will require comprehensive multi-omics studies and the development of new bioinformatics tools for data integration and analysis (Tunstall et al., 2020; Bianconi et al., 2023).

8.3 Collaborative efforts and global initiatives

The complexity of disease resistance in sheep necessitates collaborative efforts and global initiatives to accelerate research progress. International consortia and collaborative networks can facilitate the sharing of genomic data, resources, and expertise, thereby enhancing the reproducibility and scalability of research findings. Initiatives such as the One Health approach, which emphasizes the interconnectedness of human, animal, and environmental health, can provide a holistic framework for studying disease resistance in sheep (Ransom et al., 2020; Bianconi et al., 2023). Additionally, partnerships between academic institutions, industry, and government agencies can drive the translation of research findings into practical applications, such as the development of genomic selection tools and vaccines for disease-resistant sheep breeds (Estrada-Reyes et al., 2019b; Haehling et al., 2020). By addressing these future directions and research gaps, we can advance our understanding of disease resistance in sheep and develop innovative strategies to improve animal health and productivity.

9 Concluding Remarks

The genomic and transcriptomic analyses conducted across various studies have significantly advanced our understanding of disease resistance in sheep. Key findings include the identification of specific genes and pathways associated with resistance to gastrointestinal nematodes and other diseases. For instance, studies have highlighted the importance of Th2 polarized responses and the up-regulation of genes linked to inflammation control in resistant sheep. Additionally, genetic markers associated with resistance to *Haemonchus contortus* and mastitis have been identified, suggesting that selective breeding could enhance disease resistance. The identification of conserved gene expression changes in resistant sheep further supports the feasibility of breeding programs aimed at improving disease resistance.

The findings from these studies have profound implications for the future of sheep disease management. The identification of genetic markers and differentially expressed genes provides a foundation for developing selective breeding programs aimed at enhancing disease resistance. This approach could reduce the reliance on chemical treatments, thereby mitigating the risk of drug resistance and promoting sustainable livestock management practices. Moreover, the integration of genomic and transcriptomic data into breeding programs could lead to the development of sheep breeds with enhanced resistance to a variety of diseases, including gastrointestinal nematodes, mastitis, and paratuberculosis.

Genomics and transcriptomics have proven to be invaluable tools in unraveling the complex mechanisms underlying disease resistance in sheep. These technologies have enabled the identification of key genes and pathways involved in immune responses, providing insights that were previously unattainable. As research progresses, the integration of genomic and transcriptomic data will likely lead to more precise and effective breeding strategies, ultimately enhancing the health and productivity of sheep populations. The continued exploration of these molecular techniques holds great promise for advancing our understanding of disease resistance and improving the overall resilience of livestock to infectious diseases.

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Conflict of Interest Disclosure

The authors affirm that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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