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Review

New Developments of Gastric Cancer Biomarker Research

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Dr. Hualin Fu obtained his PhD from the University of Southern California in 2007. He did his post-doctoral fellow training in UCLA Hillbolom Islet Research Center from 2007 to 2009. He is now an Assistant Professor at Shanghai Jiao Tong University. His current research interests include epigenetic regulation specifically TET1 and p53-EZH2 pathway in gastric carcinogenesis, the relation between H. Pylori and EBV infections and gastric cancer and the effect of immune cell microenvironment on gastric cancer.

Abstract

Gastric cancer is a deadly disease with high incidence and mortality rate in China. Early detection and treatment of gastric cancer showed significantly better 5-year survival rate. Conventional screening methods of gastric cancer include barium meal or endoscopic screening. There is a great need to find new biomarkers of gastric cancer for simpler, faster, and non-invasive screening of gastric cancer. A large array of molecules such as protein markers, metabolite markers, RNA markers, breath organic molecules have been identified as potential markers of gastric screening. Among them, pepsinogens and gastrin-17 have been applied in large scale of population screening. New species of metabolite markers, microRNA markers and breath molecules may further enhance the simplicity, sensitivity and specificity of gastric cancer screening.

Keywords: Gastric cancer; Biomarker; Protein; RNA; Volatile organic compound; Metabolite

Introduction

Gastric cancer is the No. 2 cancer in China by incidence [1]. The survival rate of gastric cancer patients is often low because of the late detection of the disease [2]. Methods are urgently needed to screen patients with possible gastric cancer diseases at early stage of development. The purpose of gastric cancer

biomarker research is to find early markers of gastric cancer with possible applications of gastric cancer early detection. Traditional gastric cancer biomarkers are usually serum protein markers. Today, the definition of cancer biomarkers is extended to other type of molecules such as RNAs, small molecular metabolites or even volatile organic gas molecules from breath (Fig. 1). In this short review, we will summarize the recent progress on the gastric cancer biomarker discovery.

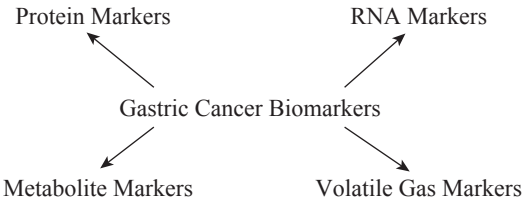

Fig. 1 Summary of gastric cancer biomarkers.

Serum Protein Biomarkers of Gastric Cancer

Serum protein biomarkers of gastric cancer can be divided by gastric cancer-specific markers and general tumor markers. A group of serum protein biomarkers of gastric cancer are gastric tissue specific or related to gastric-specific infections. Proteins such as Pepsinogen I (PGI, also called PGA), Pepsinogen II (PGII, also called PGC) and Gastrin 17 are considered specific markers of gastric cancer because of their gastric specific gene expression. Pepsinogens are the precursor of pepsins, the main proteases produced by the stomach. Since PGs are rarely expressed in other organs, so pepsinogen level can reflect the function of the stomach. The decrease PGI level is an important indicator of gastric cancer progression. In clinical practice, PGI measurement often needs to be used in combination with other indicators. The final diagnostic results need to be confirmed with X ray or endoscopy to verify whether the patients are suffering from gastric cancer [3, 4]. Gastrin 17 is a truncated peptide of the gastrin protein, a hormone secreted by the gastric antrum, which is important for gastric acid secretion[5]. Pepsinogens mainly produced from the the upper part of gastric body while gastrin 17 mainly secreted by the bottom half of the gastric body. Measurement of Pepsinogens and Gastrin17 can detect the specific positions of gastritis [6]. TFF3 (Trefoil factor 3) is a protein mainly expressed in goblet cells of intestine and colon. However, TFF3 positive goblet-like cells are found in intestinal metaplasia, an important precancerous stage of gastric cancer. For this reason, TFF3 level quantitation might help with gastric cancer detection [7, 8]. H. Pylori antibodies, CagA antibodies, anti-parietal cell antibodies are related to gastric specific infections, which reflect ongoing or past gastric infections that could be related to gastric cancer development [7, 9-13]. These gastric disease related antibodies are useful biomarkers for assessing gastric cancer risk.

Literature search also found many other proteins considered as gastric cancer screening markers although most of them are not specific to gastric cancer. These proteins are either general tumor markers or proteins that are associated with signaling related to carcinogenesis such as cell proliferation, angiogenesis or inflammation. These proteins include CEA (Carcino-embryonic Antigen) ([14], CA125 (Cancer Antigen 125) [14], CA19-9 (Cancer Antigen 19-9) [14, 15], AFP (Alpha-Fetoprotein) [16, 17], Pyruvate M2 Kinase [15, 18], serum amyloid A [19, 20], macrophage migration inhibitory factor [21, 22], Leptin [23], dickkopf [24, 25], olfactomedin 4 [26], VAP-1 [27, 28], UPA [29, 30], Cathepsin B [30-32], HMW kininogen [33], P53 antibody [34, 35], cytokeratin 18 [36-38], RegIV [39], IPO-38 [40], S100A6 [41], thrombin light chain [42], fibrinopeptide A [43, 44], angiopoietin-like protein 2 [45-47]. CEA, CA125, CA19-9, AFP, M2 Pyruvate Kinase are common tumor markers also overexpressing in other type of cancers [48-54]. p53 antibodies usually indicates p53 gene mutations, which also happened in many type of cancers [55]. cytokeratin 18, RegIV are apoptosis related proteins indicating cell death during gastric cancer development [56, 57]. Other proteins such as serum amyloid A, macrophage migration inhibitory factor, Leptin, dickkopf, olfactomedin 4, VAP-1, UPA, Cathepsin B, HMW kininogen, IPO-38, S100A6, angiopoietin-like protein 2, thrombin light chain and fibrinopeptide A might be related to cancer-related inflammation, extracellular matrix remodeling, angiogenesis and blood coagulation abnormalities.

Protein biomarkers of gastric cancer have been applied in large scale population screening in Japan and Korea. In A Japanese study, pepsinogen screening, with PGI < 70 ng/ml, and PGI:PGII < 3.0 as the cutoff value, could detect gastric cancer with the sensitivity of 84.6% and specificity of 73.6% [58]. A South Korea study using PGI:PGII < 3.0 as an indicator for gastric cancer, a detection sensitivity of 59.2% and specificity of 61% was achieved [3]. Although the pepsinogen serum screening appeared to be effective in gastric

cancer screening, the specificity and sensitivity of detection still needs to be improved. There is great difference among the Japanese or Korean studies using the same pepsinogen assay, which indicates that there are possible confounding factors, such as ethnicities or diet and social habits, which may affect the outcome of pepsinogen screening. It is necessary to develop some new methods for serum screening of gastric cancer.

Metabolic Markers of Gastric Cancer

The most notable metabolic difference between cancer cells and normal cells is that cancer cells relies heavily on glycolysis for energy while normal cells rely on oxidative phosphorylation, a phenomenon called Warbug effect [59]. The level of lactate, a by-product of glucose glycolysis, was constantly found to be increased in gastric patient serum or tissue samples [60, 61]. Cancer cells also have a high rate of protein synthesis. Accordingly, many metabolic studies showed an increase of amino acids, such as glycine, methionine, asparagine, aspartate and tyrosine in gastric cancer patients [60]. Cancer cells also have a high rate of nucleotide synthesis for the increasing demands of DNA synthesis and DNA repair. Reports also suggested altered nucleotide metabolites in certain type of cancers [62-64]. Few researches studied the fatty acid metabolism metabolites in gastric cancer patients. However, both increased fatty acid synthesis (FASN) and increased fatty acid oxidation (CPT1A) have been associated with cancer development [65-67]. Fatty acid oxidation metabolites such as acetone and β-hydroxybutyrate have been identified as potential biomarkers of gastric cancer [68, 69].

RNA Markers of Gastric Cancer

Traditionally, RNA is considered an unstable species of biomolecules, thus unsuitable to be used as biomarkers for cancer. However, recent research suggested some serum non-coding RNA could also be potential gastric specific markers. Long non-coding RNA HULC and H19 were reported to be promising novel biomarkers in plasma of patients with gastric cancer [70-75]. MicroRNA is a relatively stable species of RNA in the serum. Potential serum microRNA biomarkers included miR-187, miR-371-5p and miR-378, microRNA-21, miR-195, miRNA-206, MiR-16-5p and MiR-19b-3p. Serum miR-187, miR-371-5p and miR-378, microRNA-21, miR-627, miR-629 and miR-652 levels are positively related to gastric cancer while serum miR-195, miRNA-206, MiR-16-5p and MiR-19b-3p levels are negatively correlated with gastric cancer [76-81]. miR-378 alone could discriminate GC patients from healthy controls with 87.5% sensitivity and 70.73% specificity. High levels of miR-21 were associated with an increased tumor size and an advanced pT stage. Low expression of miR-195 is a potential marker for gastric cancer. Serum miRNA-206 was down-regulated in GC patients compared with healthy controls. An important issue in using microRNA as a tumor biomarker is to choose a correct reference gene. Analysis showed that miR-16 and miR-93 were the most stably expressed reference genes for serum microRNA analysis of gastric cancer patients and healthy controls [82].

Volatile Organic Compounds as Markers of Gastric Cancer

Breath analysis is an another appealing method for cancer detection because of its convenient, painless, noninvasive way of sampling. Several studies have highlighted the potential of breath analysis for gastric cancer detection. The identified volatile organic compounds from gastric cancer patients included hexanoic acid, phenol, methyl phenol, ethyl phenol, 2-propenenitrile, 2-butoxy-ethanol, furfural, 6-methyl-5-hepten-2-one, hexadecane, 4-methyloctane, 1,2,3-trimethylbenzene, α-methyl-styrene, acetone, tetradecane, 3-methylpentane, hexane, 2,3-dimethylpentane, 2-methylhexane, and dodecane [83-86]. In addition, 2-butanone and menthol have been found at lower levels in gastric cancer patients comparing to controls. Using a combination of 4 VOCs, gastric cancer patients could be differentiated from gastritis patients (the integrated area under the ROC curve is 0.91) [69]. While with a model using a combination of 8 VOCs, gastric cancer patients could be discriminated from precancerous gastritis controls with 73% sensitivity, 98% specificity and 92% accuracy [84]. It has been a concern that breath analysis might be confounded by H. pylori infection or smoking behaviors. However, recent study showed that breath analysis with a breath-sensing nanoarray was not affected by ages, sex, smoking, drinking habits, H. pylori infection or proton pump inhibitor medications [84].

Conclusions

New biomarkers have been continuously discovered for gastric cancer early detection. However, protein biomarkers of gastric cancer are the only kind of biomarkers that go into clinical applications. Protein markers are relatively easy to detect and proteins such as pepsinogens are closely related to gastric physiology, which makes them easier to adopt in clinic applications. Metabolic biomarkers are also easy to detect in the patient blood, however, their specificities to gastric cancer has not been firmly established. RNA biomarkers may help to elucidate more detailed mechanisms of gastric cancer while their analysis is more complicate than the analysis of protein biomarkers. MicroRNAs might be useful biomarkers for gastric cancer detection because of their stability in the patient plasma. Breath biomarkers have the advantage of easy sampling but the analysis of breath biomarkers might be more expensive than other biomarkers. Nonetheless, metabolic biomarkers, RNA biomarkers and breath biomarkers hold great promise for the future of gastric cancer early detection.

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