Ain Shams University
Faculty of Medicine
Obstetric and Gynaecology department

BCL2 Oncogene Expression in Normal Endometrium , Endometrial Hyperplasia and Endometrial Carcinoma

Thesis
Submitted for Partial Fulfillment
of Master Degree in Obstetric and
Gynaecology

Presented by
Manar Ismail BassiounyHannout
M.B. , B.Ch.
Ain Shams University

Under Supervision of

Dr. Ali Elyan Kalaf Allah
Professor of Obtetric and Gynaecology
Ain Shams University

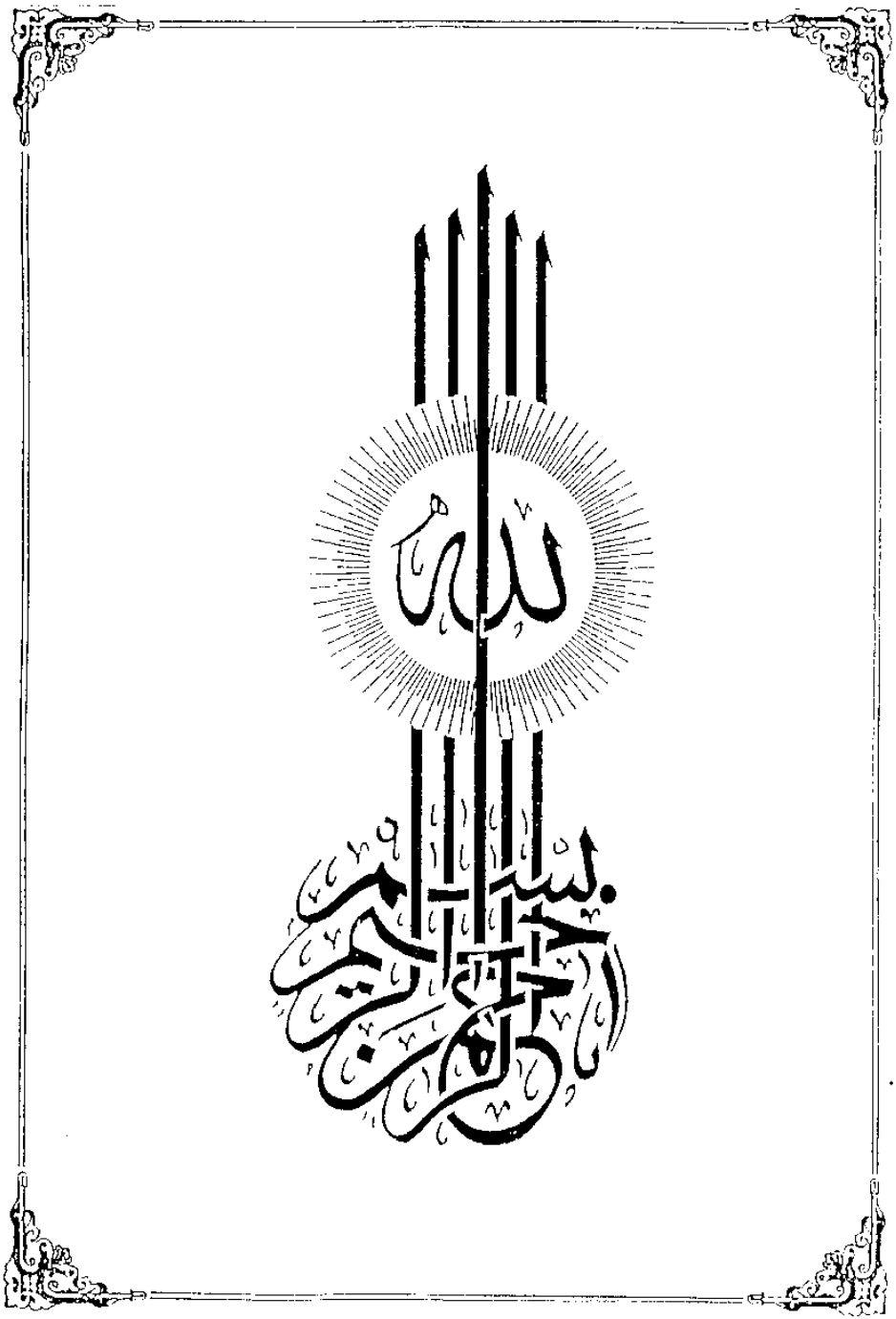
Dr. Mohamed Ahmed Laban
Lecturer of Obstetric and Gynaecology
Ain Shams University

Dr. Mohamed Saber Mohamed
Lecturer of Histology
Ain Shams University

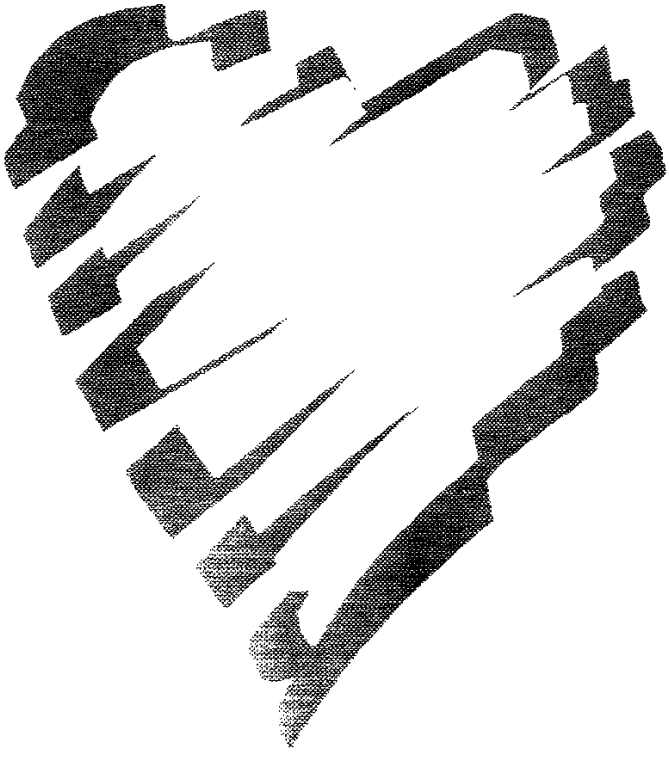
1998

بسم الله الرحمن الرحيم

" وقل ربي زدني علماً "



To my Family



ACKNOWLEDGEMENT

First, I must thank God for the enormous help and supports allowing me finish this thesis and present it in this final form.

Special thanks and my deepest gratitude to ***Prof. Dr. Ali Elyan, Professor of Obstetic and Gynaecology*** *for his supervision and fatherhood support which help me a lot in carrying out this work.*

I would like to extend my special thanks to ***Dr. Mohamed Laban, Lecturer of Obstetic and Gynaecology*** *for his valuable assistance, advice and remarks as well as his patiancy, which I appreciated very much.*

I also appreciate the kind help of ***Dr. Mohamed Saber, Lecturer of Histology*** *for assisting me in the tecnical part of my work.*

Finally, I would like to express my deepest thank and gratitude for every one helped me in presenting this work specially ***The Scientific Research and Technology Academy*** *and all my professors whom without their help this thesis would have never seen in its current form.*

LIST OF CONTENT

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION
&
AIM OF WORK

INTRODUCTION

A well-established concept about growth kinetics of a neoplastic cell population is that an increase in the latter is the result of the two main processes of cell production and cell loss. Cell loss, which is a primary characteristic of solid tumour growth, is due to different biologic mechanisms, including spread, differentiation and death. Cell may be caused by external events such as immune reaction necrosis) or under genetic control (apoptosis). It has been often claimed that apoptosis (programmed cell death) is a determinant of in vivo tumour growth and development and is largely responsible for continuous cell loss on many solid tumours. Experimental evidence supports the role of oncogenes and tumours suppressor genes in regulating the expression of programmed cell death. Convincing data indicate that BCL2 proto-oncogene to be responsible for specific prevention of apoptosis in several situations *(Silvestrini R et al 1994)*

BCL2 gene, the first gene identified that inhibit apoptosis, whose name derived from its association with B-Cell lymphona. It has been identified by its proximity to a translocation site on chromosome 18q21. The BCL2 protein has been localized to the membrane of mitochondria, the nuclear envelope and endoplasmic reticulum. This gene was at first detected in follicular and diffuse lymphomas and has also been detected by immunchistochemical procedures in a limited number of non-lymphoid tissues under different physiologic conditions *(Pietenpol JA.1994)*

Programmed cell death "apoptosis" is an active cellular process characterized by distinctive morphological changes that include condensation of nuclear chromatin, cell shrinkage, disruption of cytoskleton and plasma membrane blebbing. The molecular hallmark of apoptosis is degradation of the cell's nuclear DNA into oligonucleosomal length fragments, as the result of activation of endogenous endonucleases.

Apoptosis, plays an important role in a wide variety of phsiological situation. In hematopoietic system, apoptosis is thought to maintain cell number at homeostatic level. In mammals, theBCL2 gene was found to regulate cell death (apoptosis). When exprewssed in transgenic mice, BCL2 prolongs cell survival. Expression of BCL2 can prevent programmed cell death of myeloid and lymphoid cells when certain growth factors are withdrawn. It can also prevent death of neurons deprived of nerve growth factor and prevent cell deaths mediated by c-myc expression, furthermore BCL2 can block p53 mediated apoptosis. BCL2 can not, however, prevent all types of phsiological cell deaths, as expression of BCL2 fails to protect cells against cytotoxic T-cell killing. There are therefore, at least two phsiological cell-death mechanisms:

1) those regulated by BCL2 as in many cases of growth factor withdrawal, and
2) cytotoic T-cell killing upon which BCL2 has no effect.

The ability of ced-9 to inhibit programmed cell death in c-elegans resembles the ability of BCL2 gene to inhibit apoptosis in mammalian cells. Recent work has shown that expression of the human BCL2 gene

in c-elegans prevents cell deaths that are normally mediated by ced-3 and ced-4. This is strong evidence that BCL2 is the homologus of ced-9 and implies that BCL2 is likely to act in mammalian cells by inhibiting the effect of the mammalian homologues ced-3 and ced-4 ***(Vaux DL 1993)***.

The effect of BCL2 are not limited to protecting cells from growth factor withdrawal. BCL2 protects mammalian cells from sodium azide, colchicine, DNA, RNA and protein synthesis inhibitors, steroids, heat shock and irradiation ***(Baffy G et al 1993)***.

Role of BCL2 in oncogenesis:

Transfection of BCL2 into NIH3T3 cells, although failing to induce transformation in vitro causes tumouras when transfected into normal haemopoietic cells does not immortalise them or induce proliferation but prolongs cell survival of growth factor deprived hoemopoietic cell line. Transfected BCL2 in association with activated transgenic c-myc gene prolongs cell survival and occasionally promoted proliferation which is growth factor independent ***(Barada M 1992)***

Rossella Silvestrini etal 1994 studied the BCL2 protein as a prognostic indicator strongly related to P53 protein in lymph node-negative breast cncer patient and they found that a significantly higher fraction of BCL2 positive cells was observed in small ER-positive, slowly proliferating, and P53-negative tumors than in large, ER-negative, rapidlyproliferating, and P53-positive tumours. A strongerassociation was observed between BCL2 and P53 expression than between these variables and

[3H]thymidine-labeling index. In univariate analysis, BCL2 and P53 expression, [3H]thymidive-labeling index, tumor size, and ER status were indicaters for relapse-free and, with the exception of tumor size, over all survival within 6 years of surgery.

It is widely recognized that endometrial carcinoma represents the most frequent type of genital malignancy in women. Endometrial hyperplasia has been linked with endometrial cancer for many years and it has since long been proposed to be a precursor of endometrial cancer.

Cancer is considered to be a genetic disease in on theory of its etialogy and from the study of celkular genes, it was derived a greater understanding of the molecular events that occur in tumour cells and many of the players that orchestrate normal cell growth and differentiation, they include the viral oncogenes and their cellular counter parts, the proto-oncogenes which are highly conserved during vertebrate evolution and which may provide the substrate upon which the mulfitude of carcinogenic stimuli can play.

Multiple risk factors for endometrial cancer have been identified and divided into three categories: variant of normal anatomy or physiology, frank abnormality or disease and exposure to external carcinogens. Obesity, nulliparity and late menopause are all variants of normal anatomy or physiology classically associated with endometrial carcinoma, these factors appear to have 5 fold increase in the risk of endometrial cancer. Diabetes mellitus and hypertension are frequently associated with endometrial cancer, a prophylactic use of tamoxifen in women without breast cancer increase the rixk of