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Biomarkers used for ovarian cancer – an overview

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ABSTRACT

Disease progression is a complex process which involves multiple sequential steps leading to cellular changes, altered signaling pathways and metabolic events. Cancer is a very wide spread disease in the world. Among the various types of cancers, ovarian cancer is the leading cause of death in gynecological malignancies. Biomarkers are cellular, biochemical, molecular or genetic alterations by which a normal, abnormal or simply biological process can be predicted or monitored. Various Biomarkers like Cancer Antigen 125, HCG, Human Kallikreins, Membrane Tyrosine Kinase Receptors, HE 4 and Mesothelin etc. are used to identify pathological processes before individuals become symptomatic or to identify individuals who are susceptible to cancer.

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Introduction

Disease progression is a complex process which involves multiple sequential steps leading to cellular changes, altered signaling pathways and metabolic events. [1] Cancer is a very wide spread disease in the world. It proceeds through the accumulation of genetic and epigenetic changes that allow cells to break free from the tight network of controls that regulate the homeostatic equilibrium between cell propagation and cell death. [2]

Among the various types of cancers, ovarian cancer is the leading cause of death in gynaecological malignancies. It starts in the ovaries--the female reproductive organs that produce eggs but that tends to exhibit scant, vague symptoms such as bloating and feeling full quickly. [3] It consists of serous, endometrioid, mucinous and clear cell histological types.

Till date there is no accurate non-invasive diagnostic test for the various types of ovarian cancer. [4, 5] Intensive clinical research studies are going on for the development of newer and early detection therapies in ovarian cancer. So, detection of the genetic, molecular and clinical actions enables the development of target based therapy and aids in preventive measures [1] including the development of biomarkers. [6]

Biomarkers

Biomarkers are cellular, biochemical, molecular or genetic alterations by which a normal, abnormal or simply biological process can be predicted and/or monitored. They are measurable in biological media, such as human tissues, cells or fluids. [6] Many biomarkers with potential clinical applications are discovered due to the advances in fields of genomics, proteomics and molecular pathology.

Biomarkers are used to identify pathological processes before individuals become symptomatic. It also helps to monitor patients with established cancer for recurrence as well as early detection of asymptomatic patients. They are also aiding in the diagnosis of symptomatic patients, surveillance of individuals known to be at high risk of cancer. [7]

The ideal biomarkers should easy to measure using standardized and inexpensive methods and have a clearly defined cut-off value. It should have high predictive power (high sensitivity and specificity) and able to express in accessible material like cells and body fluids. [8]

There are mainly three types of biomarkers which include DNA biomarker, RNA biomarker and Protein biomarker.

DNA Biomarker

DNA based biomarkers are Single Nucleotide Polymorphism (SNP), chromosomal aberrations like translocation of BCR-ABL genes, change in DNA copy number, instability of microsatellite and change in methylation of promoter-region of gene. Mutations in oncogenes, tumour-suppressor genes and mismatch-repair genes can also serve as DNA biomarkers.

RNA Biomarker

RNA based biomarkers are differentially expressed transcripts and regulatory micro RNA. Pattern-based RNA-expression analysis has provided increased prognostic capability [9] and also response to neoadjuvant therapy. [10] The transcript levels of enzymes are important for melanoma, leukaemias, lymphomas and carcinomas of the lung, prostate and colon. [11, 12]

Protein Biomarker

Protein biomarkers are cell membrane receptors like CD20, tumor antigens, carbohydrate determinants. The expression of HER2/NEU and cytokeratins can be used to refine the prognosis of breast cancers.

As pattern-based RNA biomarkers frequently outperform single RNA markers in tumor classification, prognosis or prediction of response to therapy, protein-based 'fingerprints' may outperform individual protein markers.

Biomarkers can be identified with the help of Genomic techniques (Northern blotting, Microarray), Proteomic techniques (2D-PAGE, LS/MS, SELDI-TOF), Metabolomic techniques (Analysis of metabolic pathways) and Lipidomic techniques (Analysis of lipids). [13]

Because of its influence in disease and in several normal physiological conditions such as age, genetic and environmental factors restrict their role in certain circumstances. [1] In this review, we are focusing in ovarian cancer biomarkers, their uses in detection, diagnosis and prognosis of ovarian cancer.

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Cancer Antigen 125 (CA125)

Cancer Antigen 125 (CA125) is a high-molecular weight (200 to 500 kDa) glycoprotein, also known as muc16 that binds to a monoclonal antibody. [14, 15] Its expression was associated predominantly with the Go/G_1 phase of the cell cycle. Interferons may stimulate the cell surface presentation of several tumor-associated antigens and in particular interferon has been found to induce the expression of Cancer Antigen 125 in ovarian cancer cell line in vitro. [16] The addition of dexamethasone to interferon treated cells increased Cancer Antigen 125 expression synergistically. It is reported that serum levels of CA 125 is elevated in stage II ovarian cancers [17] as well as multiple benign diseases both gynecological and non-gynecological conditions. [18, 19] It is a useful indicator of ovarian cancer recurrence, but as a biomarker for presymptomatic detection, it has low sensitivity and low specificity. CA 125 levels are elevated in people who have pancreatitis, kidney or liver disease, indicating its limited utility as a cancer diagnostic tool.

Human Chorionic Gonadotrophin (HCG)

Human Chorionic Gonadotrophin (HCG) is a hormone produced normally by the placenta, whose level is elevated in the blood of patients with certain types of ovarian cancers (Germ cell tumours) and choriocarcinoma. [20]The presence of increased serum levels of Human Chorionic Gonadotrophin and its metabolites is generally considered to be a sign of a poor prognosis and it has been suggested that HCG might directly modify the growth of the cancer, leading to a worse outcome. The clinical use of free HCG as a tumor marker has been limited to a small number of patients owing to a short half life and rapid renal clearance. [21] An elevated blood level of Human Chorionic Gonadotrophin is also be found in the urine of pregnant women and therefore may not be useful as a marker under this condition. [22]

Human Kallikreins

The human tissue kallikrein family consists of 15 genes, encoding each a secreted serine protease with trypsin or chymotrypsin like activity. [23] All the 15 genes are located on chromosome 19q13.4 having similarities in significant homology at the nucleotide level, protein level and similar genomic organization. [24, 25] Some of these proteases are involved in several cancer related processes including cell-growth regulation, angiogenesis, invasion and metastasis. [26, 27] Twelve kallikrein genes have been found to be up-regulated in Epethelial Ovarian Cancer (EOC) and many kallikreins hold promise as diagnostic and prognostic biomarkers for this malignancy. [26, 28] Moreover, Luo et al. [29] reported that elevated serum human kallikrein 10 was significantly related to advanced stage, serous histotype, high-tumour grade, large residual disease, lack of response to chemotherapy and poor survival.

Human Telomerase Reverse Transcriptase

Telomeres are specific DNA–protein complexes, located at the ends of chromosomes; those are progressively shortened with each cell division [30]. It is a ribonucleoprotein enzyme complex that uses its own integral RNA as a template for synthesis of telomeric repeats to compensate for the normal loss of terminal DNA sequences during mitosis. [31] The human Telomerase Reverse Transcriptase (hTERT) represents the catalytic subunit of this enzyme complex. [32] An immuno-histochemical study on archival tissue sections showed a moderate to strong nuclear human telomerase reverse transcriptase staining in serous epithelial ovarian cancers. [33] The prognostic relevance of human telomerase reverse transcriptase in epithelial ovarian cancers and survival for patients is still need to be detected.

Membrane Tyrosine Kinase Receptors

Epidermal Growth Factor Receptor (EGFR), also named ERB1, is a plasma membrane tyrosine kinase receptor. Hepatocyte growth factor receptor (c-Met) is a tyrosine kinase receptor, which sends signals to the nucleus via the Mitogen Activated Protein Kinase (MAPK), the phospholipase C/protein kinase C and the phosphatidylinositol 3-kinase (PI3K) pathways. Moreover, epidermal growth factor receptor may also enter the nucleus and directly act as transcriptional factor. [34] After binding of its ligand hepatocyte growth factor (HGF)/Scatter Factor (SF) activates MAPK, PI3K and Signal Transducers and Activators of Transcription (STAT) signaling pathways. [35] An immunohistochemical study revealed that advanced epithelial ovarian cancer had c-Met over expression. [36] Lassus et al. [37], who assessed serous epithelial ovarian cancer, observed that an increased copy number of epidermal growth factor receptor was associated with poor response to chemotherapy and shorter survival.

Soluble Epidermal Growth Factor Receptor

Soluble Epidermal Growth Factor Receptor (sEGFR/sErbB1) found in human serum is a 110-kDa glycoprotein which is encoded by a 3.0 kb alternate mRNA transcript of the epidermal growth factor receptor gene. [38, 39] Patients with epithelial ovarian cancer have considerably lower serum epidermal growth factor receptor concentrations than healthy women and also the concentrations of the soluble epidermal growth factor receptors are inversely associated with serum concentrations of follicle-stimulating hormone and luteinizing hormone. [39, 40] Serum soluble epidermal growth factor receptor concentrations seem to be most useful for detecting epithelial ovarian cancer among younger, pre-menopausal women. It can be useful in conjugation with established biomarker of ovarian cancer like Cancer Antigen 125. Moreover, sEGFR concentrations exhibit an age-disease interaction, decreasing with age in healthy women, but not in patients with epithelial ovarian cancer. [39] Altogether, these observations suggest that gonadotropic hormones may regulate serologic soluble epidermal growth factor receptor, and this regulatory pathway may be altered in patients with EOC.

Human Epididymis Protein 4

Human Epididymis protein 4 (HE 4) designated WFDC2 because it contains two Whey acidic protein (WAP) domains and a “four disulfide core” made up of eight cysteine residues. The HE 4 gene resides on human chromosome 20q12-13.1, a region that harbors a locus of 14 genes encoding protein domains that have homology with WAP. Among these WAP genes is Secretory Leukocyte Protease Inhibitor (SLPI), which is also over expressed in ovarian carcinomas. [41, 42] This marker is actually a marker of mullerian differentiation. It is distributed in a region of the cytoplasm with a perinuclear pattern reminiscent of the endoplasmic reticulum and the golgi apparatus. Ovarian carcinomas secrete HE 4 as an N-glycosylated protein. As there is only one predicted glycosylation site in it, the difference between the insect cell secreted Human epididymis 4 and the form secreted by ovarian carcinoma cells may simply reflect species-specific differences in glycosylation patterns. Human epididymis 4 is a biomarker for certain subtypes of ovarian carcinomas (i.e., serous and endometrioid types). The specificity and sensitivity of HE 4 serology is comparable to that of Cancer Antigen 125 and that HE 4 is less frequently positive in patients

with nonmalignant disease. A very real possibility is that the combination of HE 4 and CA 125 serology may result in a test with sufficient sensitivity and specificity to be used for the detection of early ovarian cancer. It is formally possible that Human Epididymis 4 is also filtered by the kidneys into the urine. If true, Human epididymis 4 may also represent an interesting target for the development of a urine test for ovarian cancer. [43]

Soluble Cytokeratin Fragments

Soluble cytokeratin fragments are soluble forms of fragments of cytokeratin, which represent important structural elements of the cell cytoskeleton. They have been identified in sera from patients with different malignancies, including epithelial ovarian cancer. [44, 45] Soluble cytokeratin fragments are useful for the detection of response to the chemotherapy but not prognostic of survival in patients with ovarian cancer. [44]

Tissue Matrix MetalloProteinases

Tissue Matrix Metalloproteinases (MMP) represent a large family of zinc and calcium-dependent proteolytic enzymes, those are able of degrading most components of the extracellular matrix and those are involved in tumor invasion and metastasis. [46] MMP-2, MMP-7, MMP-8, MMP-9 and membrane type-1 (MT1). MMP have been detected in epithelial ovarian cancer. [47, 48] MMP-9 could have a dual role in epithelial ovarian cancer by promoting tumor progression when expressed in the stroma and acting against tumor growth when expressed in tumor epithelium.

Mesothelin

Mesothelin is a 40-kDa glycosylphosphatidylinositol-linked glycoprotein present on normal Mesothelial cells. [49] In normal tissues, the expression of mesothelin has subsequently been shown to be largely restricted to mesothelial cells, although immunoreactivity has also been reported in epithelial cells of the trachea, tonsil, fallopian tube and kidney. Mesothelin has been shown to be over-expressed in ovarian carcinoma and it seems that mesothelin may be utilized as a new tumor marker as the antigenic target of a therapeutic cancer vaccine ovarian carcinoma. [50]

Conclusion:

Cancer is a very complex and unpredictable disease. There is no single evidence which states that because of imbalance or irregulation of specific metabolite or chemical the particular type of cancer happens. Ovarian cancer is the major cause of death in females. There are various invasive types of diagnostic techniques available.

But with the advancement in the technology now it is possible to search for some non invasive type of techniques. That includes the study of biomarkers present in the specific type of cancerous cells.

As biomarkers are easily measurable with high specificity and sensitivity. Currently the most used biomarkers for ovarian cancer includes CA 125, HE4 and Tissue matrix metalloproteinase.

Intensive research work is going on for the development of such biomarkers and we hope that they will be highly useful in treatment of ovarian cancer in near future.

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