Serum Vascular Endothelial Growth Factor in Ovarian Cancer

Thesis

Submitted for partial fulfillment of
M.D Degree in Obstetrics and Gynecology

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2012

أهمية قياس مستوى عامل نمو بطانة الأوعية الدموية فى مصل الدم فى حالات أورام المبيض الخبيثة

رساله

توطئه للحصول على درجة الدكتوراه
فى أمراض النساء والتوليد

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Acknowledgement

I would like to express my sincere tanks and iam greatly honored for Prof. Mohamed Abd El-Hamid Yehia, Professor of Obstetrics and Gynecology, Faculty of Medicine – Ain Shams University for supervising this work.

I would like also to extend my sincere appreciation and iam extremely grateful to Prof. Maged Ramadan Abu-Seeda, Professor of Obstetrics and Gynecology, Faculty of Medicine – Ain Shams University for supervising this work.

I would like also to express my deepest gratitude to Prof. Khaled Kamal Ali, Professor of Obstetrics and Gynecology, Faculty of Medicine – Ain Shams University, for his continuous encouragement and guidance to accomplish this work.

I gratefully acknowledge the support and assistance of Prof. Ismail Khalil El-Lamie, Professor of Obstetrics and Gynecology, Faculty of Medicine – Ain Shams University to finish this work.

I would like to express my thanks and appreciation to the soul of Prof. Mahmoud Ismail Hassan, The Head of Oncology Diagnostic Unit & Professor of Biochemistry

& Molecular Biology, Faculty of Medicine – Ain Shams University .

I would like also to acknowledge the valuable help, effort and meticulous revision of this work by Dr. Adel Shafik Salah El-Din, *Lecturer in Obstetrics and Gynecology, Faculty of Medicine – Ain Shams University.*

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AP-1	Activator protein-1 (a transcription factor that regulates gene expression in response to cytokines and growth factors)
APC	antigen presenting cells
BcL	B-cell lymphoma/ leukemia
bFGF.....	Basic fibroblast growth factor
COX	Cyclooxygenase
DC	Dendritic cells
EGF	Epidermal growth factor
EOC.....	Epithelial ovarian Cancer
ER.....	Estrogen receptor
Ets.....	E-twenty six transcription factors.
Flt-1	Fms-like tyrosin kinase.
HER-2.....	Human epidermal growth factor receptor-2
HIF	Hypoxia inducible factor
HRE.....	Hyoxia response element
HRP	Horseradish peroxidase.
IGF	Insulin like growth factor
IL	Interleukin
KDR/FLK.....	Kinase insert domain receptor / fetal liver kinase.
KGF.....	Keratinocyte growth factor
Mabs	Monoclonal antibodies
MMP.....	Matrix metallo-proteinase
MVD.....	Mean vascular density
NO	Nitric oxide
NSAID.....	Nonsteroidal anti-inflammatory drugs
OHSS.....	Ovarian hyperstimulaiton syndrome
PA.....	Plasminogen activators
PAI	Plasminogen activator inhibitor
PDGF.....	Platelet derived growth factor

List of Abbreviations (Cont…)

PDGFR	Platelet derived growth factor receptor
PFS	Progression – free survival
PG.....	Prostaglandin
PLGF	Placental growth factor
RECIST	Response Evaluation Criteria in Solid Tumors
RTKIs	Receptor tyrosin kinase inhibitors
sVEGFR	Soluble vascular endothelial growth factor receptor
TGF	Transforming growth factor
TMB	Tetramethyl-benzidine substrate
TNF	Tumor necrosis factor
VEGF	Vascular endothelial growth factor
VEGFR.....	Vascular endothelial growth factor receptor
VHL.....	Von Hipple-Lindau
VPF.....	Vascular permeability factor
VVO	vesiculo-vacular organelle

Introduction

Ovarian cancer is the leading cause of mortality in gynecologic malignancies and the fifth most common cause of death among all malignancies in women. The patient's best chance for prolonged survival is provided through complete resection of all macroscopic disease. The prognosis is worse if the patients have 2cm or larger residual tumor after primary cytoreductive surgery. For this reason, the prediction of optimal resectability is important *(Saygili et al., 2002).*

Angiogenesis is an essential requirement for tumor growth and metastasis. Without angiogenesis, tumors grow as in situ and will not expand beyond 2-3mm in diameter. VEGF is the most important angiogenic factor *(Shen et al., 2000).*

VEGF is crucially involved in various steps of ovarian carcinogenesis. VEGF expression as well as serum levels were shown to be associated with dismal prognosis of ovarian cancer (Shortened disease – free and overall survival) *(Hefler et al., 2006).*

Currently, angiogenesis appears to be the most promising therapeutic target for ovarian cancer and large phase III trials with anti angiogenic therapeutics are conducted world wide *(Mahner et al., 2010).*

Aim of the Work

- Evaluation of preoperative serum VEGF levels in ovarian carcinoma in relation to various clinical, surgical and pathological variables (age, histo-pathological type, stage, grade, omental and L.N metastasis, presence of ascites, level of cytoreduction and recurrence).
- Follow up of cases of ovarian cancer with serial evaluations of serum VEGF, 3,6 and 12 months postoperatively.
- Correlation between serum VEGF and CA125 levels.

Chapter (1)

Biology of Vascular Endothelial Growth Factor

Structure of VEGF:

Vascular endothelial growth factor (VEGF) is a disulfide-linked, 34-45 KD homodimeric glycoprotein expressed by a wide variety of normal and transformed cells. Alternatively known as vascular permeability factor (VPF), VEGF was originally noted for the ability to increase microvascular permeability, and subsequently for the capacity to act as a selective endothelial mitogen *(Nowak et al., 2008)*.

VEGF/VPF is a basic, heparin binding, glycoprotein, which binds specifically to receptors on endothelial cells. It has specific mitogenic activity on endothelial cells, and it is apparently devoid of mitogenic activity for other cell types *(Woolard et al., 2009).*

Members of the VEGF family include VEGF-A (hereafter VEGF), VEGF-B, VEGF-C, VEGF-D and VEGF-E (a virally encoded protein) and placental growth factor (PlGF), all showing various degrees of homology with VEGF *(Girling and Rogers, 2009).*

The most significant of the VEGF family is VEGF-A that is produced in five isoformes, generated by alternative splicing of the VEGF-A gene *(Fraser, 2006).*

The isoformes are composed of 206-, 189-, 165-, 145-, and 121-amino acid residues (fig. 1). The shorter isofmres, VEGF 145 and VEGF 121, are acidic, do not bind heparin, and are secreted peptides that may act as diffusible agents. The longer isoformes, VEGF-189 and VEGF-206 are basic, with a high affinity for heparin, and remain sequestered in the extra cellular matrix, presumably bound to heparan sulfate proteoglycans. VFGF-165 which is the predominant molecular species is in part secreted and in part matrix bound *(Ferrara, 2004).*

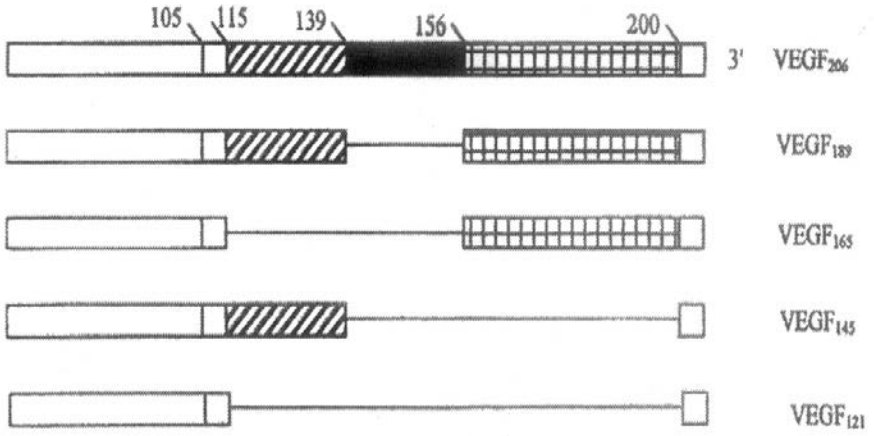

Fig. (1): Structural motifs of VEGF exonic regions in the cDNA that encodes VEGF/ VPF products, full-length form VEGF206, and alternatively spliced transcripts encoding 121-, 145-, 165, and 189-aa VEGF isoformes *(Geva and Jaffe, 2000).*

The various isoforms not only differ in efficiency of secretion and affinity for heparin, but also in the relative potency of vascular permeabilizing and mitogenic activities *(Bastide et al., 2008).*

The human VEGF-A gene has been localized to chromosome 6p21.3, composed of eight exons, separated by seven introns *(Geva et al., 2000).*

The primary VEGF-A transcript derives from a single VEGF-A gene, coding for eight exons. The amino acids encoded by exons 1 to 5 and 8 are conserved in all isoformes, whereas variable alternative splicing occurs in exons 6 and 7, which encode two distinct heparin-binding domains. The presence or absence of these domains influences solubility and receptor binding. The heparin-binding domain encoded by exon-6 determines binding to the extra-cellular matrix, and therefore isoformes containing this domain (VEGF-A 189 and VEGF-A 206) are bound tightly to cell surface heparin- containing proteoglycans in the extra-cellular matrix, whereas those lacking the domain are diffusible. VEGF-A 165, which contains only one heparin-binding region encoded by exon7, is moderately diffusible, and VEGF-A 121, which lacks the domains encoded by both exons 6 and 7 is highly diffusible *(Hoeben et al., 2004).*

Plasmin liberates the heparin binding forms of VEGF that can bind to cell-surface and extracellular