The Molecules of Life: Understanding Biological Systems through Systems Biology

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I. Introduction

Bovine respiratory disease (BRD) remains the leading cause of morbidity and mortality in beef production systems, despite decades of dedicated research in vaccine development, diagnostics, and management scheme advancements[1,2]. Specifically, BRD remains a highly prevalent disease complex in modern production systems due to, in part, the relative variability of individual clinical presentation and apparent prevalence both within and across pens and populations and to the lack of rapid, sophisticated disease detection systems at a commercial level[3-5]. Omics research, the comprehensive evaluation of cellular and molecular systems through high-throughput biochemical assays and computational analysis platforms, has emerged as a leading field for investigating infectious disease in livestock , particularly BRD[6]. In recent years, omics-based methodologies have utilized and integrated genomic, transcriptomic, proteomic, and metabolomic approaches to provide a more holistic view of host-pathogen relationships, transmission dynamics, genetic and environmental risk factors, and predictive features associated with BRD outcomes. Both ours and other researchers' current research philosophy stands to utilize technological advancements in biochemistry, computing, and statistical modeling, in order to improve both the pathophysiological process, microbial community structure, and immunological response in cattle which either resist or develop naturally occurring BRD. Here, we explore recent advancements in sequencing and bioinformatic research focused on BRD, centering on genomic, transcriptomic, and metagenomic approaches, to shed light on its complex etiology and potential solutions for future diagnostic and prognostic tool development.

II. Genomic Insights into Bovine Respiratory Disease

The field of genomics involves comprehensively sequencing and analyzing the genetic material of an individual (host or pathogen) or pool of organisms (termed metagenomics)[7]. This area of research, in conjunction with BRD, is often in effort to provide insights into genetic predispositions to disease acquisition and severity, traits and/or virulence factors important for host adaption and infectivity, or cataloguing the complex community structures associated with health and disease outcomes. Genomic sequencing studies focused on the host (cattle) have identified novel genetic variants associated with susceptibility to BRD in commercial production settings. Through genome-wide association studies (GWAS) and whole-genome sequencing (WGS) efforts, previous research has determined genes and genomic regions susceptible to mutagenic changes linked to immunological response and susceptibility to respiratory pathogens[8-11]. These findings provide valuable insights into the genetic basis of BRD

susceptibility and resilience which provide foundational information for building future breeding and management program development research.

Metagenomic sequencing of the gut and respiratory microbiome has provided insights into the microbial communities associated with BRD onset and progression. This area of omics research aims to characterize the composition and functional potential of respiratory microbiota, identifying shifts in microbial diversity and abundance correlated with BRD treatment outcomes and mitigation schemes[12-14]. For example, this research approach has been leveraged to uncover viral community structures and potentially novel viral species never before reported in cattle affected with BRD in commercial feedlot operations[15-17]. Further research has been conducted to investigate the relationship between the bacterial microbiome and resistome (i.e., the composition of antimicrobial resistance genes), BRD development and/or mortality, and management tactics, such as metaphylaxis or vaccination[18-20]. Collectively, these metagenomic-based studies offer novel insights into influences which BRD development possesses on the microflora of cattle, aid in accumulating causal inferences to BRD management and disease pathogenesis, and provide innovative hypotheses towards the development of advanced diagnostic and control measures against BRD in large-scale commercial operations.

III. Transcriptomic Signatures of Bovine Respiratory Disease

Transcriptomics, or the comprehensive study of RNA from a cell or tissue, allows for the focused assessment of molecular functionality, genomic regulation, and shared co-expression patterns[21]. Through transcriptome assessment, researchers can define conserved gene expression patterns of cattle under various biological conditions, aiding in the identification of novel regulatory pathways and potential biomarkers to recognize and treat early-onset BRD[21,22]. To this end, both our laboratory and several others have sought to identify gene expression patterns and identifiable molecules which can be leveraged for predicting BRD outcomes in high-risk beef cattle upon their arrival to a production operation[23-27]. Here, such genomic features such as increased type-I interferon production, alternative complement, and M1 macrophage scavenging and activity, and decreased specialized pro-resolving mediator production and lipid metabolism are highly indicative of cattle who go on to develop BRD in the first 28 days of production. Moreover, this methodology has been leveraged to improve our understanding of how conventional BRD-control tactics, such as metaphylaxis and vaccination against BRD pathogens, influence long-term immunomodulation and metabolism in beef cattle[28-30]. Furthermore, transcriptome evaluation research is not limited to the host, as previous research has leveraged gene expression profiles from organisms such as *Mannheimia haemolytica* and *Histophilus somni* to improve genomic annotations and functional properties of these pathogenic bacteria[31,32]. Collectively, through the comparison gene expression patterns between cattle and/or pathogens in context to BRD, researchers have identified key regulatory pathways involved in cellular homeostasis, inflammation, and specific immune functions that offer potential biomarkers for early BRD detection, monitoring treatment responses, and developing targeted therapies to mitigate disease progression in affected cattle.

IV. Proteomic and Metabolomic Markers of Bovine Respiratory Disease

Proteomics, the extensive evaluation of proteins produced or modified by an organism or system via high-throughput assays, allow for the discovery of functional features into BRD mechanisms[22,33]. This approach is typically in effort for novel protein identification, quantification, and post-translational modifications in relation to disease outcomes or interventions. For example, proteomic analyses of bronchoalveolar lavage and serum samples have identified potential protein biomarkers and post-translational mechanisms associated with virus-induced BRD pathogenesis, lung inflammation, and negative therapeutic outcomes in cattle[34-36]. Likewise, this technology has been utilized in BRD vaccination trials, leveraging peripheral lymphoid tissue in calves vaccinated and challenged with viral agents; such research improves our perception of vaccine efficacy and supports new concepts concerning BRD vaccine discovery and development research[37].

Metabolomics, the evaluation and quantitative analysis of small molecules produced during cellular metabolism, provides a snapshot of metabolic states and biochemical changes within a biological system[38,39]. Within BRD-focused research, studies have provided possible diagnostic molecules to differentiate cattle undergoing wildtype viral challenge from those responding to attenuated viral vaccinations[35,40]. Additionally, blood metabolomic studies have revealed metabolic signaling patterns and dysregulation associated with BRD onset and progression in cattle[41-45]. From these novel challenge studies, differences in metabolites associated with energy metabolism, oxidative stress, and immune function in cattle provide potential targets for rapid or real-time BRD diagnosis assay development in production systems.

V. Conclusion

Technological advancements in high-throughput biochemical assays and data analysis techniques have unlocked new possibilities for BRD researchers to assess management schemes, develop novel prognostic, diagnostic, and therapeutic tools, and comprehensively assess common tools and tactics employed in commercial cattle production systems, such as vaccines and metaphylaxis. Next-generation sequencing and high-throughput omics research have improved our understanding of BRD by untangling the genetic, molecular, and microbial component causes. Genomic, transcriptomic, metagenomic, proteomic, and metabolomic approaches provide comprehensive insights into BRD pathogenesis, host-pathogen interactions, and potential therapeutic targets. Leveraging these multidimensional datasets holds promise for developing precision diagnostics and targeted therapeutic and management strategies to mitigate the impact of BRD on cattle health and productivity. Continued interdisciplinary collaboration and technological innovation are essential for translating sequencing research findings into practical solutions for BRD prevention and control in cattle production systems.

VI. References

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