Clinical and Translational Research
SERPINH1 promoted the proliferation and metastasis of colorectal cancer by activating PI3K/Akt/mTOR signaling pathway

Jin XS et al. SERPINH1 activating PI3K/Akt/mTOR signaling pathway in CRC
Abstract

BACKGROUND
Serpin peptidase inhibitor clade H member 1 (SERPINH1) was initially recognized as an oncogene implicated in various human malignancies. Nevertheless, the clinical relevance and functional implications of SERPINH1 in colorectal cancer (CRC) remain largely elusive.

AIM
To investigate the effects of SERPINH1 on CRC cells and its specific mechanism.

METHODS
Quantitative real-time polymerase chain reaction, western blotting analysis, The Cancer Genome Atlas data mining and immunohistochemistry were employed to examine SERPINH1 expression in CRC cell lines and tissues. A series of in-vitro assays were performed to demonstrate the function of SERPINH1 and its possible mechanisms in CRC.

RESULTS
SERPINH1 demonstrated elevated expression levels in both CRC cells and tissues, manifested at both mRNA and protein tiers. Elevated SERPINH1 levels correlated closely with advanced T stage, lymph node involvement, and distant metastasis, exhibiting a significant association with poorer overall survival among CRC patients. Subsequent investigations unveiled that SERPINH1 overexpression notably bolstered CRC cell proliferation, invasion, and migration in vitro, while conversely, SERPINH1 knockdown elicited the opposite effects. Gene set enrichment analysis underscored a correlation between SERPINH1 upregulation and genes associated with cell cycle regulation. Our findings underscored the capacity of heightened SERPINH1 levels to expedite G1/S phase cell cycle progression via phosphatidylinositol 3-
kinase/AKT/mechanistic target of rapamycin pathway activation, thereby facilitating CRC cell invasion and migration.

CONCLUSION

These findings imply a crucial involvement of SERPINH1 in the advancement and escalation of CRC, potentially positioning it as a novel candidate for prognostic assessment and therapeutic intervention in CRC management.

**Key Words:** Serpin peptidase inhibitor clade H member 1; Colorectal cancer; Proliferation; Cell cycle; Phosphatidylinositol 3-kinase/AKT/mTOR

Jin XS, Chen LX, Ji TT, Li RZ. SERPINH1 promoted the proliferation and metastasis of colorectal cancer by activating PI3K/Akt/mTOR signaling pathway. *World J Gastrointest Oncol* 2024; In press

**Core Tip:** The expression of serpin peptidase inhibitor clade H member 1 (SERPINH1) was observed to be elevated in both colorectal cancer (CRC) cells and tissues at mRNA and protein levels. Increased SERPINH1 expression demonstrated a close association with the T stage, lymph node status, and distant metastasis in CRC patients, displaying a significant correlation with poor overall survival. Subsequent investigations revealed that the overexpression of SERPINH1 markedly enhanced the *in vitro* proliferation, invasion, and migration capabilities of CRC cells. Conversely, the knockdown of SERPINH1 resulted in the opposite effects. In addition, our study validated that the overexpression of SERPINH1 could stimulate the G1/S phase cell cycle transition through the activation of the phosphatidylinositol 3-kinase (PI3K)/AKT/mechanistic target of rapamycin (mTOR) pathways. Additionally, it was observed that the overexpression of SERPINH1 facilitated cell invasion and migration by modulating the PI3K/AKT/mTOR pathway. These findings emphasize the pivotal role of SERPINH1 in
promoting CRC progression, providing insights into its potential as a therapeutic target for CRC treatment.

INTRODUCTION
Colorectal cancer (CRC) ranks among the prevailing malignancies globally, posing a significant global health challenge. Despite advances in early detection and therapeutic modalities, CRC continues to be a significant contributor to cancer-related morbidity and mortality. Deciphering the molecular mechanisms driving CRC progression is imperative for the advancement of innovative diagnostic and therapeutic approaches.

The serpin peptidase inhibitor, clade H [heat shock protein 47 (HSP47)], member 1, commonly referred to as serpin peptidase inhibitor clade H member 1 (SERPINH1) or HSP47, is a molecular chaperone protein primarily known for its role in collagen biosynthesis and extracellular matrix homeostasis\(^1\). The synthesis of HSP47 consistently mirrors that of collagen in developing tissues, various cell lines, and pathological conditions associated with collagen, such as fibrosis\(^2\).

Emerging evidence suggests that SERPINH1 may also play a pivotal role in cancer biology. The upregulation of SERPINH1 has been observed in various cancer types, and it has been associated with tumor growth, metastasis, and poor clinical outcomes\(^3-5\). For instance, increased SERPINH1 expression regulated EMT and gastric cancer metastasis via the Wnt/\(\beta\)-catenin signaling pathway\(^6\). A study conducted by Pan \textit{et al}\(^6\) demonstrated that SERPINH1 holds promise as a candidate biomarker for stratifying Clear cell renal cell carcinoma patients into low- and high-risk groups. Furthermore, SERPINH1 has been shown to be associated with dasatinib responses and interstitial subtypes\(^7\), and circCAMSAP1 promotes NPC proliferation and metastasis by binding to the 3’ untranslated region of SERPINH1 nasopharyngeal carcinoma\(^4\). Additionally, it has been reported that SERPINH1 (HSP47) enhances CRC cell survival by suppressing apoptosis, elevating AKT phosphorylation, and downregulating the expression of the AKT-specific phosphatase PHLPP1 in response to chemotherapy exposure\(^8\). However, in addition to the effect on CRC cells treated with chemotherapy,
the role of SERPINH1 in CRC progression and its underlying molecular mechanisms remain poorly understood in the current scientific literature.

In this study, we observed a marked elevation of SERPINH1 expression in both CRC cell lines and tissues. Subsequent *in vitro* experiments revealed that the overexpression of SERPINH1 resulted in a substantial enhancement of CRC cell proliferation, invasion, migration, and tumorigenic potential. Conversely, the silencing of SERPINH1 had the opposite effect, inhibiting these cellular processes. Furthermore, we extended our inquiry to elucidate the molecular mechanisms associated with SERPINH1-mediated effects. It was evident that the upregulation of SERPINH1 accelerated the transition from G1 to S phase of the cell cycle. Of particular significance, this transition was initiated by SERPINH1 through the activation of AKT signaling, concurrent with the downregulation of mechanistic target of rapamycin (mTOR) activity and FOXO1 transcriptional competence. Moreover, we observed that the inhibition of the mTOR pathway had the capacity to induce the suppression of invasion, migration, and proliferation in cells with elevated SERPINH1 expression. The results of this study indicate that SERPINH1 may act as an oncogene in the progression of CRC and could serve as a valuable prognostic indicator for this malignancy.

**MATERIALS AND METHODS**

*Specimen collection*

CRC tissues were collected from the Third Affiliated Hospital of Wenzhou Medical University. The specimen was stored at -80 °C immediately after surgery. All patients were diagnosed with CRC. Approval for this study was obtained from the Ethics Committee of the Third Affiliated Hospital of Wenzhou Medical University. The clinicopathological information of the patients can be found in Table 1.

*Transfection*

To investigate the role of SERPINH1 in CRC, HCT116 were transfected with SERPINH1 overexpression plasmids or control vectors using lipofectamine 3000 according to the
manufacturer’s instructions. To knock down SERPINF1 expression, HCT8 were transfected with SERPINF1-specific small interfering RNA (siRNA) or non-targeting control siRNA using lipofectamine 3000 according to the manufacturer’s instructions.

**Immunoblot**
CRC cells and tissues were harvested and lysed in immunoprecipitation buffer. Protein quantification was performed using the BCA method, and 20 µg of protein samples were subjected to electrophoresis. Subsequently, membranes were exposed to primary antibodies overnight at 4 °C. Following this, horseradish peroxidase-conjugated secondary antibodies were applied and incubated for 1 h. Protein bands were visualized using the ChemiDocXRS+ System.

**Cell counting kit-8 proliferation assay**
According to the manufacturer’s instructions, the proliferation of CRC cells was detected by cell counting kit 8 (CCK-8) assay (APExBIO, Houston, United States). Ten microliters of CCK-8 solution were added to each well and incubated at 37 °C for 2 h. The absorbance at 450 nm was measured three times every 24 h using spectrophotometry.

**5-ethynyl-2’-deoxyuridine incorporation assay**
5-ethynyl-2’-deoxyuridine (EdU) assays were conducted utilizing the cell-light EdU DNA cell proliferation kit (RiboBio, Guangzhou, China) as per the manufacturer’s instructions. The quantification of positive cells was determined based on the ratio of red to blue fluorescence staining.

**Colony formation assay**
A total of 1000 cells per well were seeded into a six-well plate and allowed to proliferate until reaching confluence. Following 2-3 wk of incubation, the cells were fixed with 4% paraformaldehyde for 15 min, stained with 0.1% crystal violet solution for 10 min, and
the number of colonies was enumerated. The mean values were derived from three independent experiments.

**Transwell assay**

Transwell chambers with 8 μm pore size were employed following the manufacturer’s protocol. CRC cell suspension (1 × 10^5 cells/well) in serum-free medium was seeded into the upper chamber, while medium supplemented with 10% foetal bovine serum was added to the lower compartment. Subsequently, residual cells above the chamber were wiped away using a cotton ball, and migrated cells adhering to the membrane were fixed with 4% paraformaldehyde and stained with crystal violet. The stained cells were randomly photographed and counted from three different visual fields.

**Cell cycle test**

Each well of the 6-well plate was inoculated with 100,000 cells. The cells were collected and treated with 1 mL DNA staining solution and 10 μL penetrant solution for 30 min. Immediately afterward, the samples were examined by flow cytometry.

**Statistical analysis**

Statistical analyses were conducted using SPSS software. The data are expressed as means ± SD or standard error of the mean (SEM) derived from three independent experiments. Statistical significance was assessed using the t-test or analysis of variance (ANOVA), with a significance level set at P < 0.05.

**RESULTS**

**SERPINH1 is up-regulated in CRC**

We first examined the expression of SERPINH1 in publicly available CRC datasets using The Cancer Genome Atlas (TCGA) database. The results revealed a significant up-regulation of SERPINH1 in CRC tissues compared to normal tissues (Figure 1A). Furthermore, increased expression of SERPINH1 was linked to poor overall survival
[overall survival (OS), \( P = 0.014 \) and disease-free survival (DFS), \( P = 0.034 \)] in COAD (Figure 1B and C). In order to confirm this finding, quantitative real-time polymerase chain reaction (qPCR) was employed to assess the expression levels of SERPINH1 mRNA in 50 freshly collected CRC tissues and their corresponding adjacent normal tissues. As illustrated in Figure 1D, the expression of SERPINH1 mRNA in CRC tissues demonstrated a substantial elevation when juxtaposed with that in adjacent non-malignant tissues \((P < 0.05)\). Intriguingly, individuals with lymph node metastasis displayed elevated SERPINH1 mRNA levels in CRC tissues relative to those without lymph node metastasis \((P < 0.05, \text{Figure 1E})\). Western blotting and qPCR analysis revealed heterogeneous expression levels of SERPINH1 in FHC cells and seven CRC cell lines (Figure 1F and G). Moreover, western blotting demonstrated higher SERPINH1 protein expression levels in 8 pairs of CRC tissues compared to their corresponding normal colorectal tissues (Figure 1H). Immunohistochemistry also showed the same results (Figure 1I). This finding is consistent with previous studies that have reported elevated SERPINH1 expression in various cancer types, suggesting its potential role in tumorigenesis.

**High SERPINH1 expression is associated with several aggressive features and poor prognosis of CRC**

To further explore the clinical relevance of SERPINH1 in CRC, we analyzed the association between SERPINH1 expression and clinicopathological features. Elevated SERPINH1 expression exhibited significant associations with advanced tumor stage \((P < 0.05)\), lymph node metastasis \((P < 0.01)\), and distant metastasis \((P < 0.001)\), underscoring its association with aggressive characteristics of CRC (Table 1). We also performed survival analysis, which revealed that patients with high SERPINH1 expression had significantly poorer OS compared to those with low SERPINH1 expression (Figure 1J, \( P < 0.001 \)). This suggests that SERPINH1 expression level may serve as a prognostic marker for CRC, with high expression indicative of a worse clinical outcome.
The overexpression of SERPINH1 promotes the proliferation, invasion, migration, and tumorigenesis of CRC cells

To investigate the functional role of SERPINH1 in CRC, we conducted in vitro experiments using CRC cell lines. The efficiency of SERPINH1 overexpression was verified by western blot and qPCR analysis (Figure 2A). CCK-8 assay, clonal formation assay, and EdU assay showed that overexpression of SERPINH1 promoted the proliferation of HCT116 cells (Figure 2B-E and I). In addition, SERPINH1 overexpression as measured by transwell significantly enhanced the invasion and migration of HCT116 cells (Figure 2F and G). Overexpression of SERPINH1 significantly inhibited the apoptosis ratio of HCT116 cells (Figure 2H and J) and increased the proportion of S-phase cells and decreased the number of G0/G1 phase cells (Figure 2K and L).

The downregulation of SERPINH1 inhibited the proliferation, invasion, migration, and tumorigenicity of CRC cells

To elucidate the effect of SERPINH1 knockout in CRC cells, lentiviral vectors carrying short hairpin RNA specifically targeting SERPINH1 were used to silence endogenous SERPINH1 expression in HCT8 cells (Figure 3A). As shown in Figure 3B-E and I, knockdown of SERPINH1 significantly inhibited cell growth and proliferation. In addition, the invasion and migration capacity of SERPINH1 knock-down cells was lower than that of control cells (Figure 3F and G). Meanwhile, knockdown of SERPINH1 significantly promoted the apoptosis ratio of HCT8 cells (Figure 3H and J) and decreased the proportion of S-phase cells and decreased the number of G0/G1 phase cells (Figure 3K and L). These above results proved that SERPINH1 led to a significant increase in cell proliferation, invasion, and migration of CRC cells.

The function analysis of SERPINH1 in colorectal adenocarcinoma
Further analyses were conducted to assess the function of SERPINH1 in colorectal adenocarcinoma (COAD). To elucidate the potential molecular mechanism of SERPINH1 in COAD, we employed the LinkedOmics database to investigate the biological role of SERPINH1. Figure 4A illustrates the genes positively and negatively correlated with SERPINH1. The top 50 genes are shown in Figure 4B and C. Figure 4D shows a summary of the biological functions of SERPINH1 co-expressed genes in the COAD cohort. In addition, we also studied the function of SERPINH1 negative gene and positive gene in COAD. Kyoto Encyclopedia of Genes and Genomes analysis showed that SERPINH1 functions were enriched in metabolism, infection, adhesion, phosphatidylinositol 3-kinase (PI3K)/AKT, etc. (Figure 4E and F). Combining the above results, it can be concluded that SERPINH1 co-expressed genes may participate in tumor progression and play a role through the PI3K/AKT pathway, which provides important clues for further study of the molecular mechanism of SERPINH1.

**SERPINH1 facilitated the progression of CRC by activating the PI3K/AKT/mTOR and PI3K/AKT/FOXO1 signaling pathways**

To gain a deeper understanding of the molecular mechanisms by which SERPINH1 mediates its oncogenic role in CRC, we conducted an analysis of the interaction network involving SERPINH1 (Figure 5A). Building upon the pathway enrichment analysis conducted earlier, we found that SERPINH1 may be associated with the PI3K/AKT pathway. Additionally, both mTOR and FOXO1 represent pivotal downstream effectors of the PI3K/AKT signaling pathway, and are recognized participants in cell cycle regulation and proliferation\[9,10\]. Therefore, we proceeded to investigate whether the pro-proliferative effects of SERPINH1 are dependent on the PI3K/AKT/mTOR and PI3K/AKT/FOXO1 signaling pathways. Initially, we analyzed the correlation between SERPINH1 and FOXO1 and AKT expression using TCGA database. The results demonstrated a positive correlation between SERPINH1 and FOXO1 and AKT expression (Figure 5 B and C). This observation was further validated through immunofluorescence experiments (Figure 5D and E).
As depicted in Figure 6A, the phosphorylation of AKT [p-AKT (Ser473)], glycogen synthase kinase (GSK)-3β (p-GSK-3), mTOR (p-mTOR), and FOXO1 (p-FOXO1) proteins increased due to the overexpression of SERPINH1 and decreased upon its silencing. These findings imply a potential role for SERPINH1 in regulating the transcriptional activity of mTOR and FOXO1 through activation of the PI3K/AKT signaling pathway. To investigate this hypothesis, CRC cells overexpressing SERPINH1 were treated with an AKT inhibitor (LY294002). We observed a substantial reduction in the expression levels of p-AKT, p-GSK-3β, p-mTOR, and p-FOXO1 in SERPINH1-overexpressing CRC cells upon LY294002 treatment (Figure 6B). Furthermore, we assessed the proliferative capacity of SERPINH1-overexpressing CRC cells by treating them with the AKT inhibitor. EdU and CCK-8 assays demonstrated a significant inhibition of proliferation in these SERPINH1-overexpressing cells compared to control cells (Figure 6C-E). Simultaneously, flow cytometry demonstrated that the proliferation of SERPINH1-overexpressing cells treated with an AKT inhibitor was significantly inhibited compared to control cells (Figure 6F-I). These results offer further support to the notion that SERPINH1 can augment the proliferation of CRC cells by activating both the PI3K/AKT/mTOR and PI3K/AKT/FOXO1 signaling pathways. Our results demonstrated that SERPINH1 promoted CRC progression through the PI3K/AKT/mTOR signaling pathway, which is known for its role in cell growth and survival.

DISCUSSION

In this study, we have demonstrated that SERPINH1 plays a crucial role in promoting the proliferation and metastasis of CRC by activating the PI3K/Akt/mTOR signaling pathway. Our findings shed light on the molecular mechanisms underlying CRC progression and provide potential targets for therapeutic intervention. One of the key findings of our study is the upregulation of SERPINH1 in CRC tissues. This is consistent with previous studies in various cancer types[3,5,11-14], which have also reported increased expression of SERPINH1, especially in CRC[8]. However, unlike the
previous finding that SERPINH1 promoted the survival of CRC cells by resistant to chemotherapy, we found another pathway by which SERPINH1 induced CRC progression. This upregulation may be attributed to multiple factors, including the tumor microenvironment, hypoxia, and the activation of stress response pathways. The fact that SERPINH1 is elevated in CRC suggests its potential as a diagnostic and prognostic marker for this malignancy.

Past studies have suggested the engagement of the PI3K/AKT/mTOR signaling cascade in orchestrating various cellular processes, including cell growth, adhesion, migration, and viability\textsuperscript{[9,15,16]}. Activation of the AKT pathway has been demonstrated to stimulate cell proliferation and oncogenic progression through the modulation of downstream cell cycle regulators\textsuperscript{[17]}. Moreover, activated AKT triggers the phosphorylation of several downstream effectors, including mTOR, FOXO1, and GSK-3\textbeta\textsuperscript{[15,18]}. It has been experimentally confirmed that inhibitors targeting the mTOR result in cell cycle arrest and suppress cell proliferation in Epstein-Barr virus-related T- and natural killer-cell lymphomas\textsuperscript{[19,20]}. Interestingly, according to Gene set enrichment analysis of TCGA database, we observed significant enrichment of the PI3K/AKT pathway in CRC samples with high SERPINH1 expression. These findings lead us to hypothesize that SERPINH1 may regulate cell cycle control factors by targeting mTOR, thereby promoting cell cycle transition.

It has been reported that full activation of AKT requires phosphorylation at Ser473 and Thr308 sites\textsuperscript{[15,18,21]}. LY294002, a small molecule, competively and reversibly inhibits the ATP binding site of various PI3K isoforms, making it a specific inhibitor of the PI3K/AKT pathway. It suppresses tumor proliferation and prompts apoptosis in CRC cells, concomitant with decreased expression of p-AKT (Ser473)\textsuperscript{[22]}. To validate the aforementioned hypothesis, we examined the levels of p-AKT Ser473 and p-mTOR. Our investigation revealed a decrease in p-AKT and p-mTOR expression in CRC cells with SERPINH1 knockdown, whereas an increase was observed in CRC cells overexpressing SERPINH1. Additionally, AKT inhibition significantly reduced the expression of p-AKT and p-mTOR in SERPINH1-overexpressed CRC cells, accompanied by a significant
decrease in cell growth and colony formation. Furthermore, the FOXO1 transcription factors have been acknowledged for their oncogenic functions in regulating the expression of genes involved in diverse cellular processes such as apoptosis, cell proliferation, and oxidative stress.

Given that FOXO1 is one of the genes associated with cell cycle transition\(^{[10]}\), we attempted to verify whether SERPINH1-mediated cell cycle transition relies on the PI3K/AKT/FOXO1 pathway. Similarly, we observed that p-AKT and p-FOXO1 were significantly reduced in SERPINH1-silenced CRC cells, while they increased in SERPINH1-overexpressed CRC cells. Furthermore, inhibition of AKT significantly attenuated p-AKT and phosphorylated FOXO1 levels in CRC cells overexpressing SERPINH1, resulting in the inhibition of cell growth arrest and the formation of colonies. These observations imply that the enhancement of proliferation and tumorigenesis by SERPINH1 might be linked to accelerated cell cycle progression facilitated by the activation of the PI3K/AKT/mTOR and PI3K/AKT/FOXO1 pathways. Our study suggests that the inhibition of SERPINH1 could be a potential strategy for suppressing the PI3K/Akt/mTOR signaling cascade and subsequently impeding CRC cell growth and metastasis. Small molecules or biological agents that specifically target SERPINH1 may hold promise as novel therapeutic interventions.

Enrichment analysis found that SERPINH1 was negatively correlated with fatty acid metabolism. Considering that SerpinH1 was also negatively correlated with the PI3K-AKT pathway, we found that there were studies reported that miR-145 promoted fatty acid metabolism and triacylglycerol synthesis in bovine mammary epithelial cells by inhibiting FOXO1 expression\(^{[23]}\). Meanwhile, the FOXO1/CD36 signaling resulted in decreased fatty acid uptake and inhibited ATP production\(^{[24]}\). Claire C. Bastie et al also demonstrated that FOXO1 activation leads to concurrent enhancements in both fatty acid uptake and oxidation. These effects are facilitated by the enrichment of CD36 on the cell membrane, which serves as a critical mediator of fatty acid-induced metastasis in gastric cancer via the AKT/GSK-3β/β-catenin signaling pathway\(^{[23]}\). Interestingly, our study uncovered the potential for SERPINH1 to be negatively associated with fatty
acid metabolism and to promote CRC progression through activation of the PI3K/AKT/mTOR and PI3K/AKT/FOXO1 pathways. To sum up, FOXO1 and GSK-3β phosphorylation could inhibited fatty acid metabolism, partly mediated by CD36, which may be our next research direction.

It is important to note that while our study provides valuable insights into the role of SERPINH1 in CRC, there are several limitations to consider. For instance, the specific mechanisms by which SERPINH1 activates the PI3K/Akt/mTOR pathway in CRC cells require further investigation. Additionally, the in vivo and clinical relevance of our findings need to be assessed in future studies.

CONCLUSION
In summary, our study highlights the significance of SERPINH1 in promoting the proliferation and metastasis of CRC through the activation of the PI3K/Akt/mTOR pathway. This work contributes to our understanding of the molecular mechanisms underlying CRC progression and offers a potential avenue for the development of targeted therapies. Further research is warranted to fully elucidate the therapeutic potential of targeting SERPINH1 in CRC.

ARTICLE HIGHLIGHTS

Research background
The clinical significance and biological role of serpin peptidase inhibitor clade H member 1 (SERPINH1) in colorectal cancer (CRC) remains poorly understood.

Research motivation
To investigate the effect of SERPINH1 on CRC cells and its specific mechanism.

Research objectives
To further study the specific role and mechanism of SERPINH1 in CRC and provide theoretical basis for further using SERPINH1 to improve the survival rate of CRC patients.

**Research methods**
SERPINH1 expression in CRC cell lines and tissues was evaluated using quantitative real-time polymerase chain reaction, western blotting analysis, data mining from The Cancer Genome Atlas, and immunohistochemistry. A battery of *in vitro* experiments was conducted to elucidate the role of SERPINH1 and its potential mechanisms in CRC.

**Research results**
Our study reveals the potential for SERPINH1 to be negatively correlated with fatty acid metabolism and promote CRC progression by activating the phosphatidylinositol 3-kinase (PI3K)/AKT/mechanistic target of rapamycin (mTOR) and PI3K/AKT/FOXO1 pathways. Considering that FOXO1 and glycogen synthase kinase (GSK)-3β phosphorylation can inhibit fatty acid metabolism, which is partly mediated by CD36, this may be our next research direction.

**Research conclusions**
Our study uncovered the significance of SERPINH1 in promoting CRC proliferation and metastasis by activating the PI3K/Akt/mTOR pathway. This work contributes to our understanding of the molecular mechanisms underlying CRC progression and offers a potential avenue for the development of targeted therapies.

**Research perspectives**
Our study revealed the potential for SERPINH1 to be negatively correlated with fatty acid metabolism and promoted CRC progression by activating the PI3K/AKT/mTOR and PI3K/AKT/FOXO1 pathways. Considering that FOXO1 and GSK-3β
phosphorylation could inhibit fatty acid metabolism, which is partly mediated by CD36, this may be our next research direction.
## Originality Report

### Similarity Index

4%

### Primary Sources

<table>
<thead>
<tr>
<th>#</th>
<th>Source</th>
<th>Internet</th>
<th>Words</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>jeccr.biomedcentral.com</td>
<td>Internet</td>
<td>143</td>
<td>4%</td>
</tr>
<tr>
<td>2</td>
<td>gut.bmj.com</td>
<td>Internet</td>
<td>15</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>3</td>
<td><a href="http://www.researchgate.net">www.researchgate.net</a></td>
<td>Internet</td>
<td>15</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Exclude Quotes: On
Exclude Bibliography: On
Exclude Sources: < 15 Words
Exclude Matches: < 15 Words