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Review

The roles, signalling pathways and therapeutic implications of Apoc1 in cancer

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Abstract
The apolipoprotein C (Apoc) family comprises a group of low-molecular-weight proteins that are essential for modulating lipoprotein metabolism, primarily influencing lipid transport and metabolic pathways. Apoc1, a member of the Apoc family, is consistently overexpressed across various cancers, significantly correlating with poor prognosis. The multifaceted role of Apoc1 includes promoting cancer progression by activating key signalling pathways such as epithelial-mesenchymal transition (EMT), mitogen-activated protein kinases (MAPK), STAT3 and WNT3 A. Additionally, Apoc1 contributes to the regulatory networks involving lncRNAs and miRNAs, thereby influencing cancer. This comprehensive review delineates Apoc1's mechanisms within malignant tumours and assesses its prognostic implications for patients with cancer. The aim is to shed light on potential novel therapeutic strategies in oncology, potentially revolutionising patient care and thereby enhancing patient survival rates and quality of life.

Keywords Apoc1 · Cancer · Prognosis · Epithelial–mesenchymal transition · Mitogen-activated protein kinases

Abbreviations

Apoc	Apolipoprotein C
Apoc1	Apolipoprotein C1
EMT	Epithelial mesenchymal transition
MAPK	Mitogen-activated protein kinases
LPL	Lipoprotein lipase
CETP	Cholesteryl ester transfer protein
VLDL	Very-low-density lipoprotein
HDL	High-density lipoprotein
OV	Ovarian cancer
BC	Breast cancer
CC	Cervical cancer
CRC	Colorectal cancer
ESCA	Oesophageal cancer
HCC	Hepatocellular carcinoma
RCC	Renal cell carcinoma

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ccRCC Clear cell renal cell carcinoma
PCa Prostate cancer
PC Pancreatic cancer
GC Gastric cancer
OS Overall survival
DFS Disease-free survival
PFS Progression-free survival
LNM Lymph node metastasis
STAT3 Signal Transducer and Activator of Transcription 3

1 Background

Cancer has emerged as a critical global health concern in recent decades, imposing serious threats to human well-being as well as considerable financial and social burdens. In 2022, there were approximately 19.98 million new cancer cases and 9.74 million cancer deaths globally. Among males, lung, prostate, and stomach cancers were most common; among females, breast, lung, and cervical cancers predominated. Data show that one in five individuals will develop cancer in their lifetime, with cancer mortality rates at one in nine for males and one in twelve for females. Projections indicate that by 2050, new cancer cases could exceed 35 million, 77% increase from 2022, while cancer mortality may double [1–3]. These reports highlight the continued necessity for effective cancer prevention, screening, and treatment initiatives.

The progression of cancer involves dysregulated gene expressions that profoundly influence patient prognosis and disease advancement [4–7]. Apolipoprotein C1 (Apoc1) has been extensively studied as an oncogene in ovarian cancer (OV), cervical cancer (CC), colorectal cancer (CRC), oesophageal cancer (ESCA), breast cancer (BC), pancreatic cancer (PC), and other cancers [8–14]. For example, Shi et al., demonstrated that reducing Apoc1 expression in CC promotes cancer cell apoptosis, inhibits migration and invasion and suppresses tumorigenicity in vivo, highlighting its association with poor prognosis of cancer patients [11]. Guo et al., reported Apoc1 overexpression in ESCA tissues, facilitating cancer progression. Reduction of Apoc1 levels inhibits cancer cell proliferation, migration and invasion, closely correlating with various prognostic indicators [13]. Currently, only a limited number of studies have explored the association between apolipoproteins and cancer [15, 16]. However, there is a significant gap in the field regarding specific and comprehensive research on the connection between Apoc1 and cancer in real-world settings. Therefore, this review elucidates Apoc1's biological roles in cancer progression, explores associated signalling mechanisms and discusses its implications for patient prognosis, offering promising candidates for clinical applications in cancer treatment.

2 Biological roles of Apoc1

Apoc1 has been reported to play a role in lipid metabolism regulation. It modulates lipid metabolism by inhibiting lipoprotein lipase (LPL) activity, influences lipoprotein metabolism through suppression of cholesteryl ester transfer protein (CETP) activity, impacts very-low-density lipoprotein (VLDL) metabolism and promotes high-density lipoprotein (HDL) maturation. Thus, Apoc1 may indirectly influence inflammatory and immune processes by modulating lipoprotein metabolism. In diabetic patients, the function of Apoc1 is impaired, particularly its regulatory effect on CETP activity, which may be associated with the elevated plasma CETP activity observed in these patients. Apoc1 may also influence cardiovascular diseases, manifesting as either pro-atherogenic or anti-atherogenic effects. However, its direct association with cardiovascular risk remains uncertain and is subject to debate due to differing metabolic contexts. Additionally, Apoc1 has been implicated in viral infections, cancer progression, and cognitive function, though the precise mechanisms underlying these associations warrant further exploration [17, 18].

Cancer development is a multi-stage, complex process incorporating the expression and functions of various molecules that regulate cell proliferation, apoptosis, tumour migration and invasion, all of which substantially influence cancer prognosis [19–25]. Apoc1's critical role in tumour cell growth and migration underscores its oncogenic function across diverse cancers, thereby promoting cancer initiation and progression (Tables 1 and 2).

Table 1 Functional characterisation of Apoc1 in various types of cancer growth

Type	Functions	Methods	Role	Refs.
OV	Proliferation, cell cycle, apoptosis	CCK- 8, colony formation, and flow cytometry	Oncogene	[8]
BC	Proliferation	Edu, and colony formation	Oncogene	[9, 10]
CC	Proliferation, apoptosis	Edu, flow cytometry, and CCK- 8	Oncogene	[11]
CRC	Proliferation, cell cycle, apoptosis	CCK- 8, colony formation, and flow cytometry	Oncogene	[12, 23]
PC	Proliferation, apoptosis	CCK- 8, and TUNEL	Oncogene	[14]
GC	Proliferation, apoptosis	CCK- 8, MTT, flow cytometry, and colony formation	Oncogene	[22, 42]
HCC	Proliferation	Edu, colony formation, and CCK- 8	Oncogene	[24]
Glioma	Proliferation	CCK- 8, MTT, and Edu	Oncogene	[25, 33]
RCC	Proliferation, cell cycle	CCK- 8, colony formation, and flow cytometry	Oncogene	[26]
ccRCC	Proliferation	CCK- 8, and colony formation	Oncogene	[28]
PCa	Proliferation, cell cycle, apoptosis	MTT, colony formation, and flow cytometry	Oncogene	[29]
Osteosarcoma	Proliferation, apoptosis	CCK- 8, colony formation, and TUNEL	Oncogene	[30]

Apoc1 apolipoprotein C1, *OV* ovarian cancer, *BC* breast cancer, *CC* cervical cancer, *CRC* colorectal cancer, *PC* pancreatic cancer, *GC* gastric cancer, *HCC* hepatocellular carcinoma, *RCC* renal cell carcinoma, *ccRCC* clear cell renal cell carcinoma, *PCa* prostate cancer

Table 2 Functional characterisation of Apoc1 in various cancer metastases

Type	Functions	Methods	Role	Refs.
OV	Invasion, metastasis	Transwell	Oncogene	[8]
BC	Invasion, metastasis	Transwell, and wound healing	Oncogene	[9, 10]
CC	Invasion, metastasis	Transwell, and wound healing	Oncogene	[11]
CRC	Invasion, metastasis	Transwell, and wound healing	Oncogene	[12, 23]
PC	Invasion	Transwell	Oncogene	[14]
GC	Invasion, metastasis	Transwell, and wound healing	Oncogene	[22]
Glioma	Invasion, metastasis	Transwell, and wound healing	Oncogene	[25, 33]
RCC	Invasion, metastasis	Transwell	Oncogene	[26]
ccRCC	Invasion, metastasis	Transwell, and wound healing	Oncogene	[28, 43]
Osteosarcoma	Invasion, metastasis	Transwell, and wound healing	Oncogene	[30]

Apoc1 apolipoprotein C1, *OV* ovarian cancer, *BC* breast cancer, *CC* cervical cancer, *CRC* colorectal cancer, *PC* pancreatic cancer, *GC* gastric cancer, *RCC* renal cell carcinoma, *ccRCC* clear cell renal cell carcinoma

2.1 The roles of Apoc1 in cell growth

During tumour growth, Apoc1 plays a crucial role in promoting the proliferation of cancer cells, while suppressing its expression can inhibit proliferation and induce apoptosis (Table 1). For instance, Yang et al., demonstrated using CCK- 8 and colony formation assays that reduced Apoc1 expression impedes OV cell growth [8]. Similarly, Zhang et al., found high Apoc1 expression in BC cells [9, 10], which corresponded with an increased proliferative and colony-forming capacity in vitro [9]. Furthermore, Shi et al., reported that upregulated Apoc1 acts as an oncogene in CC, whereas Apoc1 knockdown suppresses cell proliferation in CC cell lines and promotes apoptosis [11]. In CRC, Ren et al., observed that silencing Apoc1 reduces colony formation after conventional culture for 10–14 days. Additionally, Western blot analysis indicated that silencing Apoc1 downregulated the protein levels of G1 phase-related cyclin D1 and G2 phase-related cyclins B1 and Bcl- 2, while caspase- 9 was upregulated, indicating that silencing Apoc1 may induce G0/G1 phase cell cycle arrest and apoptosis in CRC [12]. Takano et al., showed in PC that inhibiting Apoc1 expression suppresses cell proliferation and induces apoptosis [14]. In hepatocellular carcinoma (HCC), Hao et al., demonstrated that inhibiting Apoc1 reduces tumour volume and weight in nude mice, resulting in reduced tumour proliferation [24]. Guo et al., documented Apoc1's overexpression in oesophageal, gastric and glioblastoma cancers, where downregulation inhibits cell growth and disrupts tumour progression [13, 22, 25]. Furthermore, Jiang et al., reported Apoc1 to be highly expressed in renal cell carcinoma (RCC) tissues. Moreover, their cytometry analysis indicated that Apoc1 knockdown in RCC cells increased the proportion of cells in the G0/G1 phase while decreasing those in the S phase, suggesting that Apoc1 downregulation

can inhibit RCC proliferation by modulating the cell cycle [26]. Gui et al., reported that Apoc1 is highly expressed in clear cell renal cell carcinoma (ccRCC) and promotes tumour progression as an oncogene [27]. Subsequently, Wang et al., further validated through in vitro functional experiments that Apoc1 upregulation in the UT33 A cell line promotes cell proliferation, whereas downregulation in the 786-O cell line produced the opposite effect, confirming Apoc1's role in promoting ccRCC cell proliferation and colony formation [28]. In prostate cancer (PCa), Su et al., showed that knocking down Apoc1 induces cell cycle arrest and apoptosis, inhibiting proliferation [29]. Li et al., reported that silencing Apoc1 expression in osteosarcoma cells inhibited the proliferation of osteosarcoma cells and promoting their apoptosis [30]. In addition, Apoc1 can also store tumor formation ability of gastric cancer and ccRCC cells in nude mice [11, 26].

2.2 The role of Apoc1 in cell metastasis

Tumour migration and invasion are critical stages in cancer progression, where Apoc1 plays a pivotal role in promoting these pathological processes (Table 2). For instance, Yang et al., demonstrated Apoc1's regulation of migration and invasion in OV cells in vitro [8]. In CC, Shi et al., showed that Apoc1 knockdown hindered cell migration and invasion, with in vivo experiments confirming reduced lung metastases upon Apoc1 downregulation, highlighting its role in CC metastasis. Furthermore, xenograft tumour formation and mouse tumorigenicity experiments demonstrated that the downregulation of Apoc1 significantly reduced the number and size of lung metastases [11]. Ren et al., reported similar findings in CRC, where silencing Apoc1 diminished cell migration and invasion capabilities [12], corroborated by Lu et al., analysis of Apoc1's promotion of CRC cell migration and invasion in vitro [31]. In RCC, Jiang et al., established that Apoc1 promotes in vivo migration and invasion by modulating EMT [26]. Wang et al., further supported Apoc1's role in promoting invasion and migration in ccRCC through functional experiments [28]. Takano et al., documented Apoc1's contribution to invasiveness across various cancers including pancreatic, gastric, glioblastoma and osteosarcoma, with the inhibition of Apoc1 expression suppressing tumour cell invasion and migration [14, 22, 25, 30].

3 Mechanisms of Apoc1 in cell growth and migration

3.1 LncRNA-miRNA-Apoc1 signalling pathway

Studies have elucidated the mechanisms by which lncRNAs can modulate the expression of Apoc1 via miRNAs, thereby exerting a significant impact on cancer progression (Fig. 1). For instance, Lu et al., identified the lncRNA ZEB1-AS1-miR-335 - 5p-Apoc1 competing endogenous RNA (ceRNA) network as pivotal in CRC progression. Overexpression of miR-335 - 5p has been shown to decrease Apoc1 expression levels, while upregulation of lncRNA ZEB1-AS1 competitively increases Apoc1 expression by sequestering miR- 335 - 5p, thus promoting CRC cell invasion and migration [31]. Yang et al., demonstrated that miR- 378a- 5p functions as a tumor suppressor in ESCA by targeting Apoc1 and CEP55 [32]. In glioblastoma, Yang et al., showed that Apoc1 promotes malignancy through the TGFβ2 signalling pathway. Additionally,

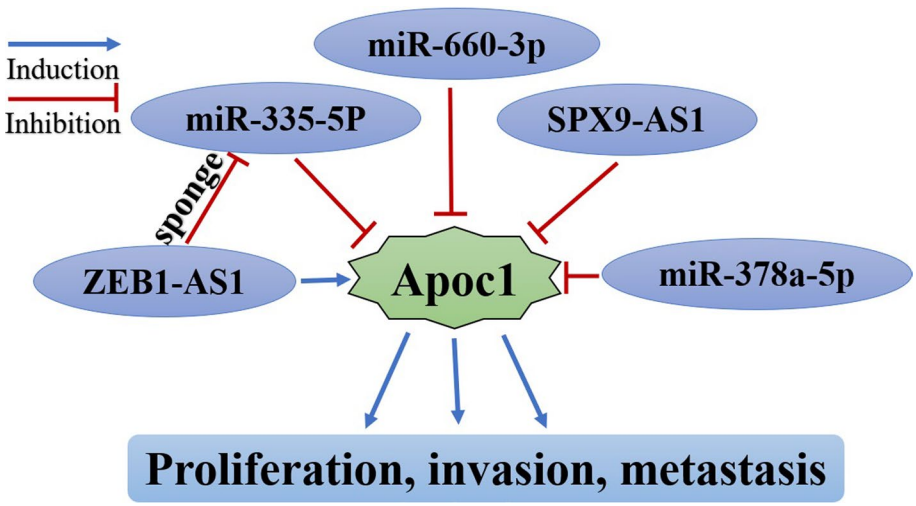

Fig. 1 The signalling mechanisms of lncRNA/miRNA/Apoc1 in cancer

their database analysis and transfection experiments revealed that miR- 660 - 3p directly targets the 3'-UTR of APOC1 mRNA, thereby inhibiting Apoc1 expression and consequently suppressing cell proliferation, migration, and invasion [33]. Furthermore, Mireya et al., demonstrated that inhibiting lncRNA SOX9-AS1 expression decreases Apoc1 levels, which in turn reduces triglyceride synthesis and inhibits migration and invasion in triple-negative breast cancer (BC) [34]. These findings underscore the role of lncRNA in modulating Apoc1 expression via miRNA regulation, thereby impacting cancer progression.

3.2 Apoc1-MAPK signalling pathway

The MAPK pathway, a vital cellular signaling cascade, pertains to fundamental biological processes such as cell proliferation, differentiation, apoptosis and pathogenesis. Apoc1 activates the MAPK signalling pathway to regulate cancer progression (Fig. 2). According to Zhang et al., blockage of JNK using SP600125 significantly elevated the APOC1-induced cell proliferation, indicating that Apoc1 promotes the occurrence and progression of BC by inhibiting the activation of the JNK/MAPK pathway [9]. Liu et al., demonstrated that in BC, silencing Apoc1 suppresses the transcription of target genes associated with growth and metastasis in vitro by inhibiting the MAPK/ERK signalling pathway [10]. In CRC, Ren et al., observed that Apoc1 knockdown decreases phosphorylated MAPK levels, influencing carcinogenesis without significant changes in phosphorylated forms of phosphorylated-Erk1/2 (p-ERK) and phosphorylated-JNK (p-JNK) [12]. Su et al., found that in PCa, Apoc1 suppression reduces survival proteins, phosphorylated Rb and p21 levels through the MAPK pathway, while increasing caspase- 3 expression, suggesting Apoc1's role in mediating cell survival, cell cycle distribution and apoptosis in PCa [29].

3.3 Apoc1-EMT signalling pathway

EMT is a critical biological process that endows epithelial-derived tumour cells with migratory and invasive properties, essential for tumour progression and metastasis [35–41]. The onset of EMT is associated with various transcription factors, protein molecules, and growth factors, involving complex molecular mechanisms and signalling transduction pathways [35]. For example, Yang et al., demonstrated Apoc1's promotion of EMT in OV [8]. In CC, Shi et al., showed that Apoc1 knockdown reduces N-cadherin, vimentin, Twist, Slug, Snail and CD44 expression, while increasing E-cadherin levels, indicating Apoc1's promotion of migration and invasion via EMT [11]. Additionally, Zhang et al., found that in BC cells, Apoc1 inhibits E-cadherin and stimulates vimentin expression, thereby affecting the EMT process [9]. An et al., highlighted that ZNF460 combined with Apoc1 promoter to facilitate Apoc1 transcription, which accelerates EMT and gastric cancer (GC) cell promotion [20]. Apco1's involvement in EMT has been documented across various cancers including RCC, GC, glioma and ccRCC in the Fig. 3 [22, 25, 26, 28, 29, 35].

3.4 Apoc1-related crosstalk signalling pathway

Apoc1-related crosstalk signalling pathways were showed in the Fig. 4. Liu et al., reported that silencing APOC1 can further restrain NF-κB by inhibiting MAPK/ERK [10]. Jiang et al., highlighted the close association between the Wnt3a signaling.

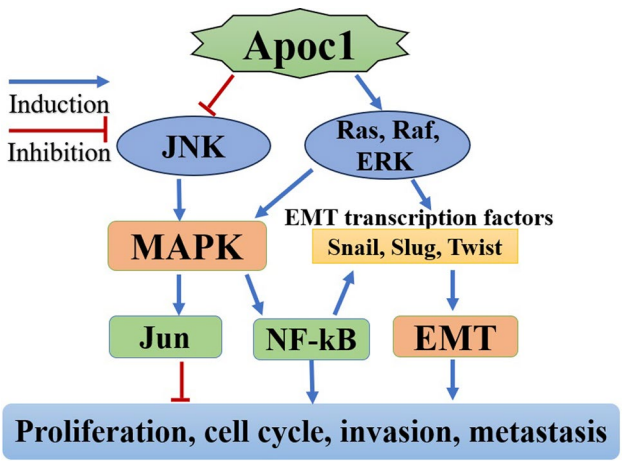

Fig. 2 The Apoc1/MAPK signalling mechanism in cancer progression

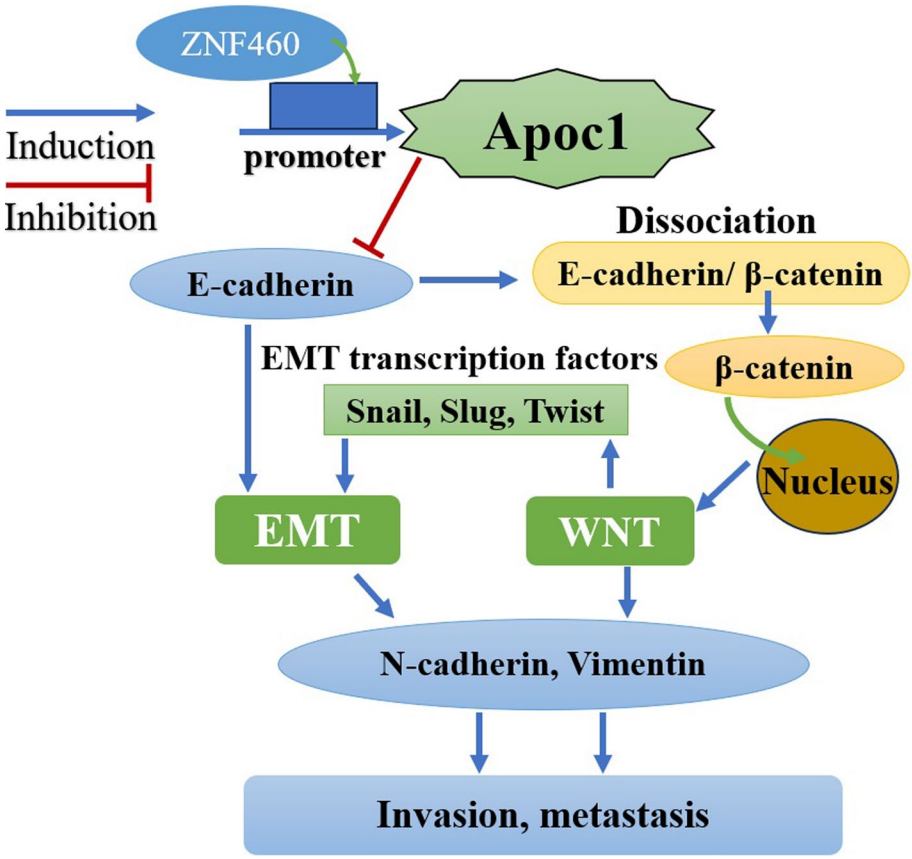

Fig. 3 The Apoc1/EMT signalling mechanism in cancer progression

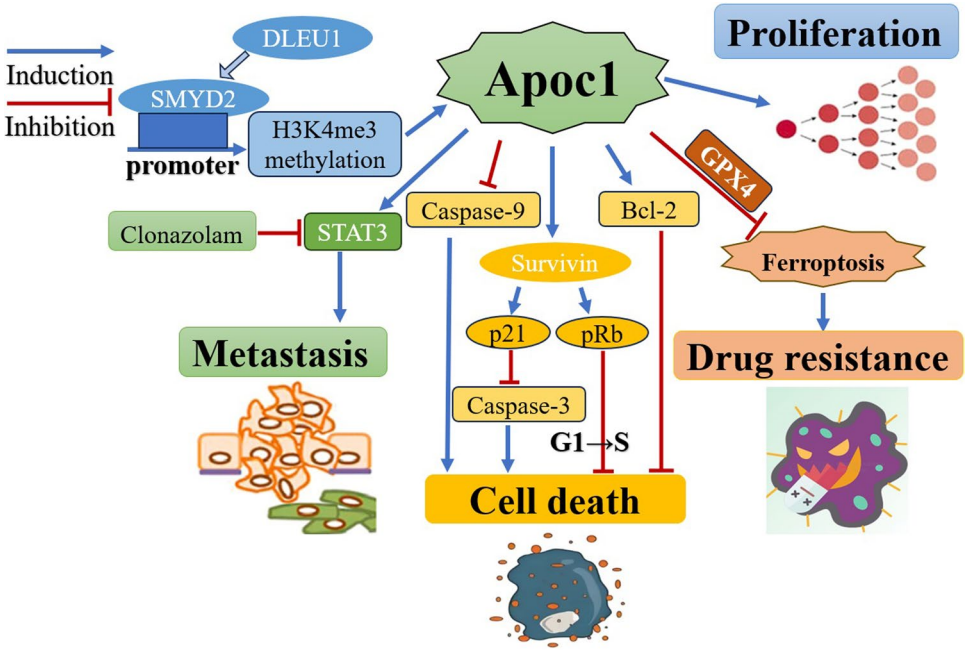

Fig. 4 The other Apoc1 signalling mechanism in cancer progression

Transfection of sh-Wnt3a effectively downregulated Wnt3a and β-catenin in RCC cells and reversed the upregulation of Wnt3a and β-catenin caused by APOC1 overexpression, which indicated that APOC1 exacerbated the malignant progression of RCC at least partially by activating Wnt3a signaling [26]. Li et al., demonstrated that silencing Apoc1 in osteosarcoma cells modulates MTCH2 expression, promoting oxidative phosphorylation (OXPHOS) while inhibiting the Warburg effect (aerobic glycolysis), thus suppressing tumour progression [30]. Xu et al., found that DLEU1 recruits SMYD2

to the Apoc1 promoter, enhancing H3 K4 me3 methylation and Apoc1 expression, thereby promoting GC cell proliferation and glycolysis [42]. Liang et al., showed that the knockdown of Apoc1 leads to a decrease in the activation of phosphorylated Signal Transducer and Activator of Transcription 3 (STAT3) in glioma cells. They also found that STAT3 inhibitor can prevent Apoc1-induced glioma cell migration [25]. Furthermore, Li et al., identified Apoc1 as a novel pre-metastatic factor in ccRCC cells, activating STAT3 to enhance metastasis [43]. Hu et al., reported that Apoc1 knockdown enhances sorafenib-induced ferroptosis through GPX4, overcoming sorafenib resistance in ESCA cells both in vitro and in vivo [44].

4 Prognostic implications of Apoc1 overexpression in patients with tumours

Apoc1 is frequently overexpressed in tumours such as cervical cancer, colorectal cancer and oesophageal cancer, with high levels correlating with poor prognosis (Table 3). In BC, elevated Apoc1 expression correlated with advanced TNM staging and lymph node metastasis (LNM) [9]. Similarly, in CC tissue, increased Apoc1 expression has been closely linked to serum SCCA, tumor differentiation and FIGO staging [11]. In CRC tissues, high Apoc1 expression has been correlated with N stage, M stage, TNM stage, shorter overall survival (OS) and Disease-Free Survival (DFS) [12, 23]. In ESCA, Apoc1 overexpression is significantly linked to LNM, tumor size and grade [13]. Patients with RCC exhibiting increased Apoc1 expression have been found to have advanced histological grading and TNM staging [26]. In ccRCC tissues, elevated Apoc1 expression was associated with larger tumour size, advanced histological grading, shorter OS and PFS (Progression-free survival) [27]. Additionally, Liang et al., reported that Apoc1 is highly expressed in tumour tissues such as glioma, pancreatic cancer and hepatocellular carcinoma [14, 22, 24, 25, 29, 30]. Further investigation is warranted to clarify its prognostic significance in these cancers. The persistent overexpression of Apoc1 observed in the majority of studies, coupled with its strong correlation with adverse prognosis, hints at its potential as a novel biomarker for predicting patient outcomes and guiding therapeutic strategies. Moreover, the expression of Apoc1 across various cancer types also renders it a promising target for personalized therapy.

5 Conclusions and prospects

Current research highlights Apoc1 as an oncogene in multiple malignancies, exerting proto-oncogenic functions by regulating cellular metabolism, growth, proliferation, apoptosis, migration and invasion. The involvement of Apoc1 in tumour progression encompasses intricate mechanisms, including modulation of protein expression, promotion of the EMT process, modulation of the MAPK signalling mechanism, participation in Apoc1-miRNA-lncRNA regulatory networks and regulation of tumour progression via the STAT3 pathway. Clinically, Apoc1 frequently shows elevated

Table 3 Expression and clinical significance of Apoc1 in various cancers

Type	Expression	Clinical significance	Refs.
BC	High	Higher TNM stage and LNM	[9]
CC	High	Tumor differentiation, FIGO staging and serum SCCA	[11]
CRC	High	TNM stage, worse OS and DFS	[12, 23]
ESCA	High	LNM, tumor size and grade	[13]
PC	High	–	[14]
GC	High	–	[22]
HCC	High	–	[23]
Glioma	High	–	[25]
RCC	High	Histological grade and TNM stage	[26]
ccRCC	High	Tumor size, histological grade, and PFS	[27]
PCa	High	–	[29]
Osteosarcoma	High	–	[30]

Apoc1 apolipoprotein C1, *BC* breast cancer, *CRC* colorectal cancer, *CC* cervical cancer, *ESCA* oesophageal cancer, *PC* pancreatic cancer, *GC* gastric cancer, *HCC* hepatocellular carcinoma, *RCC* renal cell carcinoma, *ccRCC* clear cell renal cell carcinoma, *PCa* prostate cancer, *OS* overall survival, *DFS* disease-free survival, *PFS* progression-free survival, *LNM* lymph node metastasis

expression across different cancers, typically correlating with disease severity and poor prognosis. The downregulation of Apoc1 expression holds promise for decelerating tumour progression by inhibiting cancer cell proliferation and migration, potentially improving patient prognosis, which is crucial for advancing cancer treatment strategies. Studies have established a link between Apoc1 and lipid metabolism [17]. However, there is a lack of literature investigating the association between Apoc1 expression and lipid metabolism in cancer. Future research efforts should prioritize exploration of this area. Many current studies are constrained by their dependence on in vitro experiments and the absence of in vivo validation. Further comprehensive research is required across various tumor cell lines and clinical samples to elucidate the role and regulatory mechanisms of Apoc1 in tumor progression, supported by robust experimental and clinical data. Given that the expression patterns of mRNA and proteins are influenced by various factors, such as post-transcriptional modifications and translational efficiency, it is crucial to specify whether the expression levels of Apoc1 and their associations with other relevant factors are assessed at the gene, mRNA, or protein level in the future. Apoc1 holds promise as a biomarker for tumor diagnosis, prognosis, tumor microenvironment and treatment response. Such efforts will lay a solid foundation for future targeted therapies, including antibody-based and RNA-based therapies aimed at Apoc1. Molecular targeted therapy involving drug interventions targeting Apoc1 is a crucial area of inquiry within medical oncology. Targeted therapy is significantly constrained by complex factors, including tumor heterogeneity. Furthermore, the development of targeted drugs is impeded by issues such as immunogenicity and challenges in drug delivery. Additionally, the emergence of drug resistance poses a critical challenge. These obstacles may be mitigated through combination therapies, the development of drugs that target resistance mechanisms, and the implementation of personalized treatment strategies, which could potentially enhance therapeutic efficacy and tolerability. Investigating Apoc1's expression patterns, functions, and specific molecular mechanisms within the context of immunotherapy and CAR T cell therapy holds significant promise. Utilizing advanced technologies and enhancing access to tissue samples and clinical information will further our understanding and application of Apoc1 in these innovative treatment modalities.

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Declarations

Ethics approval and consent to participate Not applicable.

Competing interests The authors declare no competing interests.

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