IMPLICATIONS OF ANGIOGENESIS IN CUTANEOUS DISORDERS

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List of Abbreviations

AA : Arachidonic acid

aaAT : Antiangiogenic antithrombin

Ab : antibody

ALK-1 : Activin receptor-like kinase-1

ANCA : Anti-neutrophil cytoplasmic antibody

Ang-1 : Angiopoietin-1

Ang-2 : Angiopoietin-2

APCs : antigen presenting cells

ATP : Adenosine triphosphate

BB : B-chain homodimer

BCC : Basal cell carcinoma

bFGF : Basic fibroblast growth factor

BHPA : N-biphenyl sulfonyl-phenylalanine hydroxamic acid

cGMP : Cyclic guanosine monophosphate

c-Kit : stem-cell factor [SCF] receptor

COX : Cyclooxygenase

CSF-1R : colony stimulating factor receptor type 1

DNA : Deoxy ribonucleic acid

EC : Endothelial cell

ECM : Extracellular matrix

EGF : Epidermal growth factor

EGFR : Epidermal growth factor receptor

EMAP-II : Endothelial monocyte-activating polypeptide-II

ERK : extracellular signal-regulated kinase protein

FGF-2 : Fibroblast growth factor-2

FGFR-1 : Fibroblast growth factor receptor-1

Flk-R : fetal liver kinase receptors

Flt : fms-like tyrosine kinase,

GC-SF : Granulocyte colony-stimulating factor

GIT : Gastrointestinal tract

GM-CSF : Granulocyte macrophage-colony stimulating factor

GRO-α : Growth-regulated oncogene alpha

HGF : Hepatocyte growth factor

HGF/SF :hepatocyte growth factor/scatter factor

HHT : Hereditary hemorrhagic telangiectasia

HHV-8 : Human herpesvirus-8

HIF-1α : hypoxia-inducible factor- 1α

HIV-1 : Human immunodeficiency virus type 1

HPV : Human papilloma virus

HS : heparin sulfate

HSPG : heparin sulfate containing proteoglycan

ICM-1 : Intercellular adhesion molecule-1

IFN-γ : Interferon-gamma

IGF-1 : Insulin growth factor-1

IL-1 : Interleukin-1

IP-10 : Interferon- gamma -inducible protein 10

KS : Kaposi sarcoma

KSHV : KS-associated herpesvirus

LFA-1 : Leukocyte function antigen-1

LIF : Leukemia inhibitory factor

LLC : Lewis lung carcinoma

mAbs : Monoclonal antibodies

MDM : Monocyte-derived macrophages

MGF : Melanoma growth factor

MGSA : Melanoma growth-stimulatory activity

MIA : Melanoma inhibitory factor

MM : Malignant melanoma

MMPs : Matrix metalloproteinases

MRI : Magnetic resonance imaging

mRNA : Messenger ribonucleic acid

MTD : Maximum tolerated dose

MT-MMP : membrane-type matrix metalloproteinase

mTOR : Mammalian target of rapamycin

NO : Nitric oxide

NOS : Nitric oxide synthase

NPR :neuropilin receptors

NSAID : Non-steroidal anti-inflammatory drugs

PA : plasminogen activator

PAF : Platelet activating factor

PAI- : Plasminogen activator inhibitor

PDECGF : platelet-derived endothelial cell growth factor

PDGF : Platelet-derived growth factor

PDGFR : platelet derived growth factor receptor

PEDF : pigment epithelium-derived factor

PEX : noncatalytic C-terminal hemopexin C domain of MMP-2

PF-4 : Platelet factor-4

PlGF : placenta growth factor

PMN : Polymorphonuclear neutrophils

PPS : Pentose polysulfate

PR3 : Proteinase 3

PWSs : Port-wine stains

RET : glial cell-line derived neurotrophic factor receptor

RGD : Arg-Gly-Asp sequence

RTK : Receptor tyrosine kinase

SCC : Squamous cell carcinoma

SV : Systemic vasculitis

SWS : Sturge-Weber syndrome

Tat : transactivator of viral gene expression

TGF-β : Transforming growth factor-beta

Tie : Tyrosine kinase with immunoglobulins and EGF

TIMP : Tissue inhibitor of metalloproteinase

Tn I : Troponin I

TNF : Tumour necrosis factor

TP : Thymidine phosphorylase

t-PA : Tissue plasminogen activator

TSC : Tuberous Sclerosis Complex

TSP : Thrombospondin

uPA : Urokinase plasminogen activator

UPAR : Urokinase plasminogen activator receptor

VCAM-1 : Vascular cell adhesion molecule-1

VE : Vascular endothelium

VEGF : Vascular endothelial growth factor

VEGFR-1 : Vascular endothelial growth factor receptor-1

VEGI : vascular endothelial cell growth inhibitor

VHL : von Hippel- Lindau

vWF : von Willebrand factor

5-FU : 5-fluorouracil

1. INTRODUCTION

Angiogenesis (also known as neovascularization) is defined as the process that involves the formation of new blood vessels from a pre-existing vessel bed, which is distinct from vasculogenesis, the *de novo* differentiation of endothelial cells (ECs) from bone marrow-derived stem cells (angioblasts) ***(Folkman, 1995).*** It is a complex process involving extensive interplay between cells e.g. endothelial cell, soluble factors e.g. vascular endothelial growth factor (VEGF), and extracellular Matrix (ECM) components ***(Liekens et al, 2001).***

The development of the blood vasculature is a complex process that begins when progenitor cells (angioblasts) differentiate into endothelial cells, coalesce and form the first vessels in the embryo (vasculogenesis). These embryonic vascular tubes give rise to new vessels by branching or sprouting (angiogenesis) that in turn can elongate, enlarge, mature or regress (vascular remodeling) in response to different stimuli. These processes are vital in the developing embryo but are mostly absent in the adult ***(Carmeliet , 2000).***

Angiogenesis was initially described in malignant tumors. It has been described subsequently in inflammatory lesions and in benign neoplasms ***(Arbiser, 1998).***

Angiogenesis is involved in the pathogenesis of several dermatological diseases such as hemangiomas, angiosarcoma, malignant melanoma, non-melanoma skin cancer (basal and squamous cell carcinoma), psoriasis, viral warts, pyogenic granuloma, rosacea, keloid scars, venous and arterial ulcers, scleroderma, vasculitis and vascular malformations such as Sturge-Weber syndrome ***(Bhushan et al., 2002).***

Angiogenesis is under the control of both stimulatory (proangiogenic) and inhibitory regulators. Proangiogenic factors include: vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), hepatocyte growth factor (HGF), granulocyte colony-stimulating factor (G-CSF), platelet derived growth factor (PDGF), tumour necrosis factor-α (TNF-α), transforming growth factor-β1 (TGF-β1), interleukins (IL-3,-8), cathepsin, $\alpha_v\beta_3$ integrin, angiopoietin-1 (Ang-1), angiopoietin-2 (Ang-2), angiotropin, angiogenin, erythropoietin, hypoxia, nitric oxide synthetase, prostaglandin E, plasminogen activator inhibitor-1 and thrombopoietin. Antiangiogenic factors include; thrombospondin-1 and-2, tissue inhibitor of metalloproteinase-1,-2,-3 and-4, angiostatin, endostatin, prolactin, restin, tumstatin, arresten, vasostatin, interleukin-1,-4,-10,-12 and-18, interferon-α,-β,-γ, platelet factor-4, 1,25 vitamin D3, retinoic

acid, angiotensin and angiotensin-2-receptor ***(Madhusudan & Harris, 2002).***

Understanding the biology of growth factors and signal transduction have led to insights on how angiogenesis is regulated and ultimately may lead to further therapies for benign and malignant tumors and inflammatory conditions. Finally, drugs used by dermatologists may have antiangiogenic activity that may underlie their efficacy in skin disease ***(Arbiser, 1999).***

Angiogenesis-targeted therapies are under trial for the management of several diseases. Several studies are concerned with the clinical applications of angiogenesis. It is used as a parameter in the prognosis of cancer as angiogenesis is one of the crucial steps in the pathogenesis of tumours ***(Liekens et al., 2001; Herbs et al., 2007).***

A major advantage of future antiangiogenic therapy for skin disease may relate to the delivery of these blood vessel-modulating treatments. Using either topical or intralesional routes, dermal vessels may be able to be targeted locally without the risks inherent to a systemic approach. This is essential as the inappropriate systemic downregulation of neovascularization could adversely affect essential