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**BCI2 Oncogene Expression in Normal
Endometrium , Endometrial Hyperplasia and
Endometrial Carcinoma**

Thesis
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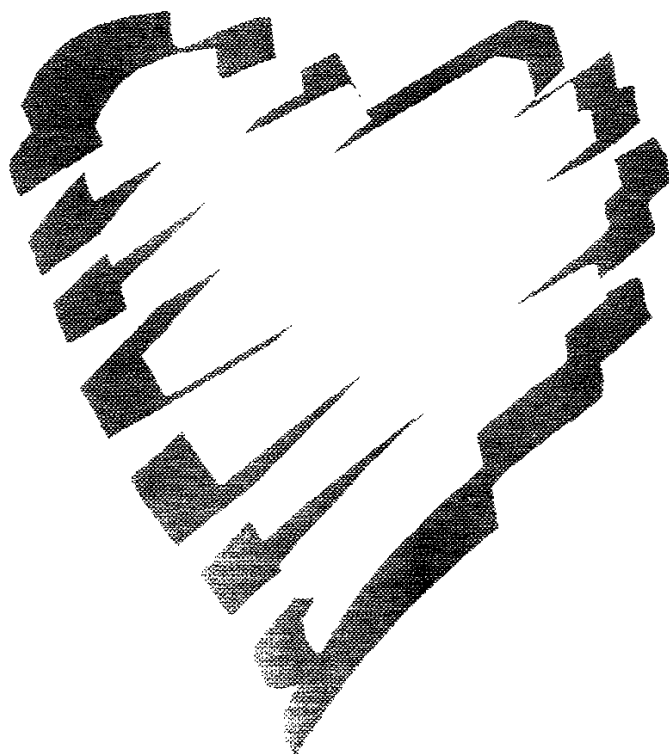
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بسم الله الرحمن الرحيم
"وقل ربّي زدني علماً"



To my Family



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**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 lymphoma. 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 immunohistochemical 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 cytoskeleton 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 physiological situation. In hematopoietic system, apoptosis is thought to maintain cell number at homeostatic level. In mammals, the BCL2 gene was found to regulate cell death (apoptosis). When expressed 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 physiological cell deaths, as expression of BCL2 fails to protect cells against cytotoxic T-cell killing. There are therefore, at least two physiological cell-death mechanisms:

- 1) those regulated by BCL2 as in many cases of growth factor withdrawal, and
- 2) cytotoxic 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 tumours 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-mycene prolongs cell survival and occasionally promoted proliferation which is growth factor independent (Barada M 1992)

Rossella Silvestrini et al 1994 studied the BCL2 protein as a prognostic indicator strongly related to P53 protein in lymph node-negative breast cancer 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]thymidine-labeling index, tumor size, and ER status were indicators 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 etiology and from the study of cellular 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 multitude 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 risk of