Sadegh Babashah *Editor*

MicroRNAs: Key Regulators of Oncogenesis

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This book is honorably dedicated to Prof. Majid Sadeghizadeh, head of Department of Molecular Genetics, Faculty of Biological Sciences, Tarbiat Modares University. Prof. Sadeghizadeh founded the PhD program for molecular genetics at Tarbiat Modares University and is known to be one of the pioneers in the field of molecular biology in Iran.

Preface

The past decade witnessed significant efforts and progresses in the area of microRNA (miRNA) research in the field of cancer. Indeed, recent miRNA studies have been a major leap in the understanding of the molecular pathogenesis of cancer. It is crystal clear that miRNAs as either onco- or tumor suppressor genes can alter biological processes fundamental to tumor initiation and progression. The connections between miRNAs and oncogenesis are widespread enough to hold miRNAs as potential therapeutic targets and novel biomarkers. In this regard, identifying the expression signatures of miRNAs provides exciting opportunities for the diagnosis, prognosis, and therapy of cancer.

This edited book *MicroRNAs: Key Regulators of Oncogenesis* aims to offer a broad framework to understand the state-of-the-art knowledge of miRNA function and illustrate features of specific miRNAs in the regulation of cancer. It has been written for graduate students, postdoctoral fellows, and scientists in cancer research, and it is also well suited for clinical oncologists and other researchers interested in this field. The contents of this book was scrupulously designed and explicitly written. Ranging from the fundamental concepts to clinical applications, this book is composed of seventeen chapters organized in two parts. The first part is devoted to delving deep into the importance of miRNAs in cancer biology. In Chap. 1, I describe the dual function of miRNAs as either oncogenes or tumor suppressors in cancer and elucidate the link between aberrant miRNA expression and cancer development and progression. Since cancer is associated with accumulation of epigenetic and genetic alterations, Chap. 2 focuses on the relationship between epigenetics and miRNA. In line with this, Chap. 3 deals exclusively with the effects of dietary agents on miRNAs and their targets in the context of cancer biology. Chapter 4 elaborates on the interplay between miRNAs and oncogenes/tumor suppressors in tumor metabolism introducing another layer of complexity to the regulatory network of metabolic pathways in cancer cells. In Chaps. 5 and 6, authors clearly describe the crucial roles of miRNAs in different types of solid tumors and hematological malignancies and also discuss the feasibility of using miRNAs as potential biomarkers. The importance of miRNAs in the pathogenesis of oncogenic viruses and the link

between miRNAs and liver inflammation during hepatocarcinogenesis is represented in Chaps. 7 and 8, respectively. Chapter 9 deciphers the mechanisms through which miRNAs modulate the activity of regulatory pathways in tumorigenesis, in particular miRNAs targeting potential pathways for therapeutic intervention. Chapter 10 reveals the regulatory mechanisms of miRNAs in apoptotic and autophagic networks, with the merit of finding application as potential drug targets for future cancer therapy. Chapter 11 describes the part played by miRNAs in drug resistance and drug sensitivity. In Chap. 12, the potential role of cancer stem cell-related miRNAs during tumor development and progression is clarified. The second part of the book highlights the clinical implications of miRNAs in cancer. In this part, Chap. 13 introduces miRNAs as potential biomarkers for diagnosis, prognosis and therapeutic intervention of cancer and the capacity of integrating miRNA data into clinical trials is discussed. Chapter 14 offers a precise description to the function of miRNAs in breast cancer and discusses their possible translation into molecular diagnostics. Chapter 15 particularizes the impact of miRNAs on drug resistance from a clinical point of view, thereby highlighting their capability to be exploited as predictors or modifiers of resistance towards chemo- and radio-therapeutics. In Chap. 16, authors meticulously address a variety of nanocarriers exploited for miRNA delivery in crafting therapeutic platforms for cancer and provide an in-depth analysis of different attributes of these nanovehicles. Finally, Chap. 17 outlines the advantages of a pulmonary drug delivery system and the strategies for miRNA-based treatment of lung cancer.

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Abbreviations

A

α-SMA	Smooth muscle alpha-actin
AA	Arachidonic acid
AAT	Androgen ablation therapy
AAV	Adeno-associated virus
ABCA1	ATP-binding cassette transporter sub-family A member 1
ABCB1	ATP-binding cassette, sub-family B (MDR/TAP), member 1
ABCC	Multidrug resistance-associated protein
ABCG2	ATP-binding cassette sub-family G member 2
AD	Adenocarcinoma
ADAM17	A Disintegrin and Metalloprotease-17
AdenoCA	Adenocarcinoma
ADM	Adriamycin
ADMA	Asymmetric ω-N^G, N^G-dimethylarginine
AFP	Alpha-fetoprotein
Ago	Argonaute
AI	Androgen independence
AID	Activation-induced cytidine deaminase
ALCL	Anaplastic large cell lymphoma
ALD	Alcoholic liver disease
ALDH1A3	Aldehyde dehydrogenase 1 family, member A3
ALK	Activin receptor-like kinase
ALL	Acute lymphoblastic leukemia
Ambra1	activating molecule in Beclin-1-regulated autophagy protein 1
AML	Acute myeloid leukemia
AMPK	AMP-activated protein kinase
AnD	Androgen-dependent
AnI	Androgen-independent
ANP32A	Acidic nuclear phosphoprotein 32 family member A
AP-1	Activator protein-1

Apaf-1	Apoptotic peptidase activating factor 1
APC	Adenomatous Polyposis Coli
APL	Acute promyelocytic leukemia
APO	Apolipoprotein
AR	Androgen receptor
ARHs	ADP-ribosylhydrolases
ARTs	ADP-ribosyltransferases
ASO	Antisense oligonucleotide
Atg	Autophagy-related gene
ATM	Ataxia telangiectasia mutated
ATO	Arsenic trioxide
ATRA	All-trans-retinoic acid
5-aza-dC	5-aza-2′-deoxycytidine

B

B-CLL	B-cell chronic lymphocytic leukemia
BAc	Barrett's adenocarcinoma
BAK1	Bcl-2 homologous antagonist/killer
BBC3	BCL2 binding component 3
BC	Breast cancer
BCL-2	B-cell leukemia/lymphoma-2BE, Barrett's esophagus
BCL6	B-cell lymphoma 6
BCLAF1	Bcl-2-associated transcription factor 1
BDNF	Brain-derived neurotrophic factor
Bif-1	BAX-interacting factor-1
BIM	BCL2-like 11
BL	Burkitt lymphoma
BM	Barrett's mucosa
BMF	Bcl-2-modifying factor
BMP7	Bone morphogenetic protein 7
BNIP2	BCL2/adenovirus E1B 19 kDa protein-interacting protein 2
BR-DIM	BioResponse 3,3′-diindolylmethane
BT-ICs	Breast tumor-initiating cells

C

c-FLIP	Cellular FLICE-like inhibitory protein
CAB39	Calcium binding protein 39
CAFs	Cancer associated fibroblasts
cALCL	Cutaneous anaplastic large cell lymphoma
CBP	CREB-binding protein
cccDNA	Covalently closed circular DNA
CCND1	Cyclin D1
CCNG1	Cyclin G1
CCNJ	Cyclin J

CDC25A	Cell division cycle 25 homolog A
CDC42	Cell division cycle 42
CDF	Diflourinated-curcumin
CDK6	Cyclin-dependent protein kinase 6
CDKN1A	Cyclin-Dependent Kinase Inhibitor 1A
CDKN1B	Cyclin-Dependent Kinase Inhibitor 1B ($p27^{Kip1}$)
CDS2	CDP-diacylglycerol synthase (phosphatidate cytidylyltransferase) 2
CDX2	Caudal-related homeobox 2
CEBPA	CCAAT/enhancer binding protein alpha
CFUs	Colony forming units
CGI	CpG islands
CHC	Chronic hepatitis c
ChIP	Chromatin immunoprecipitation
CIN	Cervical intraepithelial neoplasia
CLL	chronic lymphocytic leukemia
CML	Chronic myeloid leukemia
CMPs	Common myeloid progenitors
CNS	Central Nervous System
COL2A1	Collagen, type II, alpha 1
COPD	Chronic obstructive pulmonary disease
COPZ2	Coatomer protein complex, subunit zeta 2
COX-2	cyclooxygenase-2
CPT -1	Carnitine palmitoyl transferase-1
CPT1A	Carnitine palmitoyltransferase 1A
CRC	Colorectal cancer
CROT	Carnitine O-octanoyltransferase
CSCs	Cancer stem cells
CSF-1	Colony stimulating factor-1
CSLCs	Cancer stem-like cells
CSS	Cancer-specific survival
CTGF	Connective tissue growth factor
CTX	Cyclophosphamide

D

DEX	Dexamethasone
DFRS	Distant relapse-free survival
DHA	Docosahexaenoic acid
DHFR	Dihydrofolate reductase
DIM	Dimeric product, 3,3′-diindolylmethane
DKC1	Dyskeratosis congenita gene 1
DLBCL	Diffuse Large B-cell Lymphoma
DNMT	DNA methyltransferase
DNMT3L	DNA methylatransferase 3-like
DNR	Daunorubicin

DOT1L	DOT1-like protein
DOX	Doxorubicin
DPIs	Dry powder inhalers
DR4	Death receptor-4
DTX	Docetaxel
DUBs	Deubiquitinating enzymes
DUSP5	Dual-specificity phosphatase 5

E

E2F	E2 transcription factor family
EAC	Esophageal adenocarcinoma
EAG1	Ether-à-go-go 1
EBV	Epstein-Barr virus
EC	Esophageal cancer
ECM	Extracellular matrix
eEF1A2	Eukaryotic translation elongation factor 1A2
EGCG	Epigallocatechingallate
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EMT	Epithelial to mesenchymal transition
EOC	Epithelial ovarian cancer
EPA	Eicosapentaenoic acid
EPR	Enhanced permeability and retention
ER	Estrogen receptor
ERK5	Extracellular signal regulated kinase 5
ERRFI-1	ErbB receptor inhibitor-1
ESCC	Esophageal squamous cell carcinoma
EVI1	Ecotropic Virus Integration 1
EVL	Ena/Vasp-like
EZH2	Enhancer of zeste homolog 2

F

FAD	Flavin adenine dinucleotides
FAK	Focal Adhesion Kinase
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin embedded
FGFR1	Fibroblast growth factor receptor 1
FIP200	family interacting protein of 200 kDa
FL	Follicular Lymphoma
FNDC3B	Fibronectin type III domain containing 3B
FOXC2	Forkhead box C2
FOXF2	Forkhead Box F2
FOXO3A	Forkhead box O3
FOXO4	Forkhead box O4

FOXP1	Forkhead Box P1
Fra-1	Fos-related antigen 1
FSCN1	Fascin Homolog 1
5-FU	5-fluorouracil
Fzd3	Frizzled3

G

GAX	Growth arrest homeobox
GBM	Glioblastoma multiforme
GCN5	General control non-derepressible 5
GEMIN4	Component of gems 4
GLS1	Glutaminase 1
GLUT	Glucose transporter
GNAT	General N-acetyl-transferase
GSTP1	Glutathione S-transferase P1

H

HADHB	Hydroxyacyl-CoA dehydrogenase-3-ketoacyl-CoA thiolase-enoyl-CoA hydratase (trifunctional protein) β-subunit
HATs	Histone acetyl-transferases
HB-EGF	Heparin-binding EGF-like growth factor
HBP1	HMG box-containing protein 1
HBV	Hepatitis B virus
HBx	HBV X protein
HCC	Hepatocellular carcinoma
HCPT	Hydroxycamptothecin
HCV	Hepatitis C virus
HDACs	Histone deacetylases
HDL	High density lipoprotein
HDMs	Histone de-methylases
HER2	Human epidermal growth factor receptor 2
hESCs	Human embryonic stem cells
HGAL	Human Germinal-center Associated Lymphoma
HGS	Hepatocyte growth factor-regulated tyrosine kinase substrate
HIF-1α	Hypoxia-induced factor-1α
HIPK2	Homeodomain-interacting protein kinase-2
HK2	Hexokiase 2
HKMTs	Histone lysine methyltransferases
HLA	Human leukocyte antigen
HMEC	Human mammary epithelial cells
HMGA2	High mobility group AT-hook 2
hMSH2	Human mutS homolog 2
hMSH6	Human mutS homolog 6
HMTs	Histone methyl-transferases

HNSCC Head and neck squamous cell carcinoma
HOXD10 Homeobox D10
HPV Human papillomavirus
HSCs Hematopoietic stem cells
HSCs Hepatic stellate cells
HSPG2 Heparin Sulfate Proteoglycan 2
HSV Herpes simplex virus

I

I3C Indole-3-carbinol
IFITM1 Interferon-induced trans-membrane 1
IFN-α Interferon-α
IGF1R Insulin like growth factor 1 receptor
IL-1β Interleukin-1β
Ilk Integrin-linked kinase
IMP-1 Insulin-like growth factor 2 mRNA binding protein 1
IRAK1 Interleukin-1 receptor associated kinase 1
IRF Interferon regulatory factor
ITGA5 Integrin α5

J

JHDM1 JmjC domain-containing histone demethylase 1
JMJD1A Jumonji domain containing 1A

K

KEAP1 Kelch-like ECH-associated protein 1
KO Knockout
KRAS Kirsten rat sarcoma viral oncogene homolog
KS Kaposi's sarcoma
KSHV Kaposi's sarcoma-associated herpesvirus

L

L-OHP Oxaliplatin
LA Linoleic acid
LATS2 Large tumor suppressor 2
LC Lung cancer
LCC Large cell carcinoma
LE Lovastatin plus ezetimibe
Lef-1 Lymphocyte enhancer transcription factor-1
LIN28A *Lin-28* Homologue A
LKO Liver-specific knockout
LMO2 LIM-only protein 2
LNA Locked nucleic acid

lncRNA	long non-coding RNA
LPS	Lipopolysaccharide
LRRFIP1	Leucine rich repeat (in FLII) interacting protein 1
LSD1	Lysine-specific histone demethylase 1

M

M-RI P	Myosin phosphatase-Rho interacting protein
mAbs	Monoclonal antibodies
MAGE-A	Melanoma Antigen Family A
MALT	Mucosa-associated lymphoid tissue
MAPK	Mitogen-activated protein kinase
MAPT	Microtubule-associated protein tau
MARCKS	Myristoylated alanine-rich protein kinase c substrate
MAZ	Myc-associated zinc finger protein
MB	Medulloblastoma
MBDs	Methyl-CpG binding domains
MCL1	Myeloid cell leukemia 1
MCM	Minichromosome maintenance
mCRC	Metastatic colorectal cancer
MDIs	Metered-dose inhalers
MDS	Myelodysplastic syndrome
MDV	Marek's disease virus
MEF2C	Myocyte enhancer factor 2C
MET	Mesenchymal to epithelial cell transition
MIF	Macrophage inhibitory factor
MiR-SNPs	MicroRNA polymorphisms
MiRNA	MicroRNA
MLL	Mixed lineage leukemia
MM	Malignant melanoma
MM	Multiple myeloma
MMA	ω-N^G-monomethylarginine
MMC	Mitomycin C
MMP	Matrix metalloproteinase
2′-MOE	2′-O-methoxyethyl
MRI	Magnetic resonance imaging
MRP1	Multidrug resistance-associated protein 1
MSK1	Mitogen- and stress-activated protein kinase 1
MTDH	Metadherin
MTPN	Myotrophin
MTX	Methotrexate
MX	Mitoxantrone
MYB	Myeloblastosis
MYBL2	v-Myb myeloblastosis viral oncogene homolog-like2

N

NAD	Nicotinamide adenine dinucleotides
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
nc RNA	Non-coding RNA
NESTs	Normal esophageal squamous tissues
NF-κB	Nuclear factor-kappa B
NFIA	Nuclear factor I-A
NGS	Next-generation sequencing
NiS	Nickel sulfide
NLK	Nemo-like kinase
NK	Natural killer
NMZL	Nodal marginal zone lymphoma
NNMT	Nicotinamide N-methyltransferase
NPC	Nasopharyngeal carcinoma
NPC	Neural precursor cells
NR	Non-responder
NRAS	Neuroblastoma RAS viral oncogene homolog
NSCLC	Non-small cell lung cancer
NT	Non tumorous tissue
NZB strain	New Zealand Black strain

O

OC	Ovarian cancer
OCT4	Octamer-binding transcription factor 4
OncomiRs	Oncogenic microRNAs
OPN	Osteopontin
ORP	Oxysterol-binding-protein-related protein
ORR	Object response rate
OS	Overall survival
OSCC	Oral squamous cell carcinoma

P

p-Akt	Phosphorylated Akt
p53AIP1	p53-regulated apoptosis-inducing protein 1
PAA	Poly(amidoamine)
PAE	Poly (amino-co-ester)
PARGs	Poly-ADP-ribose-glycohydrolases
PARP	Poly ADP-ribose polymerase
4-PBA	4-phenylbutyric acid
PBMCs	Peripheral blood mononuclear cells
PC	Pancreatic cancer
PCa	Prostate cancer

PCR	Polymerase chain reaction
PDCD4	Programmed cell death protein 4
PDGFR	Platelet-derived growth factor receptor
PDK1	3-phosphoinositide-dependent protein kinase-1
PDMAEMA	Poly (2-N,N-dimethylaminoethylmethacrylate)
PDPK1	3′-phosphoinositidedependent protein kinase-1
PEG	Polyethylene glycol
PEI	Polyethyleneimine
PEITC	Phenethylisothiocyanate
PEL	Primary effusion lymphoma
PFS	Progression-free survival
PGI	Phosphogulcose isomerase
PgRNA	Pregenomic RNA
PHLPP	PH domain leucine-rich repeat protein phosphatase 2
PI3K	Phosphatidylinositol 3-kinase
PIK3R1	Phosphatidylinositol 3-kinase regulatory subunit alpha
PIK3R2	Phosphatidylinositol 3-kinase regulatory subunit Beta
piRNAs	PIWI-interacting RNAs
PKB	Protein kinase B
PKCε	P kinase C epsilon
PLA	Poly lactic acid
PLGA	Poly lactic-co-glycolic acid
PLK1	Serine/threonine-protein kinase
PLL	Poly-L-lysine
PLX4720	Specific inhibitor of B-RAF^{V600E}
PML	Promyelocytic leukemia
PP2A	Protein phosphatase 2
PPAR	Peroxisome proliferator-activated receptor
PPP2R1B	Protein Phosphatase 2, Regulatory Subunit A, Beta isoform
PPP2R2A	Protein Phosphatase 2, Regulatory Subunit B, Alpha isoform
PPP2R2A	PP2A regulatory subunit B α isoform
PR	Progesterone receptor
PRC	Polycomb Repressive Complex
PRDM1	PR domain zinc finger protein 1
PRKAA1	AMP-activated protein kinase catalytic subunit alpha-1
PRMTs	Protein arginine methyltransferases
Pre-miRNA	Precursor microRNA
Pri-miRNA	Primary microRNA
PSA	Prostate-specific antigen
PTEN	Phosphatase and tensin homolog
PTLD	Post-transplantation lymphoproliferative disorder
PTPN12	protein tyrosine phosphatase, non-receptor type 12
PTPN22	Protein tyrosine phosphatase, non-receptor type 22
PTX	Paclitaxel
PU-PEI	Polyurethane-short branch Polyethyleneimine
PUFAs	Polyunsaturated fatty acids

Q

Q-RT-PCR	Quantitative reverse transcriptase polymerase chain reaction

R

RA	Retinoic acid
RAB5A	Ras-related protein Rab-5A
RAP1A	Ras-related protein Rap-1A
RAR-α	Retinoic acid receptor-α
RASSF1A	Ras association domain family member 1A
Rb	Retinoblastoma
RBL2	Retinoblastoma-Like 2
RCC	Renal clear cell carcinoma
RdRp	RNA-dependent RNA polymerase
RDX	Radixin
RES	Reticuloendothelial system
RhoB	Ras homolog gene family member B
RIP-ChIP	Ribonucleoprotein chromatin immunoprecipitation
RISC	RNA-induced silencing complex
RKIP	the Raf kinase inhibitor protein
RNAi	RNA interference
ROS	Reactive oxygen species
RREB1	Ras-responsive element-binding protein
RRM2	Ribonucleotide reductase M2
RSSs	RNA-silencing suppressors
RSV	Respiratory syncytial virus
RTKN2	Rabbit polyclonal anti–Rhotekin 2
RVG	Rabies virus glycoprotein

S

S-TRAIL	Tumor necrosis factor related apoptosis inducing ligand
SAHA	Suberoylanilide hydroxamic acid
SAM	S-adenosylmethionine
SCC	Squamous cell carcinoma
SCLC	Small cell lung cancer
SDMA	Symmetric ω-N^{G}, N'^{G}-dimethylarginine
SECs	Sinusoidal endothelial cells
SFPQ	Splicing factor proline and glutamate-rich
SHIP	the SH2-domain-containing inositol 5-phosphatase
Shp	Small heterodimer partner
SIN	Self-inactivating
Sir2	Silent information regulator 2
siRNAs	Small interfering RNAs
SIRT1	Sirtuin 1

SIRT1	Silent mating type information regulation 2 homolog 1
SLC4A4	Na/bicarbonate cotransporter 1
SLN	Solid lipid nanoparticle
SMARCA4	SWI/SNF-related, matrix-associated, actin-dependent regulator chromatin, subfamily A, member 4
SMARCC1	SWI/SNF Related Matrix Associated actin dependent regulator of chromatin subfamily C member 1
snoRNAs	small nucleolar RNAs
SNP	Single nucleotide polymorphism
SOCS3	Suppressor of cytokine signaling 3
SOCS5	Suppressor of cytokine signaling 5
SOX4	SRY-related high-mobility group box 4
SPRED1	Sprouty-related protein 1
SPRY2	Sprouty 2
SRC	Sarcoma viral oncogene homolog
SREBP	Sterol regulatory element binding transcription factor
SRSF2	Serine/arginine-rich splicing factor 2
STARD13	StAR-related lipid transfer domain containing 13
STAT	Signal Transducer and activator of transcription
STMN1	Stathmin 1/oncoprotein 18
STS	Staurosporine
SuFu	suppressor of fused
SVR	Sustained virological response
SzS	Sézary syndrome

T

TAM	Tamoxifen
TCA	Tricarboxylic acid
TCF	T-cell factor
TCL1	T-cell leukemia 1
TCRα	T cell receptor alpha
TDX	Tomudex
TG	Triglyceride
TGF	Transforming growth factor
TGIF2	Transforming growth factor β-induced factor homeobox 2
THBS1	Thrombospondin1
TICs	Tumor initiating cells
TIMP3	Tissue inhibitor of metalloproteinase 3
TKIs	Tyrosine kinase inhibitors
TMZ	Temozolomide
TNC	Tenascin C
TNFα	Tumor necrosis factor α
TNFAIP3	Tumor necrosis factor-alpha-induced protein 3
TOP2B	DNA topoisomerase 2-beta

TP53INP1	Tumor protein p53 inducible nuclear protein 1
TPM1	Tropomyosin 1
TRAF6	tumor necrosis factor receptor associated factor 6
TRAIL	Tumor necrosis factor-related apoptosis-inducing ligand
TSA	Trichostain A
TSP-1	Thrombospondin-1
TWF1	Actin-binding protein twinfilin 1
TYMS	Thymidylate synthase

U

UCC	Urothelial carcinoma of the bladder
uPA	Urokinase-type plasminogen activator
3′ UTR	3′-Untranslated region
5′ UTR	5′-Untranslated region
UVRAG	UV irradiation resistance-associated gene

V

VCR	Vincristine
VDR	Vitamin D receptor
VE-cadherin	Vascular endothelial cadherin
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VHL	Von Hippel-Lindau tumor-suppressor gene
VLP	Virus-like particle

W

WIF1	Wnt inhibitory factor-1

Y

YAP1	Yes-associated protein 1

Z

ZAP-70	Zeta-chain(TCR)-associated protein kinase 70 kDa
ZBTB10	Zinc finger and BTB domain containing 10
ZEB	Zinc finger E-box binding homeobox

Part I
MicroRNAs: Biology and Implications in Cancer

Chapter 1
MicroRNAs and Cancer: An Overview

Sadegh Babashah

Contents

Abstract MicroRNAs (miRNAs) constitute an evolutionarily conserved class of small, noncoding RNA molecules that regulate gene expression by targeting specific mRNAs for degradation and/or translational repression. MiRNAs have been widely investigated due to their potential role in regulating a variety of cellular processes, including proliferation, differentiation, and apoptosis. Many miRNAs are implicated in various human cancers. Functional analysis of cancer-related miRNAs has proposed that they might act as either oncogenes or tumor suppressors. In fact, the link between aberrant miRNA expression and cancer development and progression can be observed either through the loss of tumor suppressor miRNAs or the over-expression of oncogenic miRNAs. This chapter aims to provide a succinct framework to gain insight into miRNA function in cancer.

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1 MicroRNAs: Biogenesis, Processing and Mode of Action

MicroRNAs (miRNAs or miRs) are a class of non-coding small RNAs of ~22 nucleotides that regulate gene expression by targeting specific mRNAs bearing partially complementary target sequences for degradation and/or translational repression (Liu et al. 2008; Babashah and Soleimani 2011). The first discovery of a small non-coding RNA dates back to 1993, when Victor Ambros and collaborators identified lin-4 in *Caenorhabditis elegans* (Lee et al. 1993). Lin-4 was believed to be a unique species until year 2000 when another small non-coding RNA, let-7, was reported in C. elegans (Reinhart et al. 2000) and in a variety of other organisms (Pasquinelli et al. 2000). Since then, hundreds of small non-coding RNA sequences (now known to be miRNAs) have been identified in a wide range of organisms from nematodes to vertebrates, plants and human. Currently, the official miRNA database miRBase lists 1,872 human miRNA gene loci, generating 2,578 mature miRNA sequences (http://www.mirbase.org, Release 20.0, June 2013). Precise attribution of miRNA effects on gene expression can be complicated by the fact that often each miRNA may control several hundred target genes directly or indirectly, whereas a single protein coding gene target could be regulated by more than one miRNA. In fact, miRNAs are predicted to target up to one-third of human transcripts (Zhong et al. 2012; Friedman et al. 2009).

The biogenesis of miRNAs begins in the nucleus with the synthesis of a relatively long double-stranded RNA molecule, known as primary (pri)-miRNA, by RNA polymerase II or III. The resultant pri-miRNA transcript is often more longer than 1 kb in length and includes a stable stem-loop hairpin structure that contains the sequence for the mature miRNA. The hairpin structure is excised in the nucleus from pri-miRNA as a ~70-nucleotide long precursor (pre)-miRNA by the nuclear RNase III endonuclease Drosha and DGCR8 (the "microprocessor complex") (Lee et al. 2003; Denli et al. 2004; Gregory et al. 2004). DGCR8 is essential as a molecular anchor for Drosha's activity on pri-mRNAs, as it recognizes the pri-miRNA at double-stranded RNA – single-stranded RNA junction and directs Drosha to cleave approximately 11 nucleotides from the base of the stem to free the hairpin from the primary transcript (Han et al. 2006). Members of the microprocessor complex have additional cellular functions, as Drosha is also involved in the processing of ribosomal RNA (Wu et al. 2000) and DGCR8 also acts as a heme-binding protein (Faller et al. 2007). The resultant pre-miRNA contains a 5′ phosphate and a distinctive 3′ two-nucleotide overhang which is signal to transport into the cytoplasm by a protein complex consisting of Exportin-5 and Ran-GTPase (Yi et al. 2003; Lund et al. 2004; Bohnsack et al. 2004) (Fig. 1.1). In cytoplasm, further processing facilitated by the second RNase III endonuclease Dicer, cuts off