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Chemerin promotes proliferation and migration of ovarian cancer cells by upregulating expression of PD-L1

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Ovarian cancer is the third-most-common malignant reproductive tumor in women. According to the American Cancer Society, it has the highest mortality rate of gynecological tumors. The five-year survival rate was only 29% during the period from 1975 to 2008 (Reid et al., 2017). In recent decades, the five-year survival rate of ovarian cancer has remained around 30% despite continuous improvements in surgery, chemotherapy, radiotherapy, and other therapeutic methods. However, because of the particularity of the volume and location of ovarian tissue, the early symptoms of ovarian cancer are hidden, and there is a lack of highly sensitive and specific screening methods. Most patients have advanced metastasis, including abdominal metastasis, when they are diagnosed (Reid et al., 2017). Therefore, exploring the mechanism of ovarian cancer metastasis and finding early preventive measures are key to improving the survival rate and reducing mortality caused by ovarian cancer.

Epithelial ovarian cancer is the most important type. Barbolina (2018) found that metastasis and diffusion of epithelial ovarian cancer to the abdominal cavity tended to be directed toward the greater omentum. Paget (1889) once proposed the theory of "seed and soil," which states that tumor cell metastasis only occurs in environments conducive to the survival and growth of tumor cells. The greater omentum microenvironment is surrounded by a monolayer of mesothelial cells, mainly fat cells. Adipocytes in the omentum can promote the metastasis of ovarian cancer cells (Nieman et al., 2011). Fat cells can secrete a large number of bioactive substances called fat factors, including lipids, hormones, proinflammatory cytokines, and a series of fat-derived signaling molecules (Chi et al., 2018). Meanwhile, leptin is positively correlated with breast cancer risk, and its receptor is overexpressed in high-grade breast cancer (Ishikawa et al., 2004). The level of omentum-1 is higher in colon and prostate cancers, and it has an antiproliferative effect (Rennier et al., 2020). In addition, expression of adipokines is increased in pleural stromal tumors as well as lung, colorectal, and prostate cancers. Chemerin (also known as retinoic acid receptor responder 2, cluster of differenciation 247 (CD247)) is an adipokine and multifunctional chemotactic protein which exerts key functions in inflammation, adipogenesis, and glucose homeostasis. Elevated levels of serum chemerin have been linked to gastric, breast, and pancreatic cancers (Goralski et al., 2019). In ovarian cancer, differential expression of chemerin may have a biological effect on different ovarian cell types (Reverchon et al., 2012; Hoffmann et al., 2018; Treeck et al., 2019), but a more specific role in this type of tumor has not been found.

In recent years, immunosuppressants have been widely used in tumor treatment. Programmed death ligand 1 (PD-L1), a member of the B7-CD28 family, was discovered in 2000 (Freeman et al., 2000). PD-L1 is expressed on many cancer cell surfaces, such as gastric, lung, liver and breast cancer cells, oral squamous cell carcinoma, and ovarian cancer cells. After combination of programmed death protein 1 (PD-1) and PD-L1, antitumor immune response is weakened through inhibition of lymphocytes (Ghebeh et al.,

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2006). The relationship between PD-L1 and tumor prognosis is still unclear, and there are conflicting research results. It has been found that synthetic leptin OB3 inhibits expression of PD-L1 and reduces proliferation of hepatocarcinoma cells (Ho et al., 2019), while obesity leads to immune aging and tumor progression, and affects the function of T cells mediated by PD-1. Obesity is also related to the change in efficacy of PD-1/PD-L1 blockers (Wang et al., 2019). Therefore, we discussed whether the adipokine chemerin affects the expression of PD-L1 in cells, and thus affects the biological function of epithelial ovarian cancer cells. It was reported that chemerin reactivates phosphatase and tensin homolog deleted on chromosome ten (*PTEN*) and suppresses PD-L1 in prostate cancer cells via modulation of a novel chemokine-like receptor-1 (CMKLR1)-mediated signaling cascade (Wise et al., 2017). Therefore, we discussed whether the adipokine chemerin affects the expression of PD-L1 in cells, and thereby affects the biological function of epithelial ovarian cancer cells.

Our first task was to detect the expression of chemerin and PD-L1 in clinical specimens and ovarian cancer cells (see "Materials and methods" for details on the specimens). Assessments of the ascites and serum samples of 12 ovarian cancer patients showed that the concentration of chemerin in ascites was significantly higher than that in serum (P<0.05; Fig. 1a). Expression of chemerin in ovarian carcinoma cell line HO8910 cells was significantly lower than that in HO8910PM cells (the highly metastatic ovarian carcinoma cell line) (Fig. 1b). Positive staining of chemerin and PD-L1 in ovarian cancer tissues was significantly higher than that in adjacent normal tissues (Figs. 1c and 1d). Using the Gene Expression Profiling Interactive Analysis (GEPIA), we found the *PD-L1* gene in stages II–IV ovarian cancers but not in stage I (Fig. 1e). Therefore, the expression levels of chemerin and PD-L1 were higher in the clinical specimens and ovarian cancer cell lines.

We then explored whether chemerin promoted proliferation and migration of ovarian cancer cells.

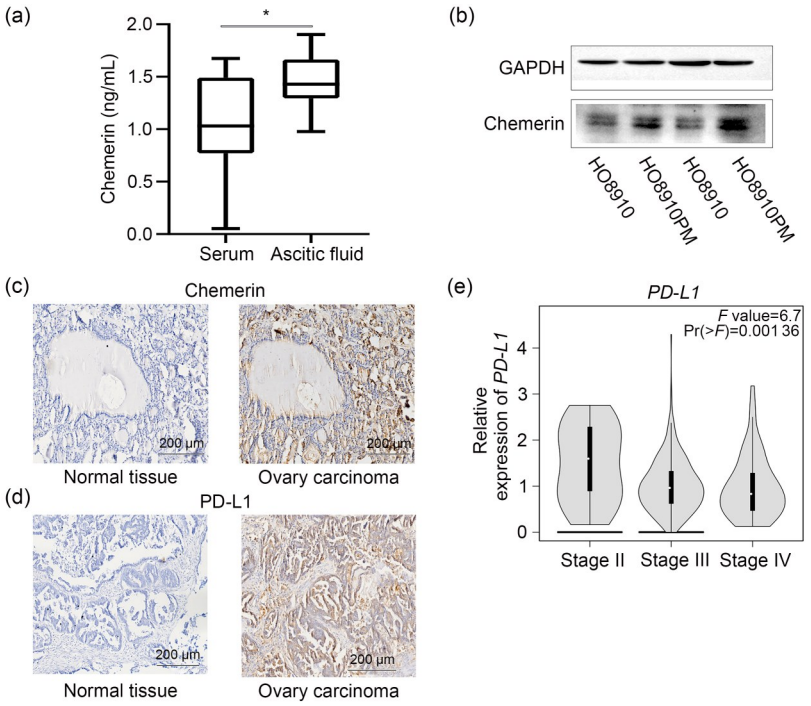

Fig. 1 Expression of chemerin and PD-L1 in ovarian cancer. (a) Expression of chemerin in serum and ascites of 12 patients with ovarian cancer was detected by ELISA (* P<0.05); (b) Levels of chemerin in ovarian cancer HO8910 cell line and high metastatic HO8910PM cell line by western blotting; (c) Expression of chemerin in ovarian cancer tissues and adjacent normal tissues by immunohistochemistry; (d) Expression of PD-L1 in ovarian cancer tissues and adjacent normal tissues by immunohistochemistry; (e) Expression of *PD-L1* gene in different stages of ovarian cancer by GEPIA. GAPDH: glyceraldehyde-3-phosphate dehydrogenase; PD-L1: programmed death ligand 1; ELISA: enzyme-linked immunosorbent assay; GEPIA: Gene Expression Profiling Interactive Analysis.

Exogenous chemerin at the concentrations of 10, 50, and 100 ng/mL was used to stimulate HO8910 and HO8910PM cells, and a scratch-wound assay showed that under 10 ng/mL exogenous chemerin stimulation, cell healing did not change significantly. After stimulation with 50 and 100 ng/mL of exogenous chemerin, cell healing was apparent at 24 h and was fastest with the 100 ng/mL chemerin treatment (Fig. 2a). A water-soluble tetrazolium (WST) assay showed that the cell proliferation rate exhibited an increasing trend after chemerin stimulation in HO8910 cells (Fig. 2b). Therefore, it is clear that chemerin promotes proliferation and migration of ovarian cancer cells.

We then investigated whether chemerin affected expression of PD-L1 in ovarian cancer cells. After stimulation of HO8910 and HO8910PM cells with 10, 50, and 100 ng/mL of exogenous chemerin, expression of PD-L1 in ovarian cancer cells increased; the highest expression was found in the 100 ng/mL group (Fig. 3a). Flow cytometry detection showed that after stimulating ovarian cancer cells with 100 ng/mL of chemerin, expression of PD-L1 reached a peak at 12 h (Fig. 3b). Therefore, chemerin upregulates expression of PD-L1 in ovarian cancer cells.

Next, we looked at whether chemerin promoted proliferation and migration of ovarian cancer cells through upregulating expression of PD-L1. Small interfering RNA (siRNA) was transfected to knock down PD-L1 expression (Fig. 4a). After chemerin stimulation, the cell proliferation rate was significantly higher than that of untreated cells, and PD-L1 knockdown significantly abolished chemerin-stimulated cell proliferation (Fig. 4b). A scratch-wound assay also showed that in HO8910PM cells, the chemerin-stimulated cell healing rate was significantly abolished by PD-L1 knockdown (Fig. 4c). We also found that the microfilament cytoskeleton protein of PD-L1 knockdown cells changed, and the filiform pseudopodia and migration process decreased, suggesting that PD-L1 can affect cell migration by altering the cytoskeleton (Fig. 4d).

Our main goal in the present study was to explore the relationship between chemerin and PD-L1 in ovarian cancer. We found that chemerin was expressed in the serum and ascites of ovarian cancer patients, and its content in ascites was significantly higher than that in serum. In addition, the expression of chemerin in ovarian cancer tissue was significantly higher than that in normal ovarian tissue, and the expression of chemerin in HO8910 cells was significantly lower than that in the high metastatic cell line HO8910PM. These results indicate that chemerin can promote metastasis of ovarian cancer cells. A previous study has found that increased serum chemerin concentration is related to the clinical stage and classification of gastric cancer (Kumar et al., 2019). Chemerin increases the invasiveness of gastric cancer, inducing p38 and extracellular signal-regulated kinase 1/2 (ERK1/2) phosphorylation and upregulation of vascular endothelial growth factor (VEGF), matix metalloproteinase-7

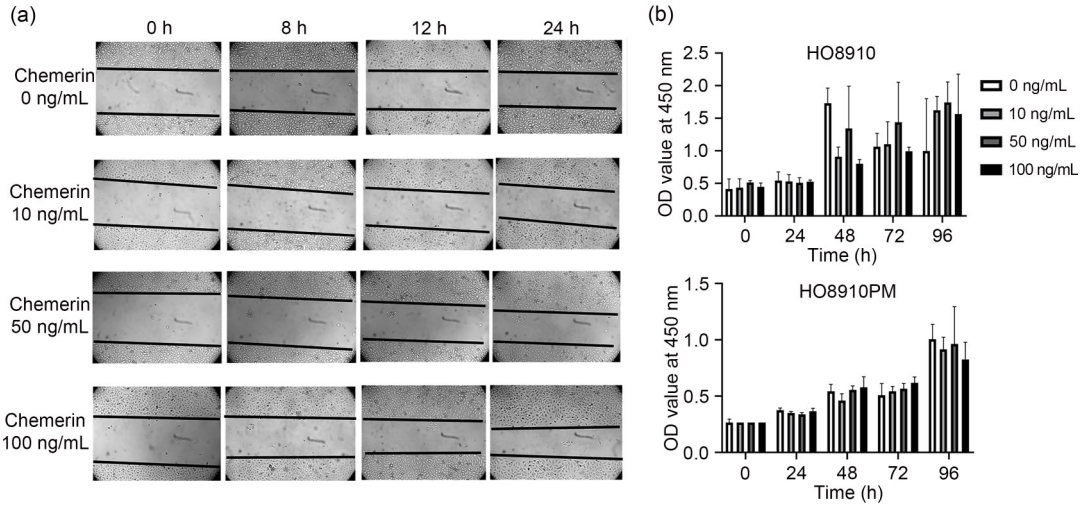

Fig. 2 Effects of chemerin on proliferation and migration of ovarian cancer cells. (a) Cell scratch-wound assay. Chemerin under different concentrations was used to stimulate HO8910 cells. (b) Proliferation of HO8910 and HO8910PM cells stimulated by chemerin. All results are expressed as mean±SEM, *n*=4. SEM: standard error of mean; OD: optical density.

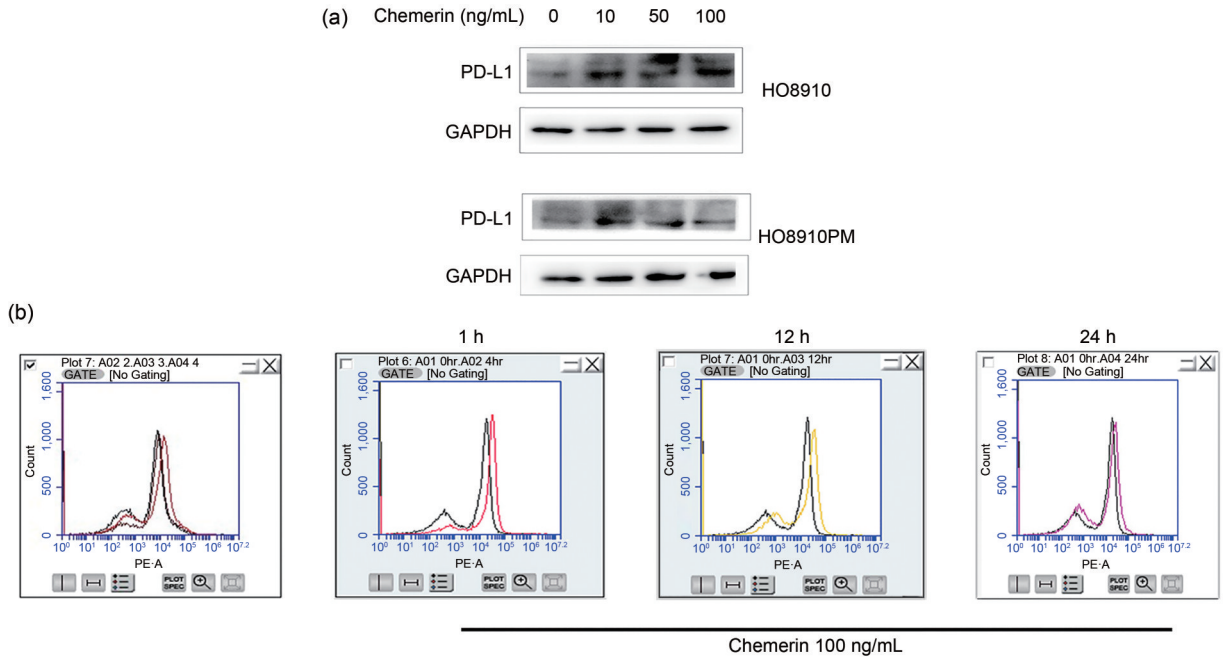

Fig. 3 Potential relationship between expression of PD-L1 and chemerin in ovarian cancer. (a) Levels of PD-L1 in HO8910 and HO8910PM cells treated by different concentrations of chemerin; (b) Expression of PD-L1 in HO8910 cells differed according to the time indicated by flow cytometry. CHEM: chemerin; GAPDH: glyceraldehyde-3-phosphate dehydrogenase; PD-L1: programmed death ligand 1; PE-A: area under the curve of fluorescence intensity.

(MMP-7), and interleukin-6 (IL-6). A review of the tumor microenvironment of ovarian cancer (Drakes and Stiff, 2018) suggested that ascites are a common concomitant symptom of ovarian cancer, and are conducive to the adhesion of cancer cells to the omentum. Adipocytes of the omentum secrete IL-6, IL-8, chemokine (C-C motif) ligand 2 (CCL2), and metformin to promote ovarian cancer metastasis. The microenvironment of intraperitoneal tumors is important for the growth and diffusion of tumor cells. Ovarian cancer is often accompanied by omental metastasis. According to the seed and soil theory proposed by Paget (1889), tumor cell metastasis only occurs in an environment conducive to the survival and growth of tumor cells. We believe that the adipokine chemerin secreted by adipocytes is involved in the formation of the intraperitoneal tumor microenvironment, which promotes metastasis of ovarian cancer cells to the omentum.

Our study found for the first time that, in HO8910 and HO8910PM ovarian cancer cells, PD-L1 is upregulated by chemerin, and chemerin promotes the proliferation and migration of ovarian cancer cells. In HO8910 cells, the proliferation and scratch healing rate reached a peak at 24 h under treatment with 100 ng/mL chemerin. In HO8910PM, the effect of chemerin was not obvious, which may have been because the chemerin concentration in metastatic ovarian cancer cell lines was higher than the optimal. We knocked down PD-L1 in ovarian cancer cells and found that cell proliferation and migration were inhibited. A previous study has found that expression of PD-L1 in tumor cells is induced by interferon (Garcia-Diaz et al., 2017). By combining with PD-1 expressed on T cells, PD-L1 expression is promoted, and apoptosis and tolerance are induced, which inhibits immunity. PD-L1 also affects tumors in several ways, by increasing survival and proliferation of cancer cells, regulating the glucose utilization rate of tumors, and inhibiting autophagy (Chang et al., 2015). PD-L1 is expressed on the surface of cancer cells, and its increased expression is related to poor prognosis in ovarian cancer (Hamanishi et al., 2007; Maine et al., 2014). Chemerin may upregulate expression of IL-6 by upregulation of p38 and ERK1/2 phosphorylation, which further affects expression of PD-L1 and promotes proliferation, migration, and metastasis of tumor cells (Wang et al., 2014; Clark et al., 2016). In addition, we found that the microfilament cytoskeleton protein changed after PD-L1 knockdown, and the filiform pseudopodia and migration process decreased, suggesting that

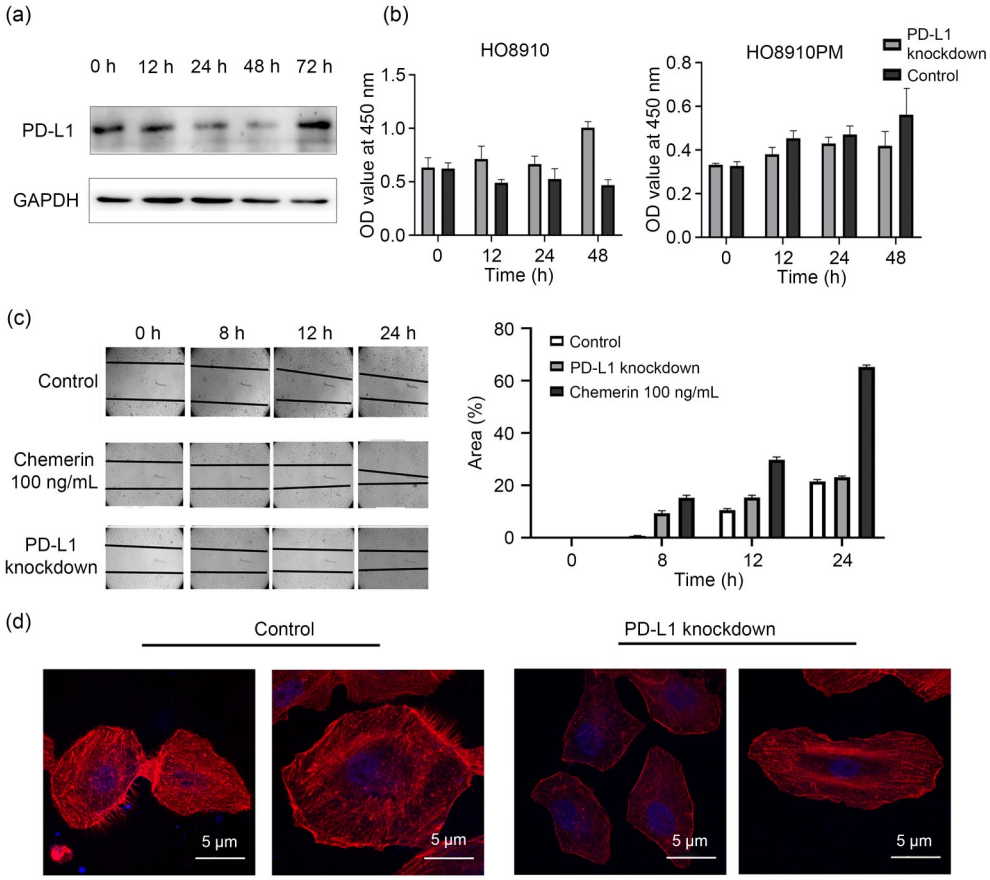

Fig. 4 Chemerin regulates cell function in HO8910 cells and further affects the expression of PD-L1. (a) Detection of HO8910 cell transfection efficiency by western blotting. (b) Proliferation of HO8910 and HO8910PM cells stimulated by chemerin after PD-L1 knockdown. (c) Cell scratch-wound assay. Chemerin at 100 ng/mL stimulated HO8910 cells with or without PD-L1 knockdown. All results (b, c) are expressed as mean±SEM, *n*=4. (d) Effect of chemerin on the cytoskeleton of HO8910 cells. CHEM: chemerin; GAPDH: glyceraldehyde-3-phosphate dehydrogenase; PD-L1: programmed death ligand 1; SEM: standard error of mean; OD: optical density.

PD-L1 can affect cell migration by changing the cytoskeleton.

The tumor microenvironment is a comprehensive system composed of tumor cells, adipocytes, and other stromal cells. Nontumor tissues adjacent to tumor cells often play an important role in tumor development. Epidemiological studies showed that obese people have a higher risk of cancer, with faster tumor growth and deterioration and higher mortality (Steele et al., 2017). Therefore, in recent years, scientists have conducted a large number of studies on the role of fat cells near tumors, and eventually discovered that fat cells in the tumor microenvironment can affect the development and deterioration of tumor tissue through their own pathological expansion (Ibrahim, 2010). The "immune escape" of tumor cells is the main mechanism of invasion and metastasis of cancer cells. Immune cells play an important role in the process of achieving immune tolerance of cancer cells, which can help cancer cells escape monitoring by the immune system by inhibiting various types of immune responses. At present, immunotherapy with T cells has been applied to the treatment of multiple types of cancer. Recent studies have shown that chemerin plays a key role in the development of a variety of malignant tumors. It has been proved that chemerin is highly expressed in oral and esophageal cancers (Kumar et al., 2016; Ghallab and Shaker, 2017). There is a positive correlation between the concentration of chemerin in serum and colorectal cancer and gastric adenocarcinoma (Zhang et al., 2014; Alkady et al., 2018). In breast cancer, compared with nonmetastatic malignant tissues, the expression of chemerin protein in cancer tissues, adjacent healthy tissues, or metastatic

lymph nodes is higher (El-Sagheer et al., 2018), but in skin and liver cancers, chemerin has been found to have an anticancer effect (Pachynski et al., 2012; Li et al., 2018). In lung and gastric cancers, chemerin is expected to become a diagnostic marker (Goralski et al., 2019). More specific roles of chemerin in tumors have not been reported. Our study suggests that chemerin upregulates expression of PD-L1 in ovarian cancer cells and promotes tumor proliferation and migration. The mechanism by which chemerin upregulates PD-L1 remains to be studied. Although existing studies have suggested that chemerin activates a variety of downstream pathways, including the phosphorylation of p42–p44 mitogen-activated protein kinases (MAPKs) (Shin and Pachynski, 2018), and recruits β-arrestin 1 and 2 to CMKLR1 or G protein-coupled receptor 1 (GPR1) (Rennier et al., 2020), the mechanism by which chemerin upregulates PD-L1 requires further investigation.

In summary, our study found for the first time that chemerin can upregulate the expression of PD-L1 in ovarian cancer cells, and thereby promote tumor proliferation and migration. It may be helpful to study further the application of immunosuppressive agents in ovarian cancer. Detection of chemerin in serum and ascites may be important for the early diagnosis of ovarian cancer. Chemerin combined with other adipokines may become a diagnostic target for ovarian cancer.

Materials and methods

Detailed methods are provided in the electronic supplementary materials of this paper.

Acknowledgments

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Author contributions

Chenxi GAO, Jinming SHI, and Jingxin ZHANG performed the experimental research and data analysis, and wrote the manuscript. Yin LI and Yi ZHANG contributed to the study design, data analysis, and writing and editing of the manuscript. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Chenxi GAO, Jinming SHI, Jingxin ZHANG, Yin LI, and Yi ZHANG declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study. Additional informed consent was obtained from all patients for whom identifying information is included in this article.

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Supplementary information

Materials and methods