Advances in cancer metastasis: from mechanisms of tumor progression to new therapeutic approaches

Essay
Submitted for partial fulfillment of Master Degree (M.Sc.) in
Clinical and Chemical Pathology

By
Rasha Mahmoud Abd Elhamid
M.B.,B.Ch Cairo University

Supervised by

Prof. Dr. Tayssir Kamel Eyada
Professor of Clinical and Chemical Pathology
Faculty of Medicine
Cairo University

Dr. Gamal Thabet Ali
Lecturer of Clinical Pathology
National Cancer Institute
Cairo University

Cairo University
2010

بسم الله الرحمن الرحيم

(قَالُوا سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ مَا
عَلَّمْتَنَا إِنَّكَ أَنْتَ العَلِيمُ الحَكِيمُ)

سورة البقرة آية (٣٢)

Abstract

Most cancer deaths are due to the development of metastasis rather than the primary tumor, hence there is an urgent need for the development of therapeutic intervention specifically targeted to the metastatic process. Therefore, it is important to understand the molecular and cellular mechanisms underlying the different steps of metastasis.Metastasis suppressor proteins and microRNAs regulate multiple steps in the metaststic cascade. They act as metastasis activators or suppreaaors.

Key words :

Metastasis suppressor proteins .

Acknowledgment

I wish to express my greatest appreciation and thanks to professor ***Dr.*** **Tayssir Kamel Eyada ,** Professor of Clinical and Chemical Pathology, Faculty of Medicine Cairo University, for her kind and continous guidance, encouragement and valuable supervision through this work.

I would like to express my deepest gratitude to **Dr. Gamal Thabet Ali**, Lecturer of Clinical Pathology, National Cancer Institute, Cairo University, for his kind supervision, generous cooperation, faithful guidance and support in order to fulfil this work.

List of contents

List of abbreviations..... i

List of figures…… viii

List of tables…… ……. x

Introduction and aim of the work…….……..... 1

Chapter I: Mechanisms of metastasis…….. 4

- Progression towards an invasive phenotype…… 4
- Genes controling metastasis…… 7
- Metastasis steps and course……. 11
- Metastatic cancer stem cells…… 41

Chapter II: Metastasis suppressor genes..... 44

- Identification of metastasis suppressor genes…….. 47
- Classification of metastasis suppressor genes……..... 50
- Biochemical and cellular functions of metastasis suppressor genes ……... 52
- Role of metastasis suppressor genes in metastatic dormancy……. 73

Chapter III: Role of microRNAs in cancer metastasis... 86

- What is microRNA?..... 87
- MicroRNA biogenesis……. 89
- Mechanism of action of microRNAs…….. 92
- Expression of microRNAs & their Role in central biological processes…….. 95

- Role of microRNAs in cancer……. 96
- Role of microRNAs in metastasis…… .. 103
- MicroRNAs as markers of metastasis……. 114

Chapter IV: Advances in cancer metastasis therapy….. 116

- Clinical targeting of metastatic colonization……... 122
- Value of metastasis suppressor protiens in cancer metastasis therapy……. 134
- MicroRNAs and metastatic cancer therapy……. 146

Summary…… 149

References…….. 153

Arabic summary……..

List of abbreviations

Ago	:Argonaute proteins
AMO	:Anti-mirna oligonucleotide
ANGPTL4	:Angiopoietin-like 4
APC	:Adenomatous polyposis coli
APL	:Acute promyelocytic leukemia
ARHGAP7	:Rho-GTPase activating protein 7
ARHGDIB	:A truncated human ras homolog gene family GDP dissociation inhibitor beta gene
ASOs	:Antisense oligonucleotides
ATRA	:All-trans Retinoic Acid
B CLL	:B cell chronic lymphocytic leukemia
bFGF	:Basic fibroblast growth factor
BMDCs	:Bone marrow-derived cells
BMP-2B	:Bone morphogenetic protein 2B
BPs	:Bisphosphonates
BRMS1	:Breast cancer metastasis-suppressor 1
BST1	:Bone marrow stromal cell antigen 2
C. elegans	:Caenorhabditis elegans
CAFs	:Cancer-associated fibroblasts
cap43	:Nickel-specific induction protein Cap43
CARD10	:Caspase recruitment domain family, member 10
CCL5	:C-C chemokine ligand 5
CDC27	:Cell division cycle 27
Cdc42	:Cell division control protein 42
CDK2	:Cyclin-dependent kinase 2
CDKN1A	:Cyclin-dependent kinase inhibitor 1A or CDK-interacting protein 1
cDNA	:Complimentary DNA
CGH	:Comparative genomic hybridization
CIC	:Cancer initiating cells
CK	:Cytokeratin
CLL	:Chronic lymphocytic leukemia
COX-1	:Cyclooxygenase 1
COX-2	:Cyclooxygenase 2
CRSP3	:Cofactor required for Sp1 transcriptional activation, subunit 3
CSC	:Cancer stem cell
CSF1	:Colony-stimulating factor 1

CTBP1	:Co-repressor C-terminal binding protein 1
CTGF	:Connective tissue growth factor
CXCL12	:C-X-C chemokine receptor ligand 12
CXCR4	:C-X-C chemokine receptor 4
DARC	:Duffy antigen receptor for chemokines
DCC	:Deleted in colon cancer
DCR	:Dicer
DFO	:Desferrioxamine
DGCR8	:Digeorge syndrome critical region gene 8
DLBCL	:Diffuse large B cell lymphoma
DLC1	:Deleted in liver cancer 1
DNA	:Deoxyribonucleic acid
dNTPs	:Deoxynucleoside triphosphates
Dp44mT	:Di-2-pyridylketone-4,4,-dimethyl-3-
Drg1	:Differentiation-related gene 1
dsRNA	:Double-stranded RNA
duplex	:Double-stranded form
E-cadherin	:Epithelial cadherin
ECM	:Extracellular matrix
EGF	:Epidermal growth factor
EGFR	:Epidermal growth factor receptor
EMT	:Epithelial–mesenchymal transition
EPCs	:Endothelial progenitor cells
ER	:Estrogen receptor
ER-a	:Estrogen receptor-a
EREG	:Epiregulin
ERK	:Extracellular signal regulated kinase
ET1	:Endothelin1
ETAR	:Endothelin A receptor
Exp 5	:Exportin-5
EZH2	:Enhancer of zeste human 2
FAK	:Focal adhesion kinase
FGF	:Fibroblast growth factor
FISH	:Fluorescence in situ hybridization
FOXC2	:Forkhead box protein C2
GDP	:Guanosine diphosphate
GFP	:Green fluorescent protein
GM-CSF	:Granulocyte macrophage-colony stimulating factor
GPI	:Glycosylphosphatidylinositol
GPR54	:G-protein coupled receptor 54

GPR56	:G protein-coupled receptor 56
GR	:Glucocorticoid receptor
GSC	:Goosecoid
GSK3β	:Glycogen synthase kinase-3β
GTP	:Guanosine triphosphate
H/E (Spl)	:Hairy and enhancer of split
HCCs	:Hepatocellular carcinomas
HCV	:Hepatitis c virus
HDAC	:Histone deacetylase (HDAC1 and 2)
HER2	:Human epidermal growth factor receptor 2
HGF	:Hepatocyte growth factor
HIF	:Hypoxia-inducible factor
HIV	:Human immunodeficiency virus
HLA-DR	:Human leukocyte antigen- DR
HMGA2	:High mobility group A2 protein
HOXD10	:Homeobox D10
HPCs	:Haematopoietic progenitor cells
HSP90	:Heat shock protein
ID1	:Inhibitor of differentiation 1
IGF1R	:Insulin-like growth factor 1 receptor
IHC	:Immunohistochemistry
I-kB	:Inhibitor of kappa B
IL8	:Interleukin 8
IRAK1	:Interleukin 1 receptor-associated kinase 1
JNK	:C-Jun NH2 terminal protein kinase
JNKK4	:JNK-activating kinase 4 (c-Jun N-terminal kinase kinase 4)
KAI1	:Kang-Ai 1
KISS1	:Kisspeptin-1
KISS1R	:KISS1 receptor
KSR1	:Kinase suppressor of Ras1
LN(M)	:Lymph node (metastasis)
LNA	:Locked nucleic acid
LOH	:Loss of heterozygosity
Loqs	:Loqacious
LOX	:Lysyl oxidase
LPA1	:Lysophosphatidic acid receptor 1
LPAR1	:Lysophosphatidic acid receptor 1
MAP2Ks	:Dual specificity MAP kinases (MAP kinase kinase)
MAPK	:Mitogen-activated protein kinase

MAPK3K	:MAP Kinase Kinase Kinase
MAT	:Mesenchymal –amoeboid transition
MEK4	:MAPK/ERK kinase 4
METs	:Mesenchymal–epithelial transitions
MHC1	:Major histocompatibility complex 1
miRISC	:MicroRNA:RISC complex
miRNAs	:MicroRNAs
MKK4	:Mitogen-activated protein kinase 4
MKK6	:Mitogen-activated protein kinase 6
MKK7	:Mitogen-activated protein kinase 7
MMCT	:Microcell-mediated chromosomal transfer
MMP	:Matrix metalloproteinase
MPA	:Medroxyprogesterone acetate
mRNA	:Messenger RNA
MSCs	:Mesenchymal stem cells
MSGs	:Metastasis suppressor genes
MT1-MMPs	:Member of the membrane-type MMP (MT-MMP)
MTCs	:Metastatic tumor cells
mTOR	:Mammalian target of rapamycin
N-cadherin	:Neuronal-cadherin
NCAM	:Neural cell adhesion molecule
ncRNA	:Noncoding RNA
ND	:Not determined
Ndrg1	:N-myc downstream regulated gene 1
NF-κB	:Nuclear factor kappa-light-chain-enhancer of activated B cells
NK	:N-terminal hairpin domain and Kringle domain
Nm23	:Non-metastatic clone 23
NME1	:Non-metastatic cells 1
NMU	:Neuromedin U
NSAIDs	:Nonsteroidal anti-inflammatory agent
NSCLC	:Non-small cell lung cancer
nt	:Nucleotides
OBL	:Osteoblast-like cells
OCL	:Osteoclast-like cells
oncomiRs	:OncomicroRNAs
OPG	:Osteoprotegerin
OPN	:Osteopontin
ORF	:Open reading frame

PACT	:Protein activator of the interferon-induced protein kinase
PARD6A	:Partitioning defective 6 homolog alpha
PARP	:Poly ADP ribose polymerase
PCR	:Polymerase chain reaction
PDCD4	:Programmed cell death 4
PDGF	:Platelet-derived growth factor
PDGFR	:PDGF receptor
PDK1	:Phosphoinositide-dependant kinase1
PEBP1	:Phosphatidylethanolamine-binding protein 1
PEG	:Polyethylene glycol
PI3K	:Phosphoinositide 3-kinase
PIK3R2	:Phosphoinositide 3-kinase regulatory, subunit 2
PIP_2	:Phosphatidylinositol-4, 5, bisphosphate
PIP_3	:Phosphatidylinositol-3, 4, 5, bisphosphate P3
PKC	:Protein kinase C
PLCγ	:Phospholipase-C gamma-1
PlGF	:Placental growth factor
Pol- III	:Polymerase III
Pol-II	:Polymerase II
PP1	:Pyrazolo [3,4-d]pyrimidines1
PP2	:Pyrazolo [3,4-d]pyrimidines 2
PR	:Progesterone receptor
pRb	:The retinoblastoma protein
pre-miRNAs	:Precursor miRNAs
pri-miRNA	:Primary miRNAs
PTEN	:Phosphatase and tensin homolog
PTGS2	:Prostaglandin G/H synthase 2
PTHrP	:Parathyroid hormone-related protein
RAC1B	:Ras-related C3 botulinum toxin substrate 1B
RANKL	:Receptor activator of NF-κB ligand
Rb	:The retinoblastoma protein
RECK	:Reversion-inducing-cysteine-rich protein with kazal motifs
RhoGDI2	:Rho-guanine nucleotide (RhoGTPase) dissociation inhibitor 2
RISC	:RNA-induced silencing complex
rit42	:Reduced in tumor, 42 kDa
RKIP	:Raf Kinase Inhibitor Protein
RNase	:Ribonuclease

ROCK1 :Rho-associated, coiled-coil containing protein kinase
ROS :Reactive oxygen species
RRM1 :Ribonucleotide reductase M1
rRNAs :Ribosomal RNA
RTKs :Receptor tyrosine kinases
RTP :Reducing agents and tunicamycin-responsive protein
SAA3 :Serum amyloid A3
SAPK :The stress-activated protein kinase
SCCHN :Squamous cell carcinoma of the head and neck
SDF1 :Stromal cell-derived factor 1
SEK1 :SAPK/ERK kinase 1
SEMA3C :Semaphorin 3C
simplex :Single-stranded form
siRNAs :Small interfering RNAs
snoRNAs :Small nucleolar RNA
SPRED1 :Sprouty-related, EVH1 domain-containing protein 1
SSeCKS :Src-suppressed C kinase substrate
STAT3 :Signal transducer and activator of transcription
STS :Sequence-tagged site
TAMs :Tumor-associated macrophages
TBX2 :T-box transcription factor
TFF :Trefoil factor (adhesion molecule)
TGFβ :Transforming growth factor-β
TGIF2 :TGFβ-induced factor homeobox 2
TIMP :Tissue inhibitors of metalloproteinase
TNC :Tenascin C
TNFα :Tumor necrosis factor-α
TPM1 :Tropomyosin 1
TRAF6 :TNF receptor-associated factor 6
TRBP :Transactivating response RNA-binding protein
TRKB :Neurotrophic tyrosine kinase receptor type 2
tRNAs :Transfer RNAs
TSP1 :Thrombospondin 1
TXNIP :Thioredoxin-interacting protein
uPA :Urokinase plasminogen activator
uPAR :Urokinase plasminogen activator surface receptor
UTR :Untranslated regions
VCAM1 :Vascular cell adhesion molecule 1
VDUP1 :Vitamin D up-regulating protein-1
VEGF :Vascular endocelial growth factor

VEGFA	:Vascular endothelial growth factor A
VEGFR3	:VEGF receptor 3
WNTR	:Wnt receptor
XBP1	:X box binding protein
ZBTB10	:Zinc finger and BTB domain-containing protein 10
ZEB2	:Zinc finger E-box-binding homeobox 2
ZO-1	:Zonula occludens 1 protein

List of figures

No.	Title	Page
1	Organ-specific barriers to metastatic infiltration	7
2	Basic steps of metastasis and hypothetical classes of metastasis genes	8
3	Metastasis progression genes expressed in the primary tumor	9
4	The metastatic cascade	13
5	The temporal course of metastasis	15
6	Transitions between epithelial and mesenchymal states during carcinoma progression	17
7	a simplified overview of signaling networks regulating epithelial–mesenchymal transitions	22
8	Different strategies of tumor invasion	25
9	Intravasation and migration of cancer cells	30
10	The fate of tumor cells in the metastatic microenvironment	37
11	a model of the evolution of a metastatic niche	39
12	Stage-specific targeting of the metastatic microenvironment	40
13	Is failure to control metastasis due to residual tumor stem cells?	41
14	Potential origin of cancer initiating cells	43
15	metastasis suppressor genes and steps in the metastatic cascade in human cancer	45
16	Timeline of discovery of metastasis suppressor genes	46
17	Identification of metastasis-suppressor activities by use of microcell mediated chromosomal transfer	48
18	Schematic showing cellular localization and proposed biochemical mechanisms for the known metastasis suppressors	52
19	Metastasis suppressor proteins function in conserved signaling pathways	53
20	KISS1, MKK4 and MKK7 promote metastatic dormancy	78
21	Diagram illustrating the biogenesis pathway of microRNAs	91

22	Schematic illustration of mechanisms of action of microRNAs	94
23	microRNA-regulated pathways in tumor metastasis	104
24	microRNAs regulating angiogenesis	112
25	Molecular distinctions between primary colorectal carcinomas and their liver metastasis	121
26	Metastatic colonization	123
27	An overwhelming number of potential rational combinations of drugs are available for metastatic colonization: angiogenesis as an example	125
28	The bone metastasis ‘vicious’ cycle	127
29	Strategies for restoring metastasis suppressor function	137
30	Targeting key genes downstream of metastasis suppressors	144