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Progress in the Study of the Correlation between Apolipoproteins and Endometrial Cancer

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Abstract

In recent years, Lipid metabolism disorder has been closely related to malignant tumors. Apolipoprotein (Apo), as an important protein in lipoprotein transport and metabolism, plays an important role in the process of tumor proliferation. Endometrial carcinoma (EC) is a common gynecological malignant tumor, and its incidence is increasing year by year; in which obesity is an independent risk factor for the occurrence and prognosis of EC. This paper discusses the correlation and possible mechanism between different types of Apo and the occurrence, development and prognosis of EC, and briefly reviews the clinical application of some drugs in EC.

Keywords

Endometrial Carcinoma, Apolipoprotein, Carcinogenesis

1. Introduction

Endometrial carcinoma (EC) is a malignant epithelial tumor occurring in the endometrium, with adenocarcinoma being the most common, and is one of the three major malignant tumors of the female reproductive tract. In recent years, the incidence rate is on the rise worldwide, with the incidence rate in China being 63.4/10 million and the mortality rate being 21.8/10 million [1] The pathogenesis of EC may be related to the continuous proliferation of endometrium due to the lack of antagonism of progesterone by long-term estrogen action, which later develops into atypical hyperplasia and eventually carcinogenesis. Factors leading to increased endogenous estrogen include obesity, diabetes, hypertension, and polycystic ovarian syndrome (PCOS). Of all EC cases, 26% -

47% of them may be related to obesity, and the relative risk of EC in obese patients is 2 - 10, and about 80% of EC patients weigh 10% more than their normal average body weight [2]. The proliferation process of tumor cells is closely related to lipid metabolism in patients, among which apolipoprotein (Apo) is an important component of plasma lipoproteins. Studies have pointed out that Apo may play an anti-tumor role [3] and is involved in several processes of EC development. But the association and specific mechanisms are still controversial. The aim of this paper is to investigate the correlation between Apo and EC, so as to provide reference to further research in Apo in the field of EC.

2. Apolipoprotein Polymorphisms

There are many types of apolipoproteins, including apolipoprotein A1 (Apo A1), apolipoprotein B (Apo B), apolipoprotein C (Apo C), apolipoprotein D (Apo D), and apolipoprotein E (Apo E), among which Apo A1, Apo B, and ApoE are closely related to EC [4].

2.1. Apo A1 & EC

2.1.1. Apo A1

ApoA1, consisting of 243 amino acids with a molecular weight of 283 kDa, is the main structural and functional protein of high-density lipoprotein (HDL). It is mainly synthesized in the liver and small intestine and is responsible for the assembly of HDL and plays an anti-atherogenic role by binding to the cell surface adenosine triphosphate binding cassette transporter A1 (ABCA1), a membrane transporter protein that transports cholesterol from intracellular to extracellular to exert anti-atherosclerotic effects. In the past, most of the attention on Apo A1 was limited to cardiovascular diseases, such as atherosclerosis, but in recent years, studies have found that Apo A1, a functionally diverse protein, has an important impact on tumorigenesis, development, and prognosis of EC. An analysis of a 72-person study showed that the median survival time of metastatic gastrointestinal cancer patients with high levels of Apo A1 was higher than those with low levels (20 months vs. 10 months, $P = 0.005$), suggesting that high levels of Apo A1 may be a good indicator of prognosis in metastatic gastrointestinal cancer [5].

2.1.2. Relationship between Apo A1 and EC

It has been shown that Apo A1 can be used as a marker for the early diagnosis of malignancy and that elevated Apo A1 levels may be negatively correlated with the risk of malignancy and positively correlated with the prognosis of patients with malignancy [6]. While in EC, it has been suggested earlier that the marker panel consisting of Apo A1, prosthyretin (TTR), and transferrin (TF) can be used as one of the tools for detecting EC, with a sensitivity of 71% and a specificity of 86% [7]. A retrospective analysis of 134 individuals by Yuhui Xu *et al.* showed that serum Apo A1 was significantly lower in endometrial hyperplasia (AEH) group [(0.970 ± 0.201) g/L] and EC group [(0.913 ± 0.163) g/L] than normal group [(1.129 ± 0.257) g/L] ($P < 0.0001$), suggesting that Apo A1 may be

involved in the development of EC [8] and that low levels of serum Apo A1, as one of the lipid characteristics of EC, play a non-negligible and important role in the progression of EC. A study by Zamanian-Daryoush *et al.* [3], who questioned the effect of Apo A1 on tumor growth and metastasis showed that overexpression of Apo A1 in transgenic mice led to metastasis and 10-fold less tumor growth when compared with mice in the Apo A1 knockout (Apo A1 KO) group and also demonstrated that pharmacological delivery of Apo A1 was effective in reducing tumor load and delaying metastasis. A clinical case-control study examined 519 patients with solid tumors and analyzed their high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), Apo A1, and other parameters, and the data showed that Apo A1 and HDL-C were significantly lower in cancer patients (n = 519) than in age-matched healthy controls (n = 928) [9]. An earlier analysis of a domestic study with 100 cases showed that patients with malignancy had both Apo and lipoprotein abnormalities, with Apo, total cholesterol (TC), TG, and HDL significantly lower than controls, and after treatment, patients had significantly higher lipid indexes except ApoB100 [10]. Another meta-analysis involving 19,216 patients also suggested that patients with high levels of HDL-C, Apo A1, and low levels of ApoB had prolonged overall survival (OS) and disease-free survival (DFS) [11], suggesting that Apo A1 can be used as a good dynamic indicator of malignancy prognosis. A study by Chang *et al.* also suggested that pretreatment serum Apo A1 levels < 1.125 mmol/L were an independent risk factor for predicting death in patients with nasopharyngeal carcinoma [12]. However, an analysis by Ma *et al.* showed that Apo A1 was an independent factor in the prognosis of hepatocellular carcinoma (HCC), and low levels of Apo A1 is a factor of poor prognosis in HCC and has the potential to be a promising therapeutic target for reducing postoperative recurrence and metastasis in HCC patients [13]. The above-mentioned studies confirm that high levels of serum Apo A1 are associated with a good prognosis in a variety of malignancies, but the literature examining the relevance of Apo A1 to EC is still scarce and remains to be further explored.

2.1.3. Mechanism of Action of Apo A1 in EC

Apo A1 may exert its effects on EC in several aspects, including: 1) increased Apo A1 is associated with improved glycemic control. EC patients often have concomitant type 2 diabetes (T2D), and diabetic patients have a 1.2- to 5.6-fold increased risk of developing EC compared with normal subjects [2], which is associated with compensatory hyperglycemia that leads to elevated insulin, and hyperinsulinemia further leads to elevated androgens, which are then converted to produce high levels of estrogens. A small randomized clinical trial in patients with T2D showed that Apo A1 levels increased sharply after a single recombinant high-density lipoprotein (reconstituted HDL, rHDL) infusion and that high levels of Apo A1 lowered blood glucose levels [14]. Another cross-sectional study also showed that low levels of Apo A1 were negatively associated with insulin resistance [15]. This mechanism also provides new ideas for the early pre-

vention of EC by exploring the correlation between glycemic control and Apo A1. 2) Anti-inflammatory effect: Apo A1 can activate the tyrosine kinase/transcription factor 3 by interacting with ABCA1 through the Janus kinase/signal transducer activator of transcription 3 (JAK/STAT) signaling pathway, thereby reducing the production of pro-inflammatory cytokines, resulting in excessive releasing of cholesterol from cells, and inhibiting the degradation of ABCA1to inhibit macrophage activation [16], which subsequently exert an anti-inflammatory effect and reduce the chronic inflammation on tumor development. 3) Maintenance of cholesterol homeostasis inside and outside the cell: an important factor in tumor development is the decrease of lipid efflux and increase of cholesterol synthesis in cancer cells, *i.e.*, dysregulation of cholesterol homeostasis [17]. A study by Lee *et al.* showed that downregulation of ABCA1 expression facilitated tumor progression [18]. HDL and Apo A1 could transfer cholesterol out of cells, thus decreasing lipid metabolism, and high levels of Apo A1 can slow down the development of EC, providing guidance for using Apo A1 levels as a tumor marker for early diagnosis of EC. 4) Immune and *in vivo* microenvironment regulation: Apo A1 has no significant inhibitory effect on the proliferative capacity of tumor cells but rather regulates the body's immune responses and *in vivo* microenvironment. It has been reported that Apo A1 reduction can weaken CD8+ T cell immune activity [19], the immune homeostasis *in vivo* is disrupted and the anti-tumor effect is weakened, thus promoting the development of EC.

Zamanian-Daryoush *et al.* found that when Apo A1KO mice were used after tumor formation *in vivo*, Apo A1 inhibited further tumor development and reduced tumor size. Apo A1 was able to inhibit myeloid suppressor cells (MDSC). MDSC are a class of immature myeloid cells and are the main cellular mediators of tumor immunosuppression. It can promote tumor growth and metastasis [20], decrease tumor chemokines such as prostaglandins (PG), CXC family chemokine receptors (CXCR), vascular endothelial growth factor (VEGF), granulocyte macrophage-stimulating factor (GM-CSF), and inhibit tumor-initiated pro-inflammatory signals, inhibit matrix metalloproteinase proteinase 9 (MMP-9) activity, and reduce tumor angiogenesis and invasion [3]. Apo A1 expression leads to a reduction in a set of bone marrow-derived suppressor cells. However, Apo A1 *in vivo* does not act directly on tumor cells, but exerts anti-tumor biological effects indirectly by altering immune cell function. Another study showed that CD+11b cells were significantly increased in transgenic Apo A1 mice, which exerted immunomodulatory effects on the tumor microenvironment by promoting the conversion of pro-tumor growth M2 macrophages to tumor growth inhibiting M1 macrophages [21]. All of the above studies suggest that Apo A1 can inhibit the development of malignant tumors through different pathways, while the specific mechanism of Apo A1 inhibition in EC still needs to be clarified.

2.2. Apo B & EC

2.2.1. Apo B

Apo B has various isoforms such as Apo B100, Apo B48, and Apo B74. Apo B100

is one of the ligands of very low density lipoprotein (VLDL) and low density lipoprotein (LDL), with a total length of 4536 amino acids and a molecular weight of about 550,000 Da, and is synthesized by the liver. The first 2152 amino acids, which are synthesized in the small intestine by editing [22], are mainly involved in the absorption, transport, and digestion of exogenous lipids.

2.2.2. Relationship between Apo B and EC

Apo B plays a central role in lipid metabolism and its predictive value in coronary atherosclerotic heart disease (CHD) has been confirmed in several studies to date, which showed positive correlation of Apo B with CHD severity, with high levels of Apo B associated with an increased risk of CHD disease [23]. The value of Apo B in oncology studies has also been explored in recent years. In a controlled analysis study, serum Apo B values in patients in the case group were found to lead to a 179-fold higher risk of developing EC than in the control group [24], suggesting the potential of Apo B as a new biological marker and therapeutic target for EC. In a follow-up study consisting of 164 individuals, Yan *et al.* found a correlation between preoperative Apo B values and tumor size in patients with hepatocellular carcinoma ($r = 0.355$, $P < 0.001$), and patients with higher Apo B values had larger tumor sizes (≥5 cm) with an OR as high as 2.221 (95% CI: 1.288 to 3.830, $P = 0.004$), while elevated Apo B was associated with poor postoperative prognosis in patients with hepatocellular carcinoma [25]. The results of a retrospective analysis on the correlation between pre-treatment serum Apo B levels and prognosis in patients with small cell lung cancer (SCLC) showed that Apo B/Apo A1 was an independent risk factor for OS in SCLC patients (HR = 1.98, 95% CI: 1.21 - 3.23, $P = 0.007$), and higher Apo B/Apo A1 levels had poorer OS [26]. The results of a meta-analysis showed that high pre-treatment Apo B levels were associated with shorter overall OS in patients with malignancy (HR = 1.13, 95% CI: 1.02 - 1.25, $P = 0.018$) [11]. However, compared to Apo A1, studies have found a correlation between Apo B and the progression and prognosis of a variety of malignancies, although relevant literature is limited.

2.2.3. Apo B Possible Exerts Its Effects over EC by Affecting the Availability of Cholesterol

After Apo B binds to LDLR, LDL is hydrolyzed to free cholesterol by intracellular lysosomal action of cholesteryl esters, and the latter enters the cytoplasmic metabolic pool for use in membrane structures such as cells. The high metabolism of tumor cells in patients with malignant tumors leads to an increased demand for raw materials for cell synthesis, so high Apo B expression may be associated with increased cholesterol demand for cell membrane synthesis, active tumor cell growth, and some tumor factors that can contribute to elevated LDLR activity [27]. The Chinese expert consensus on lipid management in malignant tumors also suggested that dyslipidemia could provide cancer cells with more cholesterol and induce cancer cells to produce more cancer-promoting oxidized

cholesterol, thus increasing the risk of tumorigenesis [28]. On the other hand, structural abnormalities of Apo B itself can also lead to an increased risk of malignant tumorigenesis, such as gallbladder cancer [29]. There are few studies on the correlation between Apo B and malignant tumors, and the specific mechanisms are not yet clear, so this review is limited and more research and exploration are needed in the future.

2.3. Apo E & EC

2.3.1. Apo E

Apo E, consisting of 299 amino acid residues with a molecular weight of 34,000 Da, is an important component of plasma lipoproteins. It is mainly synthesized by liver and brain tissues, while human adrenal glands and ovarian granulosa cells also have the ability to synthesize Apo E. Apo E is mainly found in CM, VLDL, intermediate density lipoprotein (IDL), and some HDL, and its main function is to promote the degradation of CM, LDL and VLDL [30]. It is encoded by three alleles ($\varepsilon 2$, $\varepsilon 3$, and $\varepsilon 4$) that are located at the same gene locus, and exist in three major isoforms: E2, E3, and E4 [31]. The instability of ApoE4 conformation determines its significant association with neurodegenerative diseases and ApoE4 is a major risk factor for Alzheimer's disease. It has been proposed that the isoform E2 has the strongest antioxidant effect on cells [32].

2.3.2. The Relationship between Apo E and EC

While most previous studies on Apo E have focused on neurological or ophthalmic diseases, studies on the relationship between Apo E and malignancy have received increasing attention. The results of a study on the association of Apo E2 alleles with the coexistence of endometrial hyperplasia (EH) and EC showed that the frequency of Apo E E2 alleles was significantly higher in the EH + EC group than in the control group (P = 0.0012, PBonferroni = 0.018, OR = 2.58, 95% CI 1.49 to 4.45) [33]. A comparative analysis of gene expression profiles of patients with EC with different degrees of differentiation by Huvila *et al.* yielded no statistically significant difference in Apo E expression between highly and moderately differentiated adenocarcinomas, but in hypodifferentiated adenocarcinomas, Apo E expression was 13.1% (P = 0.001) and 9.7% of that of highly and moderately differentiated adenocarcinomas, respectively (P = 0.007), suggesting that increased Apo E expression may be a late event in the progression of highly differentiated endometrioid adenocarcinoma to hypofractionated endometrioid adenocarcinoma [34]. Apo E has been intensively studied in ovarian cancer, and Chen *et al.* [35] showed that the expression of Apo E mRNA increased more than 10-fold in ovarian cancer, and low expression of Apo E could lead to ovarian cancer. The relevance of Apo E in other malignancies is also gaining attention. Data from a Korean study showed a positive correlation between Apo E and the risk of postoperative lymphedema in breast cancer [36]. Trost *et al.* [37] showed that Apo E levels were elevated in patients with non-small cell lung cancer compared to normal lung cancer tissue, and Apo E

overexpression could be a marker of poor prognosis in lung adenocarcinoma. Zhao *et al.* [38] showed that Apo E overexpression was associated with the progression of colorectal cancer, suggesting that patients with colorectal cancer have a poor prognosis, especially those with stage II combined with liver metastases. Domestic and international studies have shown a relationship between Apo E and malignancy, while the interactions between Apo E and EC are less explored and the interactions remain a focus for further research.

2.3.3. Apo E Possibly Exerts Its Effects over EC by Affecting Its Development and Growth

The mechanisms by which Apo E employs to exert its role in tumor development are controversial, and the possible mechanisms are as follows: 1) It has been proposed that Apo E is a potential inhibitor of cell proliferation. Apo E inhibits cell migration by binding to LDLR-related proteins and inducing cyclic adenosine monophosphate (CAMP) accumulation and protein kinase A (PKA) activation, on the one hand. On the other hand, it inhibits cell proliferation by binding to proteoglycans and activating inducible nitric oxide synthase (INOS) [39], thus inhibiting the growth and spread of tumor cells. 2) Similar to Apo A1, Apo E also has immunosuppressive ability against tumors, and the results of Wei *et al.* [40] showed that tumor growth was slow in the Apo E knockout (Apo EKO) group, suggesting that inhibition of Apo E mice in the Apo E KO group, and the proportion of MDSC and CC chemokine receptor 2 (CCR2) in the spleen were significantly lower than those in the wild (WT) control group, suggesting that Apo E may likely reduce tumor-induced MDSC aggregation in the spleen by affecting the expression of proliferative factors or surface chemokine receptors, thereby enhancing the body's inhibitory effect on tumor development and affecting tumor growth. Although the specific mechanism by which Apo E exerts its effect on malignant tumorigenesis has not been fully clarified, it is highly expected that Apo E will become a new tumor marker in cancer prevention, early detection, diagnosis, and treatment of malignant tumors.

3. Treatment

3.1. Apo A1 Mimetic Peptides

Apo A1 mimetic peptides are a class of peptides with a classical amphipathic helix structure and thus can bind lipids. Based on the number of phenylpropanoid amino acid (F) residues on Apo A1, Apo A1 mimetic peptides are classified as 2F, 3F, 4F, 5F, 6F, and 7F, and among which 4F has been intensively studied. It has been shown that D-amino acid mimetic peptides containing Apo A1 (D-4F) have comparable *in vitro* properties to the action of L-4F mimetic peptides [41], including increasing pre-βHDL formation and cholesterol efflux and reducing lipoprotein oxidation *in vitro*. Even oxidized lipids show a significant binding affinity for Apo A1 mimetic peptides compared to Apo A1 [42]. While treatments with Apo mimetic peptides mainly focused on inflammation and atherosclerosis, in 2010, Su *et al.* [43] injected mice with mouse ovarian cancer cell line

ID8 subcutaneously (SQ) or intraperitoneally (IP) followed by oral or SQ treatment with Apo A1 mimetic peptides L-4F, L-5F or D-4F and experimentally found a significant reduction in tumor burden and a significant binding of Apo A1 mimetic peptide to lysophosphatidic acid (LPA) with high affinity. This binding reduced serum LPA level in mice, inhibited tumor vascular neogenesis, and affected the proliferation and invasion of ovarian cancer cells, demonstrating for the first time that Apo A1 mimetic peptide can be used as a unique class of therapeutic agent for ovarian cancer. Recently, some scholars treated EC cell lines with different concentrations of Apo A1 mimetic peptide L4F and found that L4F inhibited the proliferation of EC cell lines in a dose-dependent manner. Compared with the control group, L4F significantly increased the level of adenylate-activated protein kinase (AMPK) phosphorylation in EC cell lines, while the level of Nanog protein expression was low, indicating that L4F activates AMPK signaling pathway phosphorylation and inhibits the protein expression of Nanog, which was subsequently verified in 3D EC-like organs [9]. It is evident that Apo A1 mimetic peptide is expected to be a new therapeutic agent for cancer treatment, but a large number of samples and clinical studies are needed to further confirm its effectiveness and practicability.

3.2. Statins

Statins are a class of hydroxymethylglutaric acid monoacyl coenzyme A (HMG-CoA) reductase inhibitors, which can block the synthesis pathway of mevalonic acid (MVA), thus greatly reducing the production of endogenous cholesterol and lowering blood cholesterol levels, and are mostly used clinically for lipid lowering and prevention of cardiovascular diseases. In recent years, there has been a growing awareness of the application of statins in the prevention and treatment of tumors. A meta-analysis showed that statins reduced the overall gynecologic cancer risk (OR = 0.80, 95% CI 0.69 - 0.93) and exhibited a more significant preventive effect on the risk of EC (OR = 0.66, 95% CI 0.52 - 0.85), but did not affect the risk of other specific types of gynecologic cancers such as cervical, vulvar, and ovarian cancers [44]. Schointuch *et al.* [45] found that simvastatin could arrest cancer cells at G0/G1 phase by regulating mitogen-activated protein kinase (MAPK) and AKT/rapamycin target protein (mTOR) pathways, which in turn exerted significant anti-proliferative and anti-metastatic effects on EC cells. Statins can inhibit the proliferation of tumor cells and induce apoptosis by blocking MVA synthesis, inhibiting isoprenoid synthesis such as farnesyl [based] pyrophosphate (FPP) and geranyl pyrophosphate (GGPP) downstream of the mevalonate pathway, affecting the activation of Ras and Rho, and influencing the cytogenic transformation process [46]. Lavie *et al.* [47] found that patients with more than 1 year of statin use had a reduced risk of EC, while female patients diagnosed with cancer had significantly higher survival rates in both ovarian and endometrial cancers after statin use. Some meta-analyses have concluded that statin use is not significantly associated with the risk of EC, but others have suggested that this may be due to the limitations of sample selection,

mostly retrospective studies, and therefore more standardized prospective clinical studies are needed to explore the association between the two.

4. Conclusion

There is a close association between apolipoproteins and EC, and apolipoproteins play important roles in the occurrence, development, and prognosis of EC. Apo may exert anti-tumour effects through mechanisms such as antiinflammatory, immune regulation, lipid metabolism, an inhibitor of cell proliferation and endocrine. Although the association and specific mechanisms are still controversial, with continuous research, apolipoproteins are potentially important biological markers for predicting, diagnosing, and treating EC, which will not only facilitate future clinical work but also provide a theoretical basis for developing statins and Apo A1 mimetic peptides for the treatment of EC.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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