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Popular Article

MicroRNAs: Biogenesis and Their Role as Potential Biomarkers

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Abstract

MicroRNAs (miRNAs) are small non-coding RNAs of 17-25 nucleotides, recognized as one of the major regulatory gene families in eukaryotic cells. MicroRNAs were discovered back in 1993 when a small RNA encoded by the lin-4 locus was associated with the developmental timing of the nematode *Caenorhabditis elegans* by modulating the protein lin-14. At that time, lin-4 was thought to be a worm-specific curiosity and the scientific world took several more years to actually realize that miRNAs are expressed in several organisms and are highly conserved across different species. With the discovery of high stability of circulating miRNAs in various kinds of mammalian body fluids, the potential of circulating miRNAs as diagnostic/prognostic biomarkers of infectious diseases aroused great interest among researchers. Recent studies have revealed that miRNAs play significant roles in diverse regulatory pathways, including control of developmental timing, haemopoietic cell differentiation, apoptosis, cell proliferation, organ development and the list goes on. The field of miRNAs derives the significance in its potential to revolutionize the scientific understanding and manipulation of various physiological and pathological states. As far as human disease is concerned, some biomarkers based on circulating miRNAs have been progressed to clinical application. However, in veterinary fields, this concept is only beginning to come into view. Here is summarized different aspects of miRNAs and their role in various aspects of livestock improvement.

Keywords: miRNA, non-coding RNAs, biomarkers, small RNA, circulating

Introduction

MicroRNAs (miRNAs) are small endogenous RNAs regulating gene-expression at post-transcriptional level and are derived from regions of RNA transcripts that fold back on themselves to form short hairpins. miRNAs can be isolated from cells, tissues, as well as body fluids including serum, plasma, urine, or tears. The majority of miRNAs are transcribed from DNA sequences into primary miRNAs in nucleus of the cell and further processed into precursor miRNAs in the cytoplasm, and finally to mature miRNAs. In most cases, miRNAs interact with the 3′ untranslated region (3′ UTR) of target mRNAs which can either induce mRNA degradation or translational repression. However, interaction of miRNAs with other regions, including the 5′ UTR, coding sequence, and gene promoters, have also been reported. Under certain conditions, miRNAs can also activate translation or regulate transcription. The interaction of miRNAs with their target genes is dynamic and depends on many factors, like subcellular location of miRNAs, the abundancy of miRNAs and target mRNAs, and the affinity of miRNA-mRNA interactions. miRNAs can be secreted into extracellular fluids and transported to target cells via vesicles, such as exosomes, or by binding to proteins, including Argonautes. Extracellular miRNAs function as chemical messengers to mediate cell-cell communication. miRNAs function via base-pairing with complementary sequence within mRNA molecules. The mechanism depends on degree of complementarity between the miRNA and the target mRNA and the mRNAs are silenced by either cleavage or destabilization mechanism. miRNAs are critical for normal animal development and are involved in a variety of biological processes. Their major role is in the post-transcriptional regulation of protein expression, and their involvement was demonstrated in normal and in pathological cellular processes. In tumors, some miRNAs function as oncogenes, others as tumor suppressors; upregulation of oncogenic miRNAs (oncomiRs) has been demonstrated in cancer cells.

miRNA nomenclature

Three-letter prefix denotes species of origin (eg., hsa = Homo sapiens; bta = Bos taurus). Mir denotes pre-miRNA while miR denoted the mature form. The number simply indicates the order of discovery/naming. The nearly identical in sequence (variation of 1-2 nucleotides) they are labelled

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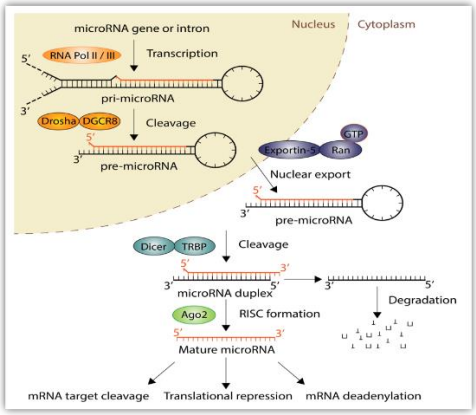
as miR-123a and miR123b (c, d, e…). The numbering after this (1/2/3…) is associated with pre-miRNAa (mir) and denotes that while they produce an identical mature miRNA (e.g., hsa-mir-194), hsa-mir-194-1 and hsa-mir-194-2 are located in different regions of the genome. The denotion as 3/5p is given when two mature microRNAs (miR) originate from opposite arms of the same pre-miRNA.

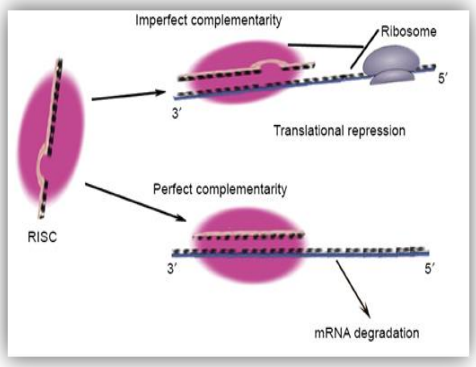
hsa-miR-123a/b-1(3/5p)

Biogenesis Of MicroRNA

Canonical Pathway

miRNAs are produced by sequential cleavage of precursor RNA transcripts by the Ribonuclease III enzymes, Drosha and Dicer. Then miRNAs are loaded to the effector protein, Argonaute, forming miRNA-induced silencing complex (miRISC). miRISC binds mRNA targets via sequence complementarity and silences the targets by translational repression and/or mRNA destabilization.





Non-Canonical Pathway

Processing of pri-miRNA into pre-miRNA does not require all the protein factors as in canonical pathway. Mirtrons, Agotrons and siRNAs are few examples of miRNAa which are processed by non-canonical pathway.

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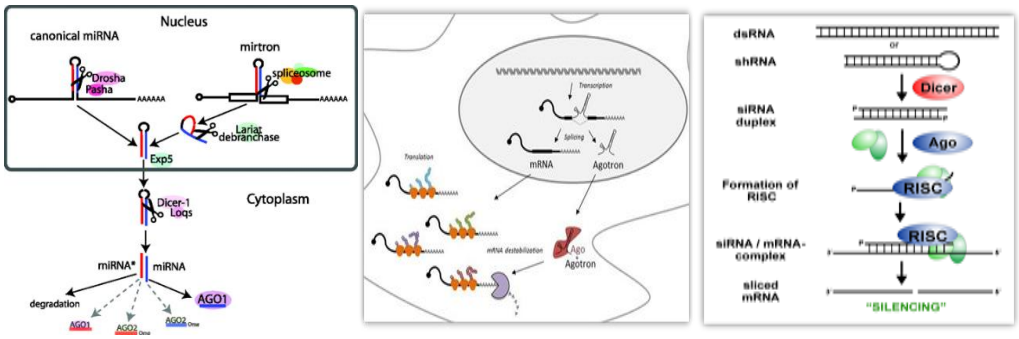

Role of miRNAs

1) **<u>As potential circulatory biomarkers</u>**

- Diagnosis, staging, prognosis and monitoring responses to therapy. Correlation between expression profiles of **circulating miRNAs** and various bacteriosis (Paratuberculosis), viral diseases (FMD, BVD) and parasitosis (Echinococcosis)
- **Present extracellularly in various body fluids** (serum, plasma, urine, saliva etc.) and can be readily detected
- **Highly stable and resistant to RNAase** activity and extreme pH and temperature
- **Protected from degradation** by being packaged in lipid vesicles (microvesicles and exosomes), in complexes with RNA binding protein or both
- miRNAs are **released from the tumour tissue** in the plasma

2) **<u>Therapeutic intervention</u>**

- Blocking of miRNAs which are up-regulating virus replication by classic or modified anti-miRNAs (antagomiRs : cholesterol-conjugated anti-miRNAs)
- Over-expression of miRNAs which inhibit virus replication.

3) **<u>miRNAs in development and organogenesis</u>**

- **Embryonic stem cell differentiation** (miR-290 cluster) aka ESCC family of miRNAs
- Proliferation and differentiation of **hematopoietic stem cells** (miR-125b)
- Orchestrate the **coordinated development of various organ systems** (eg. miR-273 for establishing left-right asymmetry during neuronal development)

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Challenges

- Presence of miRNA isomers (isomiRs) – might reduce their value as biomarkers.
- The addition or trimming of nucleotides (mostly uridines) to the 3′-end of pre-miRNAs and mature miRNAs produces isomiRs and can affect pre-miRNA processing and miRNA function, respectively.
- Using serum as a biological sample for miRNA biomarker studies might be biased.
- Difficulties in miRNA extraction can compromise yield and quality.
- Delivery and specificity for targeted cells.
- Dose of the introduced miRNA for therapeutic purpose should be well controlled.
- Developing a universal RNAi molecule against the same sequence in multiple influenza.

Future Perspectives

- To exploit the conserved nature of miRNAs for therapeutic use
- To develop more rapidly acting RNAi technology
- To formulate a suitable vehicle, to deliver the smallest RNAi quantity in a non-toxic way
- To discover & validate signature miRNA panels in complex malignancies

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