Advances in Tumor Angiogenesis: from Pathogenesis to Molecular Targeted Therapy Approaches

Essay

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By

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Abstract

Angiogenesis, the development of new blood vessels, is a fundamental physiological process. It also plays a critical role in a variety of different pathologic conditions, including tumor growth and metastasis. New blood vessels in tumors can grow by sprouting from pre-existing vessels or by recruitment of rare, circulating bone marrow-derived endothelial progenitor cells. A variety of different angiogenesis stimulators and inhibitors have been discovered including VEGF, integrin and Semaphorins. Angiogenic switch which cause a switch from the anti- to pro-angiogenic state depends on genetic and environmental factors. Antiangiogenic therapy is one of the promising tumor therapies that target tumor vasculature or angiogenic factors as VEGF-targeted therapy, integrin targeting agents and vascular disrupting agents.

Key Words:

Angiogenesis – VEGF – Integrins – Semaphorins – therapy .

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List of Abbreviation

Abbreviation	Full Name
4E-BP1	4E-binding protein 1
A2b	Adenosine 2b receptor
ABL	Abelson
ADAM17	A disintegrins and metalloproteases
AKT	A serine/threonine kinase
Arp2/3	Actin-Related Proteins ARP2 and ARP3 complex
Arg–Glu–Asp–Val	Arginine–Glutamate–Aspartate–Valine
Arg –Gly– Asp	Arginine –Glycine– Aspartate
BCL-2	B-cell leukemia 2 oncogene
BCR	Breakpoint cluster region of chromosome 22
bFGF-2	Basic fibroblast growth factor
CA4P	Combretastatin A4 phosphate
Cadherin	Calcium dependent adhesion molecules
cAMP	Cycic adenosine monophosphate
Caspases	Cysteine – aspartate residues
CD	Cluster of differentiation
CDK5	Cyclin-dependent kinase 5
CECs	Circulating endothelial cells
cGMP	Cycic guanosine monophosphate
CHL1	Close homologue of L1
COX	Cyclooxygenase
CRC	Colorectal cancer
CRMPs	Collapsin response mediator proteins
CSF	Colony stimulating factors
CT	Computed tomography
CUB	Complement binding
CXCR4	CXC Chemokine receptor 4
CYR61	Cysteine rich, angiogenic inducer, 61
DC	Dendritic cell

Abbreviation	Full Name
DCC	Deleted in colorectal carcinoma
DEL1	Developmental endothelial locus 1
Dll	Deltalike ligand
DMXAA	5,6-dimethylxanthenone-4acetic acid
DNA	Deoxyribonucleic acid
Dock180	Dedicator of cytokinesis
EC	Endothelial cells
E-cadherin	E-calcium dependent adhesion molecule
ECM	Extracellular matrix
EGFR	Epidermal growth factor receptor
EILDV	Glutamate–Isoleucine–Leucine–Aspartate–Valine
EPCs	Endothelial progenitor cells
EphB4	Ephrin B4 receptor
ErbB1	Erythroblastic leukemia viral oncogene homolog 1
ErbB2	Erythroblastic leukemia viral oncogene homolog 2
ERK	Extracellular signal-regulated kinase
Erk	Extracellular signal-regulated kinase
FARP2	FERM, RhoGEF and pleckstrin domain protein 2
FDA	Food and Drug Administration
FER	FER (FPS / FES related) tyrosine kinase
FES	Feline sarcoma oncogene
FGF-1	Acidic fibroblast growth factor
FGFR	Fibroblast growth factor receptor
flk-1	Fetal liver kinase 1
Flt	Fms-like tyrosine kinase
Fyn	FYN oncogene related to SRC, FGR, YES
GAP	GTPase-activating proteins
GDP	Guanosine diphosphate
GEF	Guanine nucleotide exchange factors
GIPC1	GAIP C-terminus interacting protein 1
Glu–Ile–Leu–Asp–Val	Glutamate–Isoleucine–Leucine–Aspartate–Valine
GLUT	Glucose transporter
GM–CSF	Granulocyte macrophage colony-stimulating factor
G–P	Glycine–proline
GPI	Glycophosphatidylinositol
GRB2	Growth factor receptor-bound protein 2
GSK3β	Glycine synthase kinase 3 β
GTP	Guanosine triphosphate
GTPase	Guanosine triphosphatease
GXXG	Glycine residues
HAMA	Human antimouse antibody
HATs	Histone acetyltransferases

Abbreviation	Full Name
HCC	Hepatocellular carcinoma
HDACi	Histone deacetylases inhibitors
HDACs	Histone deacetylases
HER-2/neu	Human epidermal growth factor receptor-2
HGF	Hepatocyte growth factor
HIF	Hypoxia inducible factor
HLA-DR	Human leukocyte antigen-DR
HOXD3	Homeobox family transcription factor
HPC	Haematopoietic progenitor cell
HPV	Human papilloma virus
H-Ras	Harvey rat sarcoma viral oncogene homolog
HUVEC	Human umbilical vein endothelial cells
IAPs	Inhibitor of apoptosis proteins
Id proteins	Inhibitor of DNA-binding proteins
IFP	Interstitial fluid pressure
IGF-IR	Insulin-like growth factor-I receptor
IL	Interleukin
JNK	Jun N-terminal kinase
kDa	Kilodalton
KDR	Kinase-insert domain–containing receptor
K-Ras	Kirsten rat sarcoma viral oncogene homolog
L1CAM	L1 cell adhesion molecule
LARG	Leukaemia-associated RHOGEF
LIMK1	LIM domain kinase 1
LLC	Lewis lung carcinoma
LYVE1	CD44 homologue lymphatic vessel endothelial hyaluronan receptor 1
mAbs	Monoclonal antibodies
MAM	Meprin A5
MAPK	Mitogen-activated protein kinase
MCP1	Monocyte chemoattractant protein 1
MEK	Mitogen-activated protein kinase kinase
MET	Mesenchymal-epithelial transition factor
MHC	Major histocompatibility complex
MICALs	Molecules interacting with CasL
MLCK	Myosin light chain kinase
MMAC/PTEN	Mutated in multiple advanced cancer 1/phosphatase and tensin homologue deleted on chromosome 10
MMPs	Matrix metalloproteinases
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MRS	MET-related sequence

Abbreviation	Full Name
MT1-MMP	Membrane type 1 matrix metalloproteinase
mTOR	Mammalian target of rapamycin
NFκB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NO	Nitric oxide
NP	Neuroplin
NRCAM	Neuronal cell adhesion molecule
p38MAPK	p38 Mitogen-activated protein kinase
p53	protein 53
p70S6K	p70S6 kinase
PAI-1	Plasminogen activator inhibitor type 1
PAK1	P21-activated kinase 1
PDZ	PSD-95/Dlg/Zo-1
PEX	MMP-2 hemopexin domain
PGF	Placenta growth factor
PGI2	Prostacyclin
PI3K	Phosphatidylinositol 3-kinase
PKA	Protein kinase A
PKB	Protein kinase B
PKC	Protein kinase C
PLC	Phospholipase C
PLEX	Plexin
PlGF	Placenta growth factor
PROX1	Prospero-related homeobox 1
PSI	Plexin/semaphorin/integrin
pvHL	Product of the von Hippel–Lindau Gene
PyMT	polyoma middle T antigen
RAF	Raf kinase
RB2/p130	Retinoblastoma-related gene
RBCCs	Recruited bone marrow–derived circulating cells
RCC	Renal cell carcinoma
REDV	Arginine–Glutamate–Aspartate–Valine
RGD	Arginine –Glycine– Aspartate
RGDfV	Arginine –Glycine– Aspartate– D-phenylalanine– Valine
RHOA	Ras homolog gene family, member A
RHOD	Ras homolog gene family, member D
RNA	Ribonucleic acid
Robo4	Rounabout homolog4
ROCK	Rho-associated coiled-coil-containing kinase

Abbreviation	Full Name
RRAS	Ras-related protein
SDF1	Stromal derived factor 1
SEA	Serine-Glutamate-Alanine
SEMA	Semaphorin
siRNA	Small interfering RNA
Src	Sarcoma (proto-oncogenic tyrosine kinases)
sVEGFR-1	Soluble form of VEGFR-1
TACE	Tumor necrosis factor α converting enzyme
TAM	Tumor-associated macrophages
TCR	T-cell receptor
TGF	Transforming growth factor
TKIs	Tyrosine kinase inhibitors
TNF-α	Tumor necrosis factor α
trkB	Neurotrophic tyrosine kinase receptor, type 2
TSP	Thrombospondins
TTPA	Tissue-type plasminogen activator
Tyr	Tyrosine
Ub	Ubiquitin
uPA	Urokinase-type plasminogen activator
uPA	Urokinase plasminogen activator
uPAR	Urokinase plasminogen receptor
VCAM1	Vascular cell adhesion molecule 1
VDAs	Vascular disrupting agents
VE-cadherin	Vascular endothelial-cell cadherin
VEGF	Vascular endothelial growth factor
VEGFR	VEGF receptor
vHL	von Hippel Lindau
v-myb	Myeloblastosis viral oncogene homolog
VPF	Vascular permeability factor

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Introduction

Angiogenesis, the development of new blood vessels, is a fundamental physiological process that promotes embryonic development, tissue repair and fertility, yet that also promotes chronic inflammation, tumour growth and tumor metastasis. New blood vessels in tumours can grow by sprouting from pre-existing vessels or by recruitment of rare, circulating bone marrow-derived endothelial progenitor cells **(Carmeliet, 2005)**. Tumor cells, macrophages and fibroblasts within tumours can secrete factors, such as vascular endothelial growth factor (VEGF), that induce blood vessel growth in tumours. Basic and clinical studies indicate that suppression of angiogenesis can inhibit tumour progression and metastasis **(Ferrara and Kerbel, 2005)**.

VEGF mediates numerous changes within the tumour vasculature, including endothelial cell proliferation, migration, invasion, survival, chemotaxis of bone marrow-derived progenitor cells, vascular permeability and vasodilation. The mammalian VEGF family consists of five glycoproteins referred to as VEGFA, VEGFB, VEGFC, VEGFD and placenta growth factor. The best characterized of the VEGF family members is VEGFA (commonly referred to as VEGF), which is expressed as various isoforms owing to alternative splicing that leads to mature 121-, 165-, 189- and 206-amino-acid proteins **(Hicklin and Ellis, 2005)**.

Many lines of investigations implicate integrins, which are key regulators of endothelial cell migration and survival, as key regulators of tumour angiogenesis. Like angiogenesis, lymphangiogenesis — the growth of new lymphatic vessels — promotes tumour metastasis **(Roma et al., 2006)**.

Tumour cells induce the growth of new lymphatic vessels within tumours and draining lymph nodes, enhancing dendritic cell trafficking to lymph nodes; increased lymphatic vessel density in tumours is also associated with increased metastasis to lymph nodes **(Hirakawa et al., 2005)**. New findings indicate that selected integrins can modulate lymphangiogenesis and may thereby affect tumour metastasis. In vitro and in vivo data have implicated a number of endothelial cell integrins in the regulation of cell growth, survival and migration during angiogenesis. These integrins include the heterodimers α1β1, α2β1, α4β1, α5β1, α6β1, α6β4, α9β1, αvβ3 and αvβ5 **(Avraamides et al., 2008)**.

The semaphorins were initially described as axon guidance factors that affect the development of the central nervous system. However, semaphorin receptors belonging to the neuropilin and plexin families were subsequently found to be expressed by multiple types of cells, including endothelial cells and many types of cancer cells. These observations were followed by studies that indicated that the semaphorins can modulate the behaviour of cancer cells and endothelial cells, and that various semaphorins can either promote or inhibit tumour angiogenesis and tumour progression by multiple mechanisms **(Neufeld and Kessler, 2008)**.

The long-standing proposition that induction of chronic angiogenesis is a hallmark of cancer is now solidly grounded in researchs involving genetic and pharmacological perturbation of elements in the vascular regulatory circuitry. The 'angiogenic switch' is increasingly recognized as a rate-limiting secondary event in multistage carcinogenesis, as documented in animal models of cancer. That this acquired capability is functionally important for manifestation of the disease has been further validated by the approval of angiogenesis inhibitors as cancer therapeutics, most notably ones targeting the vascular endothelial growth factor (VEGF) pro-angiogenic signaling pathways **(Folkman, 2007)**.

The pioneers of the clinical proof-of-concept for angiogenesis inhibitors are bevacizumab (Avastin, Genentech/Roche), a ligand-trapping monoclonal antibody, and two kinase inhibitors (sorafenib (Nexavar, Bayer) and sunitinib (Sutent, Pfizer)) targeting the VEGF receptor (VEGFR) tyrosine kinases, principally VEGFR2 **(Bergers and Hanahan, 2008)**.

The inhibition of VEGF signalling may affect tumour growth through several mechanisms. These different mechanisms have a more or less important role depending on tumour type **(Motzer et al., 2007)**.

Aim of the work:

This study aimed to review the basic principles of tumour angiogenesis and the advances in its pathogenesis, with especial empathize on the role of VEGF , intergrins and other recently discovered molecules. In addition we will review the emerging role of VEGF inhibitors as a molecular targeted therapy.