CHAPTER 27

MICRORNAS TREATMENT IN MELANOMA

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MicroRNAs (miRNAs) are evolutionary conserved, types ofsingle-stranded RNAs and approximately 21-23 nucleotidesin length. They are noncoding RNAs molecules that regulate gene expression by binding with target mRNA's 3'-untranslated region (3'UTR), causes destabilization and degradation of target mRNA.[1,2] miRNA biogenesis is multistep process. First, miRNA genes are transcribed in the nucleus by RNA polymerase II and then primary transcript (pri-miRNA) is cleaved by Drosha, an intranuclear RNase III endonuclease, and its co-factor, DiGeorge syndrome critical region gene 8 (DGCR8 or Pasha (Partner of Drosha)) to produce precursor-miRNAs (pre-miRNAs) that share a characteristic stem loop structure.[3] These pre-miRNAs are transported to the cytoplasm by exportin-5, cut by Dicer (extranuclear RNase III enzym) into mature miRNA strands, that are loaded into the RNA-induced silencing complex (RISC). Depending on the degree of complementarity between the target mRNA and the miRNA, target mRNA either be translationally repressed (in the case of weak mRNA/miRNA complementarity) or be cleaved (in the case of strong mRNA/miRNA complementarity) causing posttranscriptional gene silencing (figure 1).[4,5]

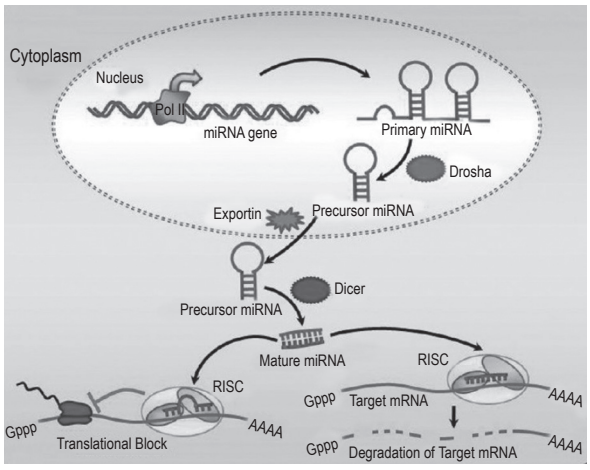


Figure 1. MicroRNA biogenesis and RNA-induced gene silencing.[5]

Transcription of primary micro RNA (Pri-miRNA) from miRNA genes is followed by cleavage to precursor mRNA (Pre-miRNA) by the Drosha nuclear RNase III. The Pre-miRNA is then exported to the cytoplasm by exportin via nuclear pore. In the cytoplasm, Pre-miRNA is further processed by RNase activity of Dicer to the mature micro RNA duplex. The duplex loads onto Argonaut ribonucleases in the RISC complex and separates. One of the mature miRNA strands (red strand) mediates small interfering RNA silencing by degrading the target mRNA or interfering with translation. The outcome of RISC formation varies with the degree of complementarity of the seed sequence of miRNA and 3' untranslated regions (UTR) of the target mRNA.

MICRORNAS AND THERAPEUTICS

With increasing interest and research investigations, it is now becoming evident that miRNA expression and function in several human diseases, including cancer not least in melanoma and play important roles in the disease processes such as psoriasis and atopic eczema (figure 2).[6,7] In this review we aim to summarize the current knowledge about miRNAs related to melanoma.

In the human skin, melanocytes are the ability to melanin production and the origin from neural crest cells. Melanocyte differentiation occurs via a series of steps, ultimately resulting in lineage specification of melanoblasts and transportation of mature melanosomes to keratinocytes. Melanocytes molecularly are recognizable by identification of melanocyte-specific proteins as tyrosinase (TYR), tyrosinase-related protein 1 and 2 (TYRP1, TYRP2/DCT), melanosomal matrix proteins (Pmel17, MART-1), microphthalmia transcription factor (MITF).[8,9] In addition to the many protein-coding genes that regulate cancer development, many non-coding genes have also been shown to play important roles in cancer prognosis, diagnosis, and therapy.

The fact that miRNAs are implicitly involved in many pathological states and that they mediate potent and specific gene silencing makes them attractive therapeutic targets. Therefore, modulating miRNA functions may provide novel therapeutic opportunities for cancer treatment.[10]

In conclusion, miRNAs and their role in disease processes is a rapidly evolving field, as evidenced by literature. Recent studies suggest that silencing or restoration of miRNA function can serve as a promising therapeutic strategy for cancer treatment. miRNA's complex involvement in the pathogenesis of many skin diseases, including melanoma, makes them ideal candidates for novel therapeutic strategies. Furthermore, as miRNAs are also associated with chemo- and radio-sensitization of cancer cells, a combination approach can also be developed for improved therapeutic outcome.

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