TUMOUR MARKERS FOR LUNG AND BREAST CANCERS

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ABSTRACT

Cancer can be defined as uncontrolled cell proliferation, with loss of apoptosis causing tissue invasion, metastasis and angiogenesis. Among the various cancers, lung cancer and breast cancer are the most common dominant cause for death in India. It was observed that out of 40,000 cases of lung cancer, 80% patient die within one year of detection of disease and only 5% survive for more than 5 years. Breast cancer is one of the most fatal cancers in the women especially middle aged and ranked one among Indians female. It has shown the highest mortality rate of 12.7 per 100,000 women. If specific biomarkers are identify for lung and breast cancer at its early stage then it will be very helpful in treatment of cancer. Predictive markers like HER2, BRCA1, CEA, CA-125, CA 15-3 are such markers with high accuracy, present in human plasma samples. It was observed that over 2/3 of cancer diagnosed at late stage the survival ratio is decreased <5 years. Therefore, the core purpose of this review is to identify such markers useful for detection of lung and breast cancer and to study them in detail.

Keywords: Lung and Breast Cancer, Biomarkers, CEA, CA-125, CA 15-3

1. INTRODUCTION

Lung cancer and breast cancer are common cancers which severely threaten human health. Each year around 17% of new cases are found for lung cancer and around 12-15% breast cancer patients were found. Lung cancer is most common in male whereas breast cancer is most common in female. In both the cancers, it is very difficult to identify the occurrence of disease in the early stage as they both are mostly asymptotic in the beginning. When the disease reached to higher level i.e late stage 2 or stage 3 then it generally show symptoms. This advance level of cancers reduces the chances of survival [1, 2] Generally positron emission tomography (PET) scan is used to identify the cancer. In addition to this determination of concentration of specific biomarkers in serum can be an important parameter for diagnosis of cancer. Tumor biomarkers are found in blood, tissue and urine and it is produced by tumor cell itself or by the host cell against the response to a malignant cell [1-3]. An ideal biomarker (tumor marker) should be sensitive, specific and should be detectable in small quantity also. Biomarkers may be immunohistochemcial marker and cell surface markers produced by genetic abnormality and hematological tumor. Various methods are available for determination of such biomarkers. Most of the methods are based on the immunological assay. These markers are used for detection of cancer with stage as well as level of recovery [4, 5]. Certain markers are diagnostic but most of them are prognostic. Combination of tumor marker detection and radiological assay gives very accurate information about cancer. In this review certain important biomarkers of lung and breast cancer are covered. This includes HER2, CEA, KRAS, ER, PR, CA15-3 and CA 125 [6-9].

2. BIOMARKERS

2.1. Human Epidermal Growth Factor Receptor 2 (HER2)

HER2 is a transmembrane receptor molecule belonging to epidermal growth factor receptor family. Its over-expression is often found associated with certain cancers. Especially in case of breast cancer, it acts as a key element for determination of tumor progression and development. HER2 is synthesized by ERBB2 gene which is a proto-oncogen. HER2 is associated with activation of many signaling pathways like mitogen activating protein kinase (MAPK), phospholipase C, protein kinase C (PKC), phosphoinositide 3-kinase, signal transducer and activator of transcription (STAT). It also promotes cell proliferation and opposes apoptosis. In breast cancer over expression of HER2 is observed in most of the cases. It is also associated with recurrence of cancer. In addition to

breast cancer, its expression level also increase with ovarian cancer, stomach cancer, adeno-carcinoma of lung, uterine cancer, gastric cancer and salivary duct carcinoma. In the common mechanism HER2 proteins are clusters together on the cell membrane and may cause tumorigenesis. HER2 level can be determined by immunohistochemical method or by fluorescence in situ hybridization (FISH). Both these methods are more accurate and reliable than the conventional cell extraction method. These methods permit to evaluate tumor cells directly along with morphological features [7, 8, 10-15].

2.2. Carcinoembryonic Antigen (CEA)
CEA is a group of highly similar glycolipids which play a vital role in cell adhesion. Production of CEA starts during the fatal development at the gastrointestinal tract and continue until the birth. During the entire life an adult may have upto 4ng/mL of CEA. But in certain cancers its level is elevated giving an important indication about the disease. At time it is seen that smokers have high concentration of this molecules. CEA was first identified by Phil Gold and Samual Freedman. It is found to be prominently associated with colon cancer. Sialofucosylated glycoforms of CEA serves as a ligand for colon carcinoma. In addition to colon cancer, its level is also raised in breast carcinoma, lung carcinoma, gastric carcinoma, pancreatic carcinoma, thyroid carcinoma and cirrhosis. CEA is produced by 29 gene various genes. Out of these 29, 18 expresses normally. But abnormality in the gene may affect its expression. Level of CEA provides vital information about tumor like its differentiation, grade, involvement of lymph node and metastasis condition. Level of CEA can be easily detected by immunohistochemical methods.[1, 6, 16]

2.3. KRAS
KRAS is responsible for production of an important protein K-Ras. This protein is a vital molecule for RAS/MAPK pathway which relays signal for outside to the nucleus. These signals are essential for growing and dividing cells. It also gives signals for maturation and differentiation. The proto oncogen KRAS is a Kirsten ras oncogen. Elimination of a single amino acid at specific nucleotide sequence activates the mutation and results into production of transformed protein. Such kind of proteins is often found associated with lung adenocarcinoma, ductal carcinoma and colorectal cancer. Level of KRAS mutation along with other biomarkers can help in diagnosis and treatment of various cancers. For example, in case of lung cancer if the patient shows KRAS mutation and EGFR wild type will have very low response rate against gefitinib or erlotinib. Mutation in KRAS gene will not only affected it proteins but will also affect the other gene of downstream genes.[9,17,18]

2.4. Anaplastic Lymphoma Kinase (ALK)
ALK is also known as ALK tyrosine kinase receptor which is produced as a result of ALK gene. ALK is responsible for cellular communication and normal function of nervous system. ALK is also found to be associated with visual system and development of synapses. It also plays a vital role in regulation of behavioral responses to various stimulating agents. It may also contrains and restricts learning and long term memory. There are various ways by which the ALK gene can be converted into oncogens. Fusion with other genes, gaining extra copies of additional genes and mutation in the actual gene are the route of mutation. In case of adenocarcinoma of lung ALK gene is fused with EML4. Expression of this gene can be determined by fluorescence in situ hybridization and RT-PCR. Its' over expression is also associated with inflammatory myofibroblastic tumors, breast cancer, anaplastic thyroid cancer, renal cell carcinoma [19-22].

2.5. Estrogen Receptors (ERs)
ERs are a group of intracellular proteins which acts as receptors and activated by hormone estrogen. ER was first identified by Elwood Jensen. There are two main classes of ERs namely ERα and ERβ. There is a high correlation seen between the breast cancer and ERs. More than 70.0% of breast cancer patients show ER positive. Immunohistochemistry is one of most common and reliable method for determination of ER concentration. ERs are also found associated with ovarian cancer, colon cancer, prostate cancer and endometrial cancer [13, 23, 24].

2.6. Progesterone Receptor (PRs)
PR is an intracellular enzyme which is also known as NR3C3. It is a nuclear receptor of subfamily 3, group C, member 3 protein. It requires progesterone for its activation. PGR gene is responsible for PR synthesis. It is found in two isoforms PR-A and PR-B. PR-B acts as a positive regulator and PR-A acts as a negative regulator. PR is mostly found associated with breast cancer. Higher expression of PRs is generally found associated with breast cancer and endometrial cancer. It was observed

that person having ER/PR positive responses to hormone therapy very well [8, 16, 25].

2.7. Breast Cancer Type 1 (BRCA1)

BRCA1 is a known to suppress tumor gene and also responsible for DNA repairing. BRCA1 and BRCA2 are proteins which expresses normally in breast and other tissue. If any of the BRCA is mutated than it will not repair the DNA but increases the risk of breast cancer. It was also observe that BRCA1 also increases the risk of prostate and ovarian cancers. Mutation in BRCA1 can be detected using nucleotide sequencing using qualitative PCR, multiplex PCR with short fluorescent fragments and multiplex ligation dependent probe amplification. Level of expression of BRAC1 is highly associated with the type and severity of cancer. Low or undetectable expression is associated with high grade and ducal carcinoma. Around 7%-8% women may have the mutated BRCA1 gene. Germ line mutation in BRCA1 is inherited and transferred to next generation [5, 26, 27].

2.8. Carcinoma Antigen 15-3 (CA 15-3)

CA 15-3 is a specific tumor marker for breast cancer. It is obtained from MUC1 gene. CA 15-3 is often found associated with CA 27-29. Both these markers are different epitopes for same antigen. These two markers are also found elevated in case of ovarian cancer, liver cancer, cirrhosis, sarcoidosis [6, 28].

2.9. Carbohydrate Antigen 125 (CA–125)

CA 125 is also known as cancer/carcinogen antigen 125. It was discovered by Robert Bast and Robert Knapp. It is produced by the expression of MUC16 gene. MUC16 belong to glycoprotein family. CA 125 contains more than 22k amino acids. This is the largest mucin which is associated with membrane. It plays vital role in ocular surface, female reproductive tract and respiratory tract. CA-125 is found associated with tumorigenesis. It is also found to be associated with tumor proliferation by various ways. MUC16 enhances cell to cell binding to enable the metastasis of tumor cell. It also promotes the tumor cell growth and motility. This leads to invasion of cells. It also reduces the sensitivity of drugs towards tumor cells. It is a serum marker for ovarian cancer but its elevated level is seen in most of the metastatic breast cancer patients as well as pancreatic cancer. CA 125 can be easily detected by immunohistochemical techniques [1, 12].

Based on the overall study and available literature, it was noted that biomarkers play important role in determination of cancer. Not only that they will also provide critical information about the type and severity of cancer. Specific biomarkers enable us to predict the effectiveness of treatment. However, in most of the markers, it was observed that the expression of these markers may be affected by various other factors. Hence the obtained results must be correlated with other biochemical and physiological conditions.

3. REFERENCES

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