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Z-score-based approach for differential diagnosis of malignant and benign liver neoplasms using transcriptional biomarkers

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Abstract

Hepatocellular carcinoma (HCC) is the most common and aggressive type of liver tumors. It is usually diagnosed at advanced stages due to lack of clear symptoms and reliable biomarkers. HCC diagnosis is further complicated by high similarity between early HCC stages and benign liver neoplasms, especially hepatocellular adenoma. Efficient methods of HCC identification are required for establishing precise diagnosis and choosing optimal treatment strategy. Our group previously identified five genes (IQGAP3, RAB3B, GPC3, PRRX1 and CENPF) specifically overexpressed in HCC, but not in benign neoplasms or normal liver tissue. Present study evaluates the diagnostic efficiency of combinational indexes generated using expression levels of these genes and z-score approach. We examined paired samples of neoplastic and normal liver tissue collected from 50 HCC patients and 15 patients with hepatocellular adenoma or focal nodular hyperplasia. Gene expression levels were estimated using RT-qPCR, z-scores were calculated for single genes and all possible gene combinations. Z-scorebased indexes were statistically processed using cohort comparison tests and ROC analysis to evaluate their usefulness for discerning HCC samples from normal liver tissue and benign neoplasms. IQGAP3, GPC3, PRRX1 and CENPF were significantly ($p<0.05$) overexpressed in HCC samples, but not in benign neoplasms, when compared to non-tumor liver tissue. RAB3B expression was increased in benign cohort and further elevated in HCC cohort.

The most efficient combinations for HCC tissue identification were RAB3B+IQGAP3+PRRX1 (if both neoplastic and non-tumor tissue samples were used, ROC AUC=0.973) and RAB3B+PRRX1+CENPF (if only neoplastic samples were processed, ROC AUC=0.961). Both combinations displayed sensitivity and specificity levels higher than 90%. In summary, RAB3B, IQGAP3, PRRX1 and CENPF are promising biomarkers for improving HCC diagnosis efficacy. Z-score calculation is a powerful tool for combining expression levels of multiple genes into one index that can be used as an efficient biomarker. Present study was funded by RFBR according to the research project ??? 18-315-00376.

Biomarkers can be used for early detection of liver cancer.In this respect, following the occurrence of various complications of the disease, and according to the expression of different biomarkers, appropriate diagnostic and therapeutic methods can be applied.On the other hand, it should be noted that many of the introduced biomarkers are not efficientand cancer patients should not be tested, because of subsequent complications. Nevertheless, biomarkers still play an important role in the diagnosis and prognosis of liver cancer. Early diagnosis of liver cancer depends on biomarker sensitivity and specificity.Serum biomarkers such as AFP are used to diagnose liver cancer in high-risk patientswith minimal invasiveness and rapid response.Combined use of biomarkers for early detection of liver cancer is prevalent. AFP, DPC and AFP-l3 biomarkers are usedin combination every six months for liver cancer detection. Recent studies introduced novel biomarkers for accurate diagnosis and early treatment of liver cancer such as AFU, GP73 and OPN. Biomarkers such asGP73, GPC3, AKR1B10 seem to be promising but require more validation.

They have no more privilege over than AFP as demonstrates for osteopontin biomarker. Heterogeneity in meta-analysis approaches to HCC management with ultrasonography and AFP in patients of 14 countries with different and distinct outcomes justifies early cancer detection requirements. Mic-RNA can be evaluated as a diagnostic or prognostic tool or therapeutic target for liver cancer. However, inconsistency of assessed molecules measured in plasma and serum revealed discrepancy observed in researches, but mir-21 and mic-122 are promising as they were not differentially expressed in utilizing RNA sequencing. Moshiri et al. introduced some additional mic-RNAs, perhaps with more potential accuracy , but those observations remain preliminary and more investigation is required because of the lack of reproducibility of the findings.The use of immunohistochemical methods and H&E staining confirms the diagnosis of liver cancer, with routine histochemical biomarkers such as CPC-3, HSP-70, Hep Par1, CK7andArg-1. Gene target therapies also indicated good curative influence. Genomics studies indicated positive CTNNB-1 & IDH potentials in HC & IC target therapies and gene target therapies can improve prognosis of liver cancer.This study showed a variety of biomarkers related to different types of liver cancer. The new biomarkers will be put to clinical trials in the near future and open

windows of hope for early detection and definitive treatment of liver cancer. Target drugs for some biomarkers may improve the survival rate of the liver cancer patients. Further studies on the signaling pathway in which biomarkers are involved will increase our knowledge of the molecular mechanism of the progression of liver cancer. Significant advances in technology are encouraging more researchers to use those advances to better identify cancer biomarkers to find a definitive and early treatment for the liver cancer.Despite numerous studies and the introduction of numerous biomarkers.

it seems that a specific biomarker that has the ability to detect liver cancer early along with AFP has not been introduced yet. Further clinical trials in different centers are required to specify the risk of liver cancer in various populations. Comprehensive data are needed to decide and select the appropriate biomarker, and future technological advances will help achieve this goal.

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