Review Article

Apolipoprotein: prospective biomarkers in digestive tract cancer

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Abstract: Digestive tract cancer, which is characterized by high morbidity and mortality, seriously affects the quality of life of patients worldwide. The digestive tract has abundant blood supply and nutriment, providing a suitable environment for tumor cells. Under chemical, physical, and biological stimuli, the activated cancer-related genes promote tumorigenesis. The synthesis of apolipoprotein occurs in the liver, intestine, and other digestive organs. However, the functions of apolipoproteins are not limited to lipid metabolism. An increasing number of studies have revealed that apolipoproteins take part in the regulation of tumor behavior. Apolipoprotein A (apoA) has recently been acknowledged as a beneficial indicator of several cancers, including colon, hepatocellular, and pancreatic cancer. Apolipoprotein E (apoE) can affect tumor susceptibility on account of genetic polymorphism. Levels of apolipoprotein C (apoC), B (apoB), and D (apoD) also impact tumor progression and the prognosis of patients. However, because of individual, racial, and genetic differences, a consensus has not yet been reached. Based on clinical data and analysis, apolipoproteins could be a novel target and marker in tumor therapy and prevention.

Keywords: Apolipoprotein, biomarker, digestive tract cancer

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Introduction

Digestive tract cancer, which includes colon cancer, hepatocellular carcinoma (HCC), esophageal carcinoma (ECC), gastric cancer, and pancreatic cancer, is a leading cause of death worldwide. Colon cancer is characterized by elevated levels of metastasis, particularly in the liver and lungs (1). Despite surgical treatment being effective, there is no specific marker for predicting patients' prognoses. α-fetoprotein (AFP) is comprehensively applied when HCC is diagnosed early. However, its application is not limited to HCC monitoring and it is also upregulated in chronic hepatitis and cirrhosis of the liver (2). Different carbohydrate antigens are commonly used as standard serum tumor biomarkers for early screening of cancer, including carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), and carbohydrate antigen 72-4 (CA72-4). However, these biomarkers are not specific to the tissues and are expressed in several types of gastrointestinal cancer. Individual circulating tumor cells are specific for colorectal and gastric cancer, but they are difficult to separate. Therefore, it is necessary to identify novel markers to differentiate and diagnose patients.

Apolipoprotein (apo) is a superfamily involved in lipid metabolism and the inflammatory response. Previous studies have revealed the potential association between apo and various types of cancer. *Apolipoprotein E* (*APOE*) in the Chinese Han population has been determined to be a risk factor for gastric cancer. *APOE* overexpression is also associated with invasion and metastasis, thereby affecting survival status (3,4). Polymorphism produces different cancer susceptibilities in various ethnicities. To date, obesity and metabolic syndrome may increase the risk of developing esophageal and gastric cancer (5). The mechanism of

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how tumorigenesis occurs in lipid metabolism has yet to be completely elucidated. However, apo, a significant participant in lipid function, may serve as a proper indicator for tumor monitoring and the prediction of clinical outcomes.

The present review aimed to elucidate the biological changes that occur in apos during gastrointestinal cancer and put forward the hypothesis that apo may serve as a valid biomarker for the clinical diagnosis of this disease.

Apolipoprotein A1 (apoA1): a multifunctional participant in cancer metabolism

Cell experiments have demonstrated that recombinant human apolipoprotein A kringle V (rhLK8) is significantly and dose-dependently suppressed in the angiopoiesis and migration of human umbilical vein endothelial cells (HUVECs) (6). *In vivo*, colorectal cancer (CRC) models involving nude mice injected with rhLK8 have been shown to markedly improve animal survival rates when compared with controls. The combined administration of rhLK8 and 5-fluorouracil (5-FU) to mice may also produce a more significant suppression of tumor metastasis when compared with singular therapy alone (7). As a non-toxic agent, rhLK8 may serve as a prospective active agent to inhibit vascular endothelial growth factor-mediated angiogenesis in various types of cancer, including in colon cancer liver metastasis. rhLK8 administered in combination with 5-FU may serve as a novel clinical chemotherapy agent. Ahn *et al.* (7) revealed significant downregulation of the apoA kringles in tumor cell migration and primary cancer development. Notably, cancer tissues are extensively necrotic in mice implanted with apoA kringles by the low density of microvessels (8).

As an indispensable component of high-density lipoprotein, apoA1 is beneficial to the antineoplastic and antiatherosclerotic processes. A recent study utilized a recombinant plasmid encoding apoA1 and P144 (anti-TGF-β peptide) in MC38 colon cancer cells to determine gene expression and colon carcinoma metastasis profiles. The animal experiment of the study above revealed that >50% of mice did not develop carcinoma and did not exhibit hepatic metastases when treated with the apoA1 and P144 overexpression fusion protein (9). Therefore, this may represent a novel drug target for the hepatic metastasis of colon cancer. In patients with low apoA1 levels, no significant differences were demonstrated in their progression-free survival when receiving bevacizumab chemotherapy. However, univariate analyses indicated that levels of apoA1 (relative risk, 1.636; P<0.001) and CEA (relative risk, 1.306; P<0.001) may serve as potential biomarkers of colon cancer and as valid indicators of prognosis (10).

Complement component 1, q subcomponent binding protein (C1QBP), serves as a regulator of apoA1 antitumor function (11). The colon cancer cells (SW620) have established interaction between apoA1 and C1QBP (11). It has been suggested that C1QBP can bind to apoA1 and inhibit its expression, thereby weakening apoA1 antioxidation, leading to carcinogenesis. Previous studies have revealed that L-4F, a mimic peptide of apoA1, exerts an anti-inflammatory effect by reducing levels of tumor necrosis factor (TNF-α) and interleukin-6 (IL-6) (12). Recent articles have also demonstrated antineoplastic activity by establishing an $APC^{Min/+}$ murine model, whereby mice were fed with chow containing L-4F. The oral administration of L-4F was revealed to reduce the number and size of tumors in the animals (13). If effectively applied to clinical patients, treatment regimens may become more simplistic. However, the discovery of specific lipids that are targeted by L-4F is required to determine the mechanisms of apoA1 mimetics.

The half-life of apoA1 (~4 days) may make it a suitable agent for assessing healthy liver synthesis. Furthermore, there is abundant gene expression in liver cells (14). ApoA1 may show the prognosis and metabolism profile of patients with various liver diseases, including liver cirrhosis, hepatitis, and liver cancer. Owing to the extreme malignancy and high incidence of HCC, the development of novel biomarkers to detect early-stage tumors has been a critical focus of present research. As demonstrated through a clinicopathologic analysis and mass spectrometry (15), apoA1 was an appropriate candidate biomarker. HCC patients with lower apoA1 levels (<1.04 g/L) carry a higher risk of relapse after resection. Lower apoA1 levels also indicate that patients may be susceptible to multiple tumors when compared with healthy individuals (apoA1 levels >1.04 g/L; P<0.05) (16).

To date, AFP has been identified in diagnostics as a classic oncofetal protein marker, the concentration of which is also elevated in other hepatic diseases. However, AFP levels do not significantly differ between patients with HCC and other hepatic diseases (17). To remedy this deficiency, the combination of two indexes may provide greater sensitivity and specificity. Ma *et al.* (16) revealed that the downregulation of apoA1 protein in HCC patients with portal vein tumor

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thrombosis, but the decrease in mRNA level has no statistical significance compared with HCC without thrombosis, which may be due to the inhibition in the translation process. Additionally, Katsuramaki *et al.* indicated that apoA1 levels decrease 7 days after resection and mildly increase on the 14th day; a change that is closely correlated with levels of prealbumin (r=0.49; P<0.001) (18). Therefore, apoA1 may adequately estimate liver reserve levels and prognosis pre- and post-operatively, particularly in patients with HCC and cirrhosis who potentially have an extremely low content of apoA1 (30 mg/dL) (18,19). A previous study involving Chinese patients with HCC set a cut-off value of apoA1 to 1.090 g/L, which distinguished different disease-free survival and outcomes (P<0.001). The study proposed that apoA1, in combination with C-reactive protein, may serve as a novel indicator of disease progression (20). Also, a previous study recorded that levels of the hepatitis C virus (HCV) and apoA1 decreased when patients were treated with histone deacetylase antagonist (21). The study above also revealed a positive correlation between HCV and apoA1, indicating that this may serve as a promising treatment for HCC patients with HCV infection.

Pancreatic ductal adenocarcinoma (PDAC) is an extremely lethal cancer that is characterized by undesirable clinical outcomes. CA19-9, a classical marker of PDAC, is comprehensively used in diagnostics and to evaluate prognosis (22). A previous study reported that apoA1 levels were increased in CA19-9-negative PDAC patients, but remained lower compared with healthy controls (P<0.001) (23). A recent study demonstrated that the combination of apoA1 and CA19-9 increased the sensitivity and specificity to 95% and 94%, respectively (24). Dong *et al.* (25) determined that apoA1 levels <1.05 g/L increased pancreatic cancer occurrence in patients who have diabetes (P<0.05). Two-dimensional gel electrophoresis analysis has also revealed that the apoA1 protein is highly expressed in tumor tissue when compared with non-tumor tissue (26). These data indicate the potential use of apoA1 in early-stage pancreatic neoplasm. L-4F, was determined to suppress pancreatic cancer progression and the inflammatory response in mice (P<0.01) (12). ApoA1 also significantly inhibits tumor progression of colon cancer and pancreatic cancer. However, determining the cut-off value is key for predicting tumorigenesis. It may well be determined by hereditary or ethnic factors, sex, or age.

A previous study of 210 individuals revealed that the median concentration of serum apoA1 was 1.21 and 1.56 g/L in ECC and healthy controls, respectively. Furthermore, survival analysis revealed a more promising curve in the latter individuals compared with the former individuals (27). Although the underlying mechanism is yet to be elucidated, apoA1 is hypothesized to inhibit the proliferation of lysophosphatidic acid-mediated cells in tumors.

ApoE: an influencing factor of cancer susceptibility and prognosis that is dependent on gene polymorphisms

Unlike apoA1, apoE is associated with tumor progression and poor prognosis in patients. Zhao *et al.* (28) revealed that apoE levels were markedly increased in patients with colorectal liver metastasis (CLM) when compared with tumors of primary cancer or with normal mucosa. In apoE$^{-/-}$ murine models of inflammation-associated CRC, mice exhibit significantly enlarged tumor sizes compared with wild-type mice (P<0.05). Pathologic alterations also identified statistical significance (29). These data indicate that apoE may accelerate cancer metastasis and progression. The possible mechanism by which this occurs may be via apoE increasing intracellular adhesion and junctions, thereby decreasing cell contact inhibition, polarizing normal cells to tumor cells.

However, further exploration of these potential mechanisms is required due to the complicacy of the *APOE* gene polymorphism. The *APOE* gene has three isoforms: mutant-type *APOE2*, wild-type *APOE3*, and mutant-type *APOE4*, respectively carrying ε2 (112Cys/158Cys), ε3 (112Cys/158Arg), and ε4 (112Arg/158Arg) on human chromosome 19 (30). Investigations into the associations between colonic cancer and *APOE* phenotypes have revealed no significant differences in ε4 allele frequency in patients with distal neoplasms. Nevertheless, *APOE* ε4 is inversely correlated with the oncogenicity of proximal adenoma and carcinoma, which has been confirmed by a statistical analysis that compared with ε3 (28). A deficiency of *APOE* ε3 may lead to colon cancer, particularly among the population over 50 years old. It might because ε3 has a weaker capacity to absorb cholesterol compared to ε4. A previous study involving Japanese males did not identify any significant differences between the susceptibility of patients with proximal colon adenomas that did or did not express the ε4 allele (31). Chinese researchers have also drawn a similar conclusion in that specific lipids, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), in patients carrying ε2/ε3,

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ε3/ε3, and ε3/ε4, exhibit no statistical difference (P>0.05). However, concentrations of TC (mean ± standard deviation; 4.28±0.62 *vs.* 5.32±0.85 mmol/L) and HDL-C (1.51±0.29 *vs.* 1.39±0.25 mmol/L) demonstrated marked differences when compared with controls (P=0.016 and P=0.035, respectively) (30). Coincidently, certain Eastern races, including Japanese and Chinese people, exhibit a similar frequency of *APOE* ε3 when compared with Caucasians, indicating some degree of genetic diversity. Souza *et al.* (32) performed a study using 87 patients with CRC and 73 controls in Brazil. The results revealed that ε4 was not homozygous in patients with CRC and only accounted for 6% in controls. Collectively, multiple factors may determine the potential association between the genotypes of *APOE* and colonic cancer, including racial variation, genetic background, diet, and physical training, which have likely led to a discrepancy in the findings of carcinogenicity of the allele ε4. A case-control study determined the effect of genotype on certain clinical features, revealing that carriers of the ε2 gene exhibit a 60% decreased risk of gastric cancer when compared with homozygous ε3 gene carriers (33). However, Chinese demographic data has revealed that the allele ε2, which participates in sera cholesterol metabolism, may be a risk factor of gastric cancer (4).

ApoE is also associated with hepatitis B virus (HBV) infection and HCC. A previous study of 199 individuals infected with HBV showed that the apoE rates in HBV-positive patients were significantly increased relative to healthy controls, with no relation to patient genotypes (34). This rise in apoE levels was also shown in liver cirrhosis patients (34,35). Concerning HBV infection, researchers have purified abundant apoE in HBV-infected cells; HBsAg and HBV-DNA were detected simultaneously (36). However, the difference in apoE levels has not been fully proven. Japanese researchers have not detected any significant differences between cancerous and matched non-cancerous tissues at the gene expression level. However, the difference has been observed at the protein level. In PDAC or pancreatic cancer tissues, the upregulation of apoE was conformed at the genetic and protein levels (37,38). Thus, lower serum levels of apoE, possibly derived from mutations and the HCV core protein, may produce undesirable outcomes. In gastric cancer, apoE promoted cancer cell migration via the PI3K/Akt signaling pathway (39). However, whether apoE levels significantly influence the tumor status of patients is yet to be fully elucidated.

Certain factors with significant effects may cover-up or hide those of apoE. ApoE adjusts the lipid secretion from other tissues to the tumor cells, provides essential lipid for tumor cells proliferation, and may cause DNA damage (40). Mrkonjic *et al.* (41) determined a statistically significant intake of fat (P<0.001), cholesterol (P=0.003), and red meat (P<0.001) in patients with CRCs, indicating that red meat intake may be a risk factor in microsatellite instability carriers. ApoE may likely be considered a promising biomarker, and its upregulation can suggest an unwanted clinical outcome (35). Furthermore, a cell proliferation assay determined that apoE was inhibited in breast cancer and melanoma, accounting for its competitive effect against growth factors when binding to cytomembrane (42).

Additionally, apoE was determined to adjust angiogenesis in other types of cancer (43,44). The ε4 allele has been reported to be a beneficial factor showing an antitumor effect. However, this has been a controversial topic among researchers.

Apolipoprotein B (ApoB): a factor associated with tumorigenesis at the mRNA and genetic level

ApoB is closely associated with intestinal cancer and hepatic metastases. Zhang *et al.* (45) revealed that patients with CRC exhibited lower apoB and LDL-C levels when compared with healthy controls (P<0.05). Furthermore, an apoB concentration <0.8 g/L indicates a more satisfactory 5-year survival rate (29%) compared with patients who exhibit higher levels (46). The silencing of apoB in HCC cells has been shown to increase the relative rate of cell proliferation compared with controls (P<0.01), indicating the anti-growth property of apoB (46). The expression and positive rate of glycated apoB have been increasingly detected in para-carcinoma tissue, adenoma, and carcinoma (P<0.05) (47). ApoB mutations may lead to the development of HCC. A consequence of apoB mutation is the truncation of apoB protein, which increases the risk of HCC development, particularly in hypocholesterolemia patients (46,48,49). By performing exon sequencing, a nonsense mutation was detected on the 26th exon, which was associated with liver cancer (48). This nonsense mutation may lead to hypercholesteremia due to lipidosis. Carriers of mutant *APOB* are susceptible to liver cancer and may exhibit familial emergence. The secretion of apoB requires abundant energy. However, in tumors, the *APOB* gene generates inactivating mutations to save energy for tumor cell proliferation.

The expression of apoB mRNA-editing enzyme catalytic polypeptide-like 3G (APOBEC3G) was determined to be

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highly expressed in liver metastases, indicating that it may have a promising predictive value for tumor metastases (50). Additionally, cancer cell invasiveness was inhibited *in vitro* by short hairpin RNA (shRNA) (51). The shRNA-associated APOBEC3 G could be considered a novel therapy for CLM and terminal cancer. Gene X (The HBx), a product of APOBEC3-mediated HBV mutations, has been demonstrated to promote the tumorigenesis of liver cells by inhibiting apoptosis. Data have revealed that transfection with HBx significantly reduces tumor cell colony formation (52). A tumor-suppressive ability was also identified in APOBEC3B by performing wound healing assays. However, no evidence has suggested that APOBEC3B is an independent indicator of tumor recurrences among HCC patients (53).

On the contrary, Ma *et al.* determined the tumorigenicity of APOBEC3B by establishing overexpression of amphimutation (E68A/E255Q), the results of which revealed that wild- and mutant-type genes promoted the invasiveness and metastasis of cells *in vitro* (54). Therefore, inconsistency exists between the conclusions of previous studies, meaning the more specific effect of APOBEC3B in HCC requires further investigation. APOBEC3B and APOBEC1 can induce base transition in ECC, which has been identified as a potential factor of oncogenicity. These were also shown to be overexpressed in ECC tissues (55,56). The upregulation of APOBEC3B mRNA usually indicates a poor prognosis and has been testified in other types of cancer. APOBEC3B may also lead to gene mutations in patients with ECC, affecting clinical outcomes.

Apolipoprotein M (ApoM): a potential indicator of cancer

ApoM has different effects on diverse types of cancers. ApoM-knockdown cancer cells have a robust proliferation and invasion capacity in HCC (57). In nude mice models, apoM markedly suppresses tumor development (58). Although the expression of apoM is similar in healthy para- and HCC tissues, mRNA and protein levels of apoM are higher in HCC compared with non-tumor tissues. apoM expression is higher still in chronic hepatitis (59,60). These results suggest that apoM may contribute to the assessment of liver injury and the clinical prognosis of patients with HCC. Both have been shown to be overexpressed in ECC tissue, and development and deficiency of apoM may fail to activate the classical NF-κB pathway. ApoM-induced autophagy inhibits hepatocarcinogenesis. As a target gene of miRNA, apoM may be regulated at the transcriptional level (58). ApoM mRNA ($P<0.05$) and protein ($P<0.001$) have also been demonstrated to be highly expressed in CRC tissue compared with normal and adjacent mucosa (61). In patients with lymphatic metastasis, elevated levels of apoM mRNA have also been detected (61,62). Vitamin D receptor (VDR) signal might be a potential mechanism in the apoM-mediated antitumor effect. ApoM could promote VDR expression in mRNA levels; similarly, knockout of *APOM* leads to a decrease of VDR (57,63). As a karyophilic protein, VDR regulates cytoskeleton expression and distribution, which enhances the adhesion of cells and inhibits the tumor progression. The interaction of VDR and apoM could serve as a promising target in cancer therapy.

Apolipoprotein D (ApoD): a hormone-dependent factor that indicates a poor prognosis

Levels of apoD have been associated with the degree of differentiation in HCC tissue. In patients with HCC, its expression may be regulated via hypermethylation (64). When compared with matched non-cancerous tissue, apoD mRNA levels in malignant tissues were reduced, but not significantly (65,66). It has been established that the overexpression of apoD indicates a poor prognosis. The potential interactions among lipids, apos, and sexual hormone receptors need to be established to determine the association between apoD and cancer. Articles regarding apoD and cancer are insufficient and fail to draw a consistent conclusion. Multiple factors can influence apoD expression, including estrogen, steroid reference substance, alcohol, and vitamin D. Determining the mechanism of apoD in human cancer may, therefore, be a challenging process.

ApoC: an important biomarker for pancreatic cancer

Previous studies have determined that the expression of apoC-I is increased in patients with neoplastic pancreas epithelium (64). Secreted ApoC-I has previously been detected in the culture medium of pancreatic cancer cells. It has also been confirmed that high levels of apoC-I are associated with poor prognosis. When utilizing small interfering RNA, a decreased expression of ApoC-I improved cell survival and prevented the spontaneous apoptosis of pancreatic cancer cells (67).

ApoC-II has been confirmed to increase cell growth and

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invasion in pancreatic cancer cell lines and could, therefore, be regarded as a predictor for cell survival (68). A recent report indicated that apoC-I and apoC-III plays a vital role in the diagnosis of gastric cancer and that the levels of apoC-I and III are lower than those in patients with mild lesions and healthy individuals (69). As an indicator of TC degradation, lower apoC-I and III suggests that patients may suffer unfavorable prognosis owing to the abnormal lipid metabolism.

Conclusions

There is currently an increasing number of issues with conventional tumor markers. The sensitivity of AFP in the early diagnosis of HCC is only 21.6%, lower than expected (70). Particularly in the differential diagnosis of HCC and chronic hepatitis, AFP levels do not exhibit significant differences and cannot reflect the TNM stage of tumors. It may, therefore, only be used to distinguish patients with HCC from the healthy population. CA19-9, a carbohydrate antigen that is used to evaluate pancreatic cancer, is inappropriate for the early screening, due to reduced sensitivity of 68-92% (22). Used alone, this marker could not, therefore, monitor cancer progression or patient prognosis accurately. Although CA19-9 is an FDA-approved tumor marker, it is primarily elevated in late-stage disease, meaning that false negatives may be encountered (71). In gastrointestinal tumors, traditional markers are limited by their low sensitivities, which lead to misdiagnosis in early-stage disease. New indexes may improve the sensitivity and specificity of biomarkers. As a potential tumor marker, apo demonstrates unique advantages. ApoA1 provides a novel approach to identify CA19-9 negative and positive PDAC with a high sensitivity of 96%, as the levels of apoA1 in the former markedly exceed those in the latter (23). Low apoA1 levels may lead to lipid metabolism disorders, which increase the risk of PDAC (72). The sensitivity (86%) and specificity (79%) of apoA1 in HCC diagnosis are also higher than those of AFP (66% and 59%, respectively) (17). Apo shows high sensitivity and specificity when compared with other conventional tumor markers. Conventional markers do not distinguish between tumors, chronic inflammation, and benign disease. Apo can differentiate these when an appropriate cut-off value is established. Furthermore, some individuals do not express the specific genes required for detection by tumor markers. As for this population, apo may be a more suitable candidate. When combined with acute-phase proteins, such as C-reactive protein and transferrin, the sensitivity and specificity of apo may further increase. The present review demonstrates that apo may serve as a more competent biomarker to screen tumorigenesis. Associating conventional and novel markers may increase the accuracy of digestive tract cancer diagnosis.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-19-2106). The authors have no conflicts of interest to declare.

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