

Role of microRNA in anticancer drug resistance

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Chemotherapy has been widely used in treatment of cancer, both as systemic therapy and as part of local treatment. Unfortunately, many kinds of cancer are still refractory to chemotherapy. The anticancer drug resistance mechanisms have been extensively explored, yet have not been fully characterized. Recent works have underlined the involvement of noncoding RNAs in cancer development, with several studies regarding their possible involvement in the evolution of drug resistance. MicroRNAs (miRNAs) are endogenous small noncoding RNAs (20–23 nucleotides) that negatively regulate the gene expressions at the post-transcriptional level by base pairing to the 3' untranslated region of target messenger RNAs. Evidence is emerging that particular microRNAs (miRNA) alterations are involved in the initiation and progression of human cancer. More recently, accumulating evidence is revealing an important role of miRNAs in anticancer drug resistance and miRNA expression profiling can be correlated with the development of anticancer drug resistance. The micro-RNA-mediated form of drug resistance adds yet another mechanism of drug resistance. So, exploiting the emerging knowledge of miRNAs for the development of new human therapeutic applications for overcoming anticancer drug resistance will be important.

Cancer is one of the leading causes of death globally. One of the major cancer treatment methods is chemotherapy. Resistance of cancer cells to chemotherapy continues to be a major clinical obstacle to the successful treatment of cancer.¹ At present, the anticancer drug resistance is considered as a multifactorial phenomenon involving several major mechanisms,² such as decreased uptake of water-soluble drugs, increased repair of DNA damage, reduced apoptosis, altered metabolism of drugs and increased energy-dependent efflux of chemotherapeutic drugs that diminish the ability of cytotoxic agents to kill cancer cell, changes in glutathione transferase expression and topoisomerase II.^{2–4} Causes of cancer-specific drug resistance are currently believed to be linked to the random drug-induced mutational events (genetic hypothesis), to the drug-induced nonmutational alterations of gene function (epigenetic hypothesis), and, recently, to the drug-induced karyotypic changes.^{2,5–8} Unfortunately, the key determinants of this phenomenon remain largely unknown.

Currently, extensive studies have indicated the existence and importance of another mechanism of nonmutational regulation of gene function mediated by means of short noncoding RNA.^{9–11} As the name implies, miRNAs are small RNAs usually 19–23 bp in length or shorter, which are produced in all mammalian cells.^{12,13} Lacking the ability to encode a protein,

these single-stranded miRNAs bind mainly to the 3' UTR of protein encoding mRNAs through sequences that are imperfectly complementary. The consequences of miRNA binding are that either the bound mRNA is silenced or degraded, resulting in reduced levels of the protein encoded by the mRNA.^{10,14} Aberrant levels of microRNA (miRNA) have been reported in a variety of human cancers.^{13,15} They have been shown to have both diagnostic and prognostic significance and to constitute a novel target for cancer treatment.^{16,17} Recently, the evidence of the roles for microRNAs in determining drug sensitivity/resistance has been emerging. This review briefly introduces microRNAs in a historical perspective and focuses on the biogenesis of microRNAs, their mode of action, mammalian microRNA functions with emphasis on their involvement in cancer—particularly anticancer drug resistance.

MicroRNA Biogenesis and Mode of Action

MicroRNAs are initially transcribed by RNA polymerase II as long primary transcripts (pri-microRNAs) that are processed in a series of endonuclease reactions into the mature miRNA species (Fig. 1).¹⁸ MicroRNAs are loaded into the RNA-induced silencing complex (RISC) and guide the degradation or translational repression of mRNA targets.¹⁹ In animals, microRNAs usually base-pair to target mRNAs with imperfect complementarity, leading predominantly to translational repression, although this may also induce some degree of mRNA destabilization.^{20,21} Prediction of animal miRNA targets generally relies upon identification of sequences in mRNA 3' untranslated regions (3'UTRs) that can base-pair with nucleotides 2–7 or 2–8 of the miRNA.²²

Role of MicroRNAs in Cancer

The microRNA field is rapidly growing; however, the biological functions of some miRNAs have just begun to be

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