شبكة المعلومات الجامعية

بسم الله الرحمن الرحيم

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

شبكة المعلومات الجامعية

جامعة عين شمس

التوثيق الالكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأفلام قد أعدت دون أية تغيرات

يجب أن

تحفظ هذه الأفلام بعيدا عن الغبار

في درجة حرارة من ١٥-٢٥ مئوية ورطوبة نسبية من ٢٠-٤٠%

To be Kept away from Dust in Dry Cool place of 15-25- c and relative humidity 20-40%

بعض الوثائق الاصلية تالفة

بالرسالة صفحات لم ترد بالاصل

Expression of vascular endothelial growth factor in some cases of gliomas (astrocytomas)

THESIS

Submitted to the Faculty of Medicine

University of Alexandria

In Partial Fulfillment of the Requirements of

The Degree of

Doctor of pathology

By

EMAN ABDELZAHER AHMED ABDELLATIF
M.B.B.Ch., Alex
Master of Pathology, Alex

FACULTY OF MEDICINE

UNIVERSITY OF ALEXANDRIA

2004

SUPERVISORS

Prof. Dr. Galila Haseeb El-Tawil

Professor of Pathology,

Faculty of Medicine,

University of Alexandria.

Prof. Dr. Ismail Ahmed Ramadan

Professor of Neurosurgery,

Faculty of Medicine,

University of Alexandria.

Prof. Dr. Amal Ebraheem Rahmy

Professor of Pathology,

Faculty of Medicine,

University of Alexandria.

Prof. Dr. Doreya Mohammed Bayoumi

Professor of Pathology,

Faculty of Medicine,

University of Alexandria.

ACKNOLWEDGMENT

I would like to express my deep gratitude and appreciation to **Prof. Dr. Galila Haseeb El Tawil,** Professor of Pathology, Faculty of Medicine, University of Alexandria for her close supervision, continuous encouragement, valuable and useful advice throughout this work.

I am greatly indebted to **Prof. Dr. Ismail Ahmed Ramadan,** Professor of Neurosurgery, Faculty of Medicine, University of Alexandria for his fatherly guidance, kind interest, and sincere help during this study.

I wish to express my particular thanks to **Prof. Dr. Amal Ibraheem Rahmy,** Professor of Pathology, Faculty of Medicine, University of Alexandria for her kind supervision and valuable advice.

My deepest thanks are to **Prof. Dr. Doreya Mohammed Bayoumi,** Professor of Pathology, Faculty of Medicine, University of Alexandria for her encouragement and generous guidance throughout this work.

I would like to express my deepest gratitude to all the professors, staff members, and technicians of the Pathology department, Faculty of Medicine, University of Alexandria for their generous support.

Also I would like to express my deepest thanks to all the members of the Neurosurgery, Radiology, and Chemotherapy Departments, for their generous help throughout this work.

List of Abbreviations

cDNA: complementary deoxyribonucleic acid.

CDKs: cyclin dependent kinases.

CIA: computerized image analysis.

CNS: central nervous system.

C.P.: clinical presentation.

CSF: cerebrospinal fluid

CT: computerized tomography.

DAB: diaminobenzidine tetra- hydrochloride.

DIG: desmoplastic infantile ganglioglioma.

DNA: deoxyribonucleic acid.

DNT: dysembryoblastic neuroepithelial tumor.

EC: endothelial cell.

EGF: epidermal growth factor.

EGFR: epidermal growth factor receptor.

ELISA: enzyme-linked immunosorbant assay.

Factor VIII-RAg: factor VIII related antigen.

FGF: fibroblast growth factor.

Flt: fms-like tyrosine kinase.

GADD45: growth arrest and DNA damage inducible gene.

HIF-1 α: hypoxia inducible factor-1α.

HPV: human papilloma virus.

ICAM-1: intercellular adhesion molecule.

ICP: intracranial pressure.

IGF-BP3, insulin like growth factor-BP3.

IHC: immunohistochemistry.

IL-8: interlukin-8.

ISH: in situ hybridization.

Kb: Kilo base.

KD: Kilo Dalton.

KDR: kinase domain region.

MDM2: murine double minute.

MEN1: multiple endocrine neoplasia type 1 gene.

MRI: magnetic resonance imaging.

mRNA: messenger ribonucleic acid.

MVD: microvessel density.

NF1: neurofibromatosis type 1.

NS: not significant.

PBS: phosphate-buffered saline.

PCNA: proliferating cell nuclear antigen.

PDGF: platelet derived growth factor.

PlGF: placenta growth factor.

PXA: pleomorphic xanthoastrocytoma.

Rb: retinoblastoma.

RT-PCR: reverse transcriptase polymerase chain reaction.

SEGA: subependymal giant cell astrocytoma.

SMC: smooth muscle cell.

SV40: simian virus 40.

TGF-β: transforming growth factor-β.

TNF-α: tumor necrosis factor-α.

VCAM-1: vascular cell adhesion molecule.

VEGF: vascular endothelial growth factor.

VEGFR: vascular endothelial growth factor receptor.

VHL: von Hippel-Lindau.

WHO: World Health Organization.

CONTENTS


INTRODUCTION

Introduction

The formation of new blood vessels from preexisting vessels, angiogenesis, is an important prerequisite for a variety of physiologic and pathologic processes including tumor growth and metastasis.[1,2] In addition, measurement of angiogenesis in various tumors has proved to be a powerful prognostic tool.[3]

In recent years there has been substantial progress in understanding the regulation of angiogenesis in both normal and neoplastic tissue.[4] Many growth factors with angiogenic properties have been identified, among them, vascular endothelial growth factor (VEGF) emerges as the most potent and specific endothelial growth factor.[5]

Gliomas are the most common primary central nervous system (CNS) tumors and account for more than half of all CNS neoplasms.[6,7]

Neovascularization is a neuropathological hallmark of high grade gliomas, proposing a significant role for the up-regulation of angiogenic factors as a critical step in glioma progression.[8,9] therefore, gliomas serve as an attractive model for the study of angiogenesis.[10]

Many researches have been directed towards the elucidation of possible mechanisms involved in the tumor-associated angiogenesis in gliomas.[11,12] There is growing evidence that VEGF is a key angiogenic factor in gliomas.[13-15]

Much of the morbidity and mortality associated with gliomas is related to the degree of tumor vascularity and the extent of peritumoral vasogenic edema.[2,16] Therefore, the unique combination of angiogenic and vascular permeability activities within the same protein, VEGF, is of particular interest in the study of gliomas, as it might prove to be a

reliable prognostic factor.[9,10]Furthermore, it may hold promise as a potential target for the newly introduced antiangiogenic therapy for gliomas.[16-18]

In recent years, increasing interest in genetic abnormalities and biologic factors, such as the tumor suppressor gene p53, and their role in gliomas has emerged.[19] p53 is thought to influence tumor development and progression through its effect on angiogenesis. A regulatory role for p53 over VEGF expression was suggested but not proved yet.[20,21]

In addition, p53 might prove to be a reliable prognostic factor in gliomas; however, considering the inconsistent results of several recent studies, it has remained controversial whether p53 actually can be related to patients' prognosis.[22]

Both VEGF and p53 can be detected by a variety of techniques, such as immunohistochemistry, in situ hybridization, and polymerase chain reaction.[23,24] Immunohistochemistry is a commonly used method with widespread pathological application; it has been known and practiced for a long time.[25]

Interpretation of the results of immunohistochemistry has been traditionally done by manual counting which yields semiquantitative results. Nowadays, computerized image analysis (CIA) rendered the procedure suitable for diagnostic and prognostic determination in surgical pathology.[26,27]

REVIEW OF THE LITERATURE