Prolactin receptor expression in breast cancer

Thesis

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Abbreviation List

Aa ..... Aminoacid

AC ..... Alkylating agent chemotherapy

AIs ..... Aromatase inhibitors

AJCC ..... American Joint Committee on Cancer

Asn ..... Glycosylation site of PRLR

ASR ..... Age Standardized Rates

BCIS ..... Breast Cancer in situ

Bcl2 ..... Anti apoptatic gene

BMI ..... Body Mass Index

BRCA1 ..... Breast Cancer Gene 1

BRCA2 ..... Breast Cancer Gene 2

CBE ..... Clinical breast examination

CMF ..... Cyclophosphamide Methotrexate Flurouracil

C-Src ..... Cellular Tyrosine Kinase Protein encoded by CSK gene

Cyclin-E ... One of the key regulators of the G1/S transition in the cell cycle

DCIS ..... Ductal Cancer in situ

EBCTCG .. Early Breast Cancer Trialists' Collaborative Group

ECD ..... Extracellular ligand-binding domain

EGF ..... Epidermal growth factor

EGFR ..... Epidermal growth factor receptor

EHBCCG . Endogenous Hormones and Breast Cancer Collaborative Group

EPIC ..... European prospective investigation in cancer

EpoR ..... Erythropoietin receptor

ER ..... Estrogen receptor

GHR ..... Growth hormone receptor

HBL 100 ... Human breast epithelial cell line

Her-2 ..... Human epidermal growth factor receptor2

HT ..... Hormonal Therapy

ICD ..... Intracellular signalling domain

IDC ..... Invasive duct carcinoma

IFNAR1 .... Interferone receptor type 1

IGF ..... Insulin-like growth factor

IGFBP ..... Insulin growth factor binding protein

IHC ..... Immunohistochemistry

ILC ..... Invasive lobular carcinoma

JAK2 ..... Janus Kinase

KI 67 ..... Protein encoded on the MKi67 gene for cellular proliferation

LCIS ..... Lobular Cancer in situ

m(Ab) ..... Monoclonal antibody

MECC ..... Middle East Cancer Consotrium

MRI ..... Magnetic resonant image

NCI ..... National Cancer Institute

Nek 3 ..... Serine/thereonine-protein kinase encoded by the NEK3 gene

NHS ..... Nurse Health Study

P53 ..... Protein 53 (tumor suppressor protein) encoded by TP5 gene

PALB2 ..... Partner and localizer of BRCA2 gene

PBS ..... Phosphate buffered saline

PCR ..... Polymerase chain reaction

PR ..... Progesterone receptor

PRL ..... Prolactin

PRLBP ..... Prolactin binding protein

PRLR ..... Prolactin Receptor

PRLRi ..... Intermediate Prolactin Receptor isoform

PS2 ..... The human pS2 gene is specifically expressed under estrogen transcriptional control in a subclass of estrogen receptor-containing human breast cancer cells

S1 ..... Short form of prolactin receptor

SEER ..... Surveillance, Epidemiology, and End Results Program

SERMs ..... Selective estrogen receptor modulators

SHBG ..... Sex hormone binding globulin

SHP-2 ..... SHP-1 and SHP-2 are two SH2 domain-containing tyrosine phosphatases

SPF ..... S-Phase Fraction

STAT5 ..... Signal transducer and activator of transcription

T47D ..... Human ductal breast epithelial tumour cell line

TM ..... Trans membrane domain

TPoR ..... Thrombopoietin receptor

WHS ..... Women Health Study

Introduction

Breast cancer in women is a major public health problem throughout the world as it is the most common cancer among women in both developed and developing countries. One in ten of all new cancers diagnosed worldwide each year is a cancer of the female breast. It is also the principal cause of death from cancer among women worldwide. More than 1.1 million cases are diagnosed and more than 410,000 patients die of it worldwide **(Ferlay et al., 2004).**

Breast cancer in Egypt

Over the last few years, Cancer Registries in North Africa (Morocco, Algeria, Tunisia, Libya and Egypt) increased in number from one to nine **(Roberto et al., 2009).**

In Egypt, breast cancer is the most common cancer among women, representing 18.9% of total cancer cases **(Elatar, 2002).**

Histologic types of breast tumor

The most common histologic types of breast cancer are ductal and lobular carcinoma. Ductal carcinoma in situ constitutes 80-85%, while lobular carcinoma accounts for only about 5% (**Li & Daling, 2007)**.

With respect to tumor biology, ductal carcinoma in situ is considered a precurser of invasive breast cancer **(Warnberg et al., 2001 & Li et al., 2006).**

With respect to invasive disease, approximately 70-73% of invasive breast cancers in developed countries are invasive ductal carcinoma and 13-16% are invasive lobular carcinomas. The remaining 15% of invasive cases is composed of a heterogenous group of several histological variants, each of which account for no more than 2% of all invasive cases **(Levi et al., 2003).**

Molecular / genetics profile

Molecular and genetics markers are widely used to discriminate subtypes of breast cancer. The distinction of tumor subtypes on the basis of tumor marker expression, particularly the distinction between tumors that express estrogen receptor (ER+) and those that do not (ER-), Correlates well with previously described phenotypic classification and has prognostic significance. Individual assays for tumor markers, including PR, HER2, P53, epidermal growth factor receptor, and especially ER, have become common clinical practice because of their utility in selecting targeted therapies and in predicting clinical course **(Li et al., 2003).**

Prolactin

PRL is a polypeptide hormone secreted by the anterior pituitary. It functions systemically as a classical endocrine factor. PRL is known since many decades to be a potent differentiation factor for the mammary epithelium **(Ben-Jonathan et al., 2008).**

It is a 598 amino acid residues (aa) glycoprotein with an electrophoretic mobility of 80-85 kDa. Upon ligand binding and sequential dimerisation it activates multiple signalling systems including Jak2/STAT5, STAT3, MAPKp44/42 and PI3K pathways **(Ben-Jonathan et al., 2008).**

PRL exerts its actions via prolactin receptor (PRLR), a member of the cytokine receptor superfamily. These receptors are nontyrosine kinases, single-pass transmembrane proteins organized into three domains: an extracellular ligand binding domain (ECD), a hydrophobic transmembrane domain (TM) and an intracellular signalling domain (ICD). Multiple PRLR isoforms resulting from alternative splicing events have been identified. Most of them are similar in their ECD, but differ in the intracellular part **(Clevenger et al., 2003).**

Thus, multiple isoforms potentially can activate distinct intracellular signalling events. The long receptor isoform was studied in details **(Clevenger et al., 2003)**. It has been suggested that the long isoform is responsible for the pro-