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ADVANCES IN BIOMARKERS FOR CANCER DETECTION AND DETERMINING OF PROGNOSTIC TRAJECTORY

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The effectiveness of the treatment of cancer is dependent on the stage at which it is detected. When detected in its early stage, the treatment can be significantly improved. However, about 50% of cancers are diagnosed when they are at an advanced stage. Detection and intervention at an early stage of precancerous stage or cancer may lead to slowing or even prevention of development of cancer and reduce mortality rate. Sensitive and specific early detection technologies as well as biomarkers that aid in determining the prognostic trajectory of cancers need to be found and should be evaluated appropriately so that they play supportive role in clinical implementation.

In order to find novel biomarkers it is important to understand the changes leading to cancer. Inflammation associated with tumor has intrigued researchers in the previous few decades, since this is the hallmark of cancer[1]. Irritation, inflammation and chronic infection often lead to various cancers. Inflammatory cells help foster proliferation, survival, and spread of the neoplasm and therefore harboring microenvironment in which tumors thrive. Inflammation is being used to develop anti-cancer therapies in recent times. Several biological regulatory processes that include processes of regulation of genesis, progression and metastasis of tumor and expression of related genes are regulated by long non-coding RNAs (lncRNAs) which are non-coding RNA molecule subset[2]. These RNAs play a significant role in regulation of processes like cellular growth, development, inflammation and angiogenesis [3-6].

In recent times, a rising body of evidence suggest the regulatory network comprising of long non-coding RNAs-micro RNA-messenger RNA has a pivotal role in the development and physiology of several tumors like hepatocellular carcinoma, gastric cancer, gall bladder cancer, and other cancers [7-9]. Networks of lncRNAs- correlated competing endogenous RNAs have been noted to have involvement in various pathophysiological pathways in glioblastoma by Zhang et al.[10] .Breast cancer survival was found by Wang et al. to be significantly effected by 6 lncRNAs that includes MIR7-3HG and LINC00536 [11].

Disturbance in the metabolic pathway of glycolysis (responsible for provision of energy in the body) also results in thriving of tumors. Otto Warburg observed that more lactic acid and reduced ATP was produced in tumor cells glycolysis and caused hypoxia even when oxygen content was high. This effect is known as 'Warburg effect' [12]. Several studies have noted when glycolysis was abnormally activated or enhanced there was progression of tumor in case of colorectal cancer, liver cancer breast cancer and so on[13-15]. The lncRNA has been reported to be a significant glycolysis regulator. Glycolysis-related lncRNA can promote hyperglycolysis is many ways and in turn cause tumorigenesis, metastasis and progression[16-18]. Thus alterations in glycolysis can be a malignancy marker and possible prognostic target.

Genomic research of cancer has contributed information on alterations in genetics and targets of therapy. Genomic study in thyroid cancer reported various signaling pathways mutation[19,20]. Methylation of DNA has been reported in various cancers which includes colorectal, gastric, hepatic, and esophageal cancers[21-30]. Even though the researches are gene centric, attention is being drawn towards the 'epigenetic machinery' and its relevance in various cancers including thyroid cancer. The sub-population of cancer cells within the tumor may vary in phenotype and molecular features. Epigenetic alterations may promote this intra-tumor heterogeneity and needs to be studied further to understand its role[31,32].

Although the means of detection of cancer in its early stage remain limited, there have been advancement in the technologies in recent times that have led to certain potential biomarkers identification having high value for diagnosis and prognosis of cancers[33].Thus advancement in the field of development of biomarkers is taking place globally. The following are several studies that have reported biomarkers having such potential.

Five genes that were noted to be methylated frequently in cancer of thyroid, AP2, RASSF1A, DACT2, CDH1, and HIN1, have been identified by Zhu et al.[34]. They also made use of these genes for understanding the epigenetic heterogeneity in cancer of thyroid. It was observed in their study that an association between the development and progression of thyroid cancer and epigenetic heterogeneity exists.

Another study carried out by Liu et al. used TCGA data and observed nine autophagy-related genes (ARGs) signatures which had association with the prognosis of patients who underwent chemotherapy. Increased expression of CXCR4 was found to be associated with survival of the patient in their study[35]. Hu et al. noted an association between poor gastric cancer prognosis and high PLEC1 expression. The raised risk of gastric cancer was found to be associated with SNPs (rs3765524 C > T, rs2274223 A > G and rs3781264 T > C). In gastric carcinoma patients being treated with fluorouracil and cisplatin, the resistance to chemotherapy remains a major hurdle [36]. Prediction of gastric carcinoma, prognosis has been linked to ten differentially expressed IncRNAs in a study done by Zhang et al. IncRNAs are associated with inflammation and there may be an opportunity for therapy using these [37].

Endoplasmic reticulum stress-related genes, EMC6, CHOP, ATF6, and XBP1, as well as apoptosis-related gene (APAF1) exhibit prognostic potential in pancreatic carcinoma. This has been reported by Xiao et al and they observed that a downregulation of APAF1 and EMC6 and an upregulation of ATF6 were associated significantly with poor prognosis in case of pancreatic cancer[38].

In case of most of the carcinomas which include cervical cancer, overexpression of secreted phosphoprotein (SPP1) was noted by Zhao et al. who performed an analysis on the pan-cancer expression data. They came to the conclusion that in cervical cancer there is significant overexpression of SPP1 when compared to normal cervical epithelial tissue and may be researched in to further since SPP1 may be a prognostic biomarker of cervical cancer[39].

Centromere protein N (CENPN) may be another prognostic biomarker which was studies by Wu et al. They used the TCGA and CGGA database to CENPN's role in gliomas' pathology. Poor prognosis was found to be associated with raised CENPN expression. They noted that inflammation and immune-related signaling and immune cells infiltration was associated with CENPN[40].

In hepatocellular carcinoma, 6 genes (RACGAP1, KIF23, MYBL2, CLSPN, DEPDC1, and CEP55) have exhibited close association with infiltration of immune cells. Pu et al. has analyzed the RNA sequencing data and traits of hepatocellular cancer and concluded that these genes may be prognostic biomarkers and may be targets of therapy in this carcinoma[41].

Transcriptome and clinical data of bladder carcinoma was used by Zheng et al. to carry out glycolysis-related IncRNA and found fifty-nine differentially expressed glycolysis related IncRNAs. Out of these 9 showed prognostic value which were AC1058983.1, MNX1-AS1, ZNF667-AS1, NR2F1-AS1, AC078778.1, MAFG-DT, AL589843.1, AC099850.3, and AC011503.2. Distinction may be made between high-risk and low risk patients of bladder carcinoma using these genes[42].

A novel therapeutic was explored by Wodi et al. in the Kasumi-1 cell line model of acute myeloblastic leukemia. They used SPHINX, a 3-(trifluoromethyl) anilide scaffold, to hinder the splice factor protein kinase activity in a cell culture model of leukemia.The activity of SRSF1 (a SR protein splice factor regulator responsible for splicing alternatively several critical genes associated with cancer) is regulated by splice factor protein kinase. Alternative splicing dysregulation is a characteristic of various cancers and the researchers noted that inhibition of splice factor kinase can bebeneficial means of therapy [43].

Leukemia and lymphomas are heterogenous in nature and making distinction between them is difficult. Chronic lymphocytic leukemia may exhibit atypical presentation leading to uncertain diagnosis. Al-Zubaidi and Hughes studied a new biomarker's role with the use of immunophenotyping flow cytometry and noted that CD200 may help differentiate between the various B-cell lymphoproliferative disorders. They suggested that this biomarker can be included as a part of the routine immunophenotyping tests[44].

A meta-analysis carried out by Chohan et al. focused on oral squamous cell carcinoma and possible biomarkers that may be of use to determine the prognosis of this cancer. Investigation was done to note the role of expression of CD 163 and CD 68 by tumor associated macrophages in oral squamous cell carcinoma. The evidence found suggested that tumor associated macrophage with CD 163 expression was associated with poor oral squamous cell carcinoma prognosis while no link was observed between prognosis and CD68 positive macrophages[45].

Isocitrate dehydrogenase gene mutation may have links with prognosis of certain cancers. A study done by Murugan and Alzahrani on about fifteen thousand solid samples of malignancy of thirty seven types of carcinomas that have been stored in atlas of cancer genome. They observed the genes of isocitrate dehydrogenases 1 and 2 mutations and reported in case of cancers in general there was a 3% mutation of the gene of isocitrate dehydrogenase 1 while in case of gliomas 34% had mutation in the gene. Evidence was found to suggest that isocitrate dehydrogenase 1 mutation had association with better prognosis. They also indicated that isocitrate dehydrogenase 1 and 2 in gliomas and other carcinomas may be targeted for therapeutic purposes[46].

The key to effective early detection and halting cancer progession remains in the collaboration between different disciplines of medical science. Understanding of biology and technological advances indicate that early detection research needs to be accelerated and bring about transformation in survival of cancer effected individuals.

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