MicroRNAs in Animal Development and Disease: A Review of Current Status and Future Directions

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ABSTRACT

MicroRNAs are diminutive, non-coding Ribonucleic acids that are essential in modulating gene expression throughout animal development and pathology. This review seeks to deliver a thorough examination of the present state of miRNA research in animal development and disease, emphasising their role in essential biological processes including embryogenesis, cell differentiation, and tissue development. We examine the function of miRNAs in many animal diseases, encompassing cancer, metabolic disorders, and reproductive problems. Additionally, Our research focuses on microRNAs (miRNAs) and their therapeutic applications, as well as their potential as biomarkers for disease diagnosis and prognosis. We delineate prospective avenues for miRNA research in animal development and pathology, underscoring the necessity for additional exploration of the intricate processes governing miRNA regulation and its implications in veterinary medicine.

INTRODUCTION

Our understanding of how genes are regulated in animals has been fundamentally altered as a result of the discovery of a family of tiny, non-coding RNAs known as microRNAs. The significance of microRNAs in many biological processes

have been increasingly clear since their discovery in the early 1990s.These activities include embryogenesis, cell differentiation, tissue formation, and the pathogenesis of illness. There is evidence that microRNAs have a role in the control of a wide variety of physiological and developmental processes in animals. These functions include growth, reproduction, and immunological function for example. Furthermore, a number of diseases that affect animals, including as cancer, metabolic abnormalities, and reproductive problems, have been reported to be associated with deregulation of microRNAs. This study aims to provide a thorough overview of microRNA (miRNA) studies in disease and animal development by focussing on the functions of miRNAs, the rules that control them, and their possible applications in veterinary medicine.

Natural short RNAs (microRNAs) regulate gene expression following transcription. MicroRNAs typically have a size of 19–24 nucleotides. Their principal role is to attach to messenger RNA (mRNA) target sequences that are complementary to one another; this enables them to interact with the translational machinery and regulate or stop the development of the protein product. Researchers found that when miRNA bound to its target mRNA, it did more than just suppress translation; it also recruited and associated mRNA decay factors, which destabilised and degraded the target mRNA and caused its expression levels to drop. Lee and co-workers found miRNAs in 1993 (Lee *et al*., 1993) in the nematode Caenorhabditis elegans. This group of organisms have to drastically reduce their LIN-14 protein expression in order to progress from the L1 to the L2 larval stage. In addition, a second gene, lin-4, was discovered to be transcriptionally dependent on the down regulation of LIN-14. It is worth noting that the lin-4 transcribed sequence did not result in a protein with any biological activity. Instead, it produced two little RNAs, one measuring about 21 nucleotides and the other around 61 nucleotides. The longer sequence was the RNA's precursor; it created a stem-loop structure. It was later discovered by this group (Wightman *et al*., 1993, Lee at al., 1993) that the smaller RNA had antisense complementarity to many locations in the 3′ UTR of lin-14 mRNA. Protein expression was decreased due to binding between these complementary regions, even if LIN-14 mRNA levels remained unchanged. To summarise, the two investigations put up the theory that lin-14 mRNA was translationally repressed and that L1-L2 advancement in C. elegans development went like this: plenty of lin-4 short RNAs paired with complimentary sites in the 3′ UTR of lin-14 mRNA.

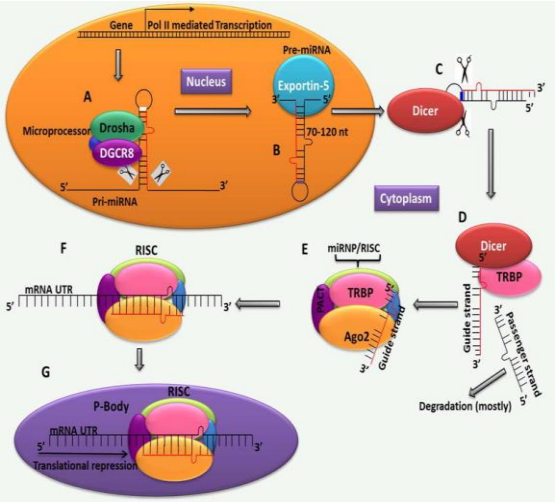

Fig. 1. Biogenesis of MicroRNAs

In mammals, microRNAs (miRNAs) regulate a number of important processes. In addition to being an important and potent mechanism in gene control, they represent a novel class of therapeutic targets. miRNAs play various physiological functions in animals and have an evolutionary conserved significance in development. Although miRNAs have poor complementarity with the mRNAs they target, they are able to influence numerous physiological processes in animals. Some have speculated that they cause mRNA degradation

by blocking the beginning of the translation process (Kato *et al*., 2008). When the first two C. elegans miRNAs, lin-4 (abnormal cell lineage-4) and let-7 (lethal-7), were altered to render them inactive, larvae displayed developmental abnormalities (Lee *et al*., 1993, Reinhart *et al*., 2000). Women have proposed that let-7 is essential for the latter stages of embryonic development and that lin-4 governs the early stages in C. elegans and possibly other creatures (Boehm *et al*., 2005, Lin *et al*., 2003). D. melanogaster has two microRNAs (miRNAs): bantam and lin-14. Studies show that overexpressing bantam enhances growth while suppressing apoptosis (Nolo *et al*., 2006). In the absence of miR-14, D. melanogaster IL1-beta convertase (DRICE) levels are elevated, suggesting that miR-14 regulates lipid metabolism and impedes cell death (Xu *et al*., 2003). In addition, a matched set of microRNAs is supplemented by conserved motifs in the 3′ UTR of two sets of Notch target genes (Stark *et al*., 2003, Lai *et al*., 2005). The GY-box motif is modulated by reduced miR-7 production, which in turn reduces the expression of downstream Notch targets, such as Cut, which leads to decreased expression of be down-regulated, which reduces vein spacing and thickening, and ultimately reduces vein thickness, causes veins to get thicker due to miR-7's regulation of the GY-box motif (Stark *et al*., 2003, Lai *et al*., 2005). Using a knockout gene method, researchers have studied the role of miRNAs in mammalian development in a number of different species. Zebrafish were engineered to lack Dicer. Additionally, mir-430 expression was seen in frogs during their early phases of development (Giraldez *et al*., 2005, Watanabe *et al*., 2005). New evidence suggests that microRNAs control late-stage mouse development, and miR-196's regulation of Hox genes provides support for this idea.mir-196 is a gene produced in the legs that suppresses the translation of certain histone modifications, including Hoxa B8, Hoxc8, Hoxd8, and Hoxa7 (Yekta *et al*., 2004; Hornstein *et al*., 2005). The degradation of muscle tissue and the early maturation of cardiomyocytes are brought about by the action of the muscle-specific microRNA miR-1, which binds to the protein HAND2 (Zhao *et al*., 2005). Some endogenous miRNAs are involved in antiviral defence systems, according to recent findings. To prevent human cells from being infected with retrovirus type 1 (PFV-1), miR-32 has inhibitory effects (Lecellier *et al*., 2005). Cancers, including B-cell lymphomas, can amplify the region of human chromosome 13q31 that contains the mir-17-92 clusters. Overexpression of mir-17-92 in B-cell lymphoma models in mice enhances carcinogenesis via c-Myc and suppresses cell death (He at al., 2005). Primitive human fibroblasts have the tumour suppressor genes LATS2, mir-372, and mir-373, and we were able to induce carcinogenesis by targeting these genes (Voorhoeve *et al*., 2006). In particular, germ cell tumours of the testicles express mir-372 and mir-373 (Voorhoeve *et al*., 2006). When it comes to managing livestock diseases, microRNAs (miRNAs) can be utilised as biomarkers that can be employed for diagnostic, prognostic, or therapeutic purposes.

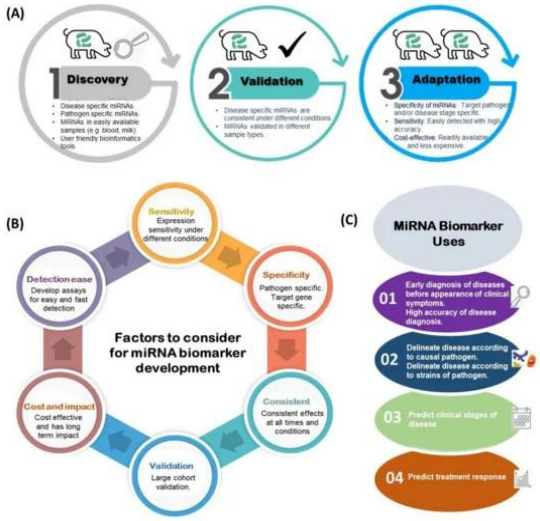

Fig. 2. miRNA regulatory functions in Farm Animals

The foregoing data suggests that miRNAs regulate many cellular functions in animals by acting on a wide variety of targets.

Potential Applications:

Up to this point, the importance of miRNAs in several biological processes connected to the onset of disease in domestic animals has been widely recognised. Thus, it is highly encouraging to use miRNAs to enhance disease resistance in livestock. Direct or indirect biomarker applications for miRNAs exist in the realm of technology. The presence of microRNAs in bodily fluids like milk, urine, saliva and blood allows for the quick identification of status of disease infection, much like circulating biomarkers. Through a roundabout way, miRNA can end up in other tech systems like genome editing and RNA interference. Mutations in the seed sequence of microRNAs or in their target genes' three primary untranslated regions can be precisely and persistently altered using genome editing with CRISPR/Cas9 technology (Aquino-Jarquin. 2017). Disease models in animals have demonstrated the efficacy of this technique when applied to miRNA-mediated therapy (Chang *et al*., 2016, Li *et al*., 2020, Li *et al*., 2018). Although inexpensive "OMICS"-based technologies have sped up miRNA identification, small sample sizes and lack of repeatability continue to be obstacles to validating miRNA functions. There has to be an all-encompassing plan to study and validate miRNA functions because livestock diseases are so complicated. It is important to take into account the various stages of cattle diseases when conducting miRNA functional investigations, as many of these diseases are chronic in nature. Diseases like mastitis, which can be caused by various infections, and disorders like JD, which can affect numerous tissues or organs, require a spatiotemporal-specific approach to understanding the regulatory role of miRNAs. Furthermore, because miRNAs can target hundreds of genes, functional validation of each miRNA gene target is challenging, expensive, and labour-intensive. Lastly, there has been little emphasis on in vivo experiments to validate miRNAs, which is a big roadblock to understanding their functions in cattle illnesses. The decreasing cost of sequencing, however, might encourage researchers to use larger samples in miRNA research. The current trend towards cheaper sequencing could make integrative investigations of miRNA functions in interaction networks more practical. This could allow for the simultaneous sequencing of numerous molecule types, including mRNAs, lncRNAs, and miRNAs. It is possible that important miRNAs will go unnoticed since reliable and sensitive methods for detecting miRNAs with low expression levels do not yet exist. The utilisation of additional technologies, such as single-cell sequencing, will further improve our comprehension of the functions of miRNAs and disease pathophysiology (Shafer, 2019). Conversely, genome editing (Urnov *et al*., 2010) and RNA interference technologies (Hannon, 2002) have the potential to facilitate the identification of miRNA target genes and their subsequent impacts on disease aetiology. The application of deep learning and machine learning techniques has the potential to enhance the classification of disease pathogens (Vilne *et al*., 2019) and the prediction of miRNA functions in infection development (Song *et al*., 2019).

CONCLUSION

Finally, microRNAs have shown great promise as key players in controlling gene expression throughout illness and development in animals. Recent research has shown that microRNAs (miRNAs) play an intricate role in controlling embryogenesis, cell differentiation, and tissue formation, among other biological processes. Furthermore, the dysregulation of

miRNAs has been associated with a variety of animal diseases, which serves as an additional indicator of their potential as diagnostic indicators and therapeutic targets. The regulatory mechanisms of microRNAs (miRNAs), their potential uses in veterinary medicine, and the creation of new treatments for animal diseases based on miRNAs should all be the focus of future research. New methods for bettering the health and welfare of animals will become possible as our knowledge of miRNAs in disease and development in animals grows.

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