REVIEW ARTICLE

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The Role of CD47 in Gynecological Oncology

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ABSTRACT

Cancer is a disease with major societal impact with 18.1 million cases reported globally in 2020. About 16% of all oncological disorders are malignant gynaecological tumours, the most common types being cervical, endometrial and ovarian cancer. The classic methods of treating these diseases are surgery, radiotherapy chemotherapy and different combinations of them, and they are directed against the tumor cell itself. This necessitates the search for more and more new and effective therapeutic approaches. Advances in genomic and molecular techniques have led to the introduction of personalized treatment tactics targeting oncogenic pathways rather than the tumor cell itself. Immuno-oncology tries to explain the different mechanisms by which cancer tries to escape from the immune response. One such mechanism is the interaction between the CD47 and SIRPα, thus producing an antiphagocytic "don't eat me" signal. The aim of this review is to address the role of CD47 in the treatment of gynecological neoplasms. In order to understand this role, the interactions involved in CD47 and its relationship with other immunological cells must be analyzed.
Key words: CD47; SIRPα; gynecologic malignancies; immuno-oncology; treatment

INTRODUCTION

Cancer is a disease with major societal impact with 18.1 million cases reported globally in 2020, of which 9.3 million cases were in men and 8.8 million in women (1). About 16% of all oncological disorders are malignant gynaecological tumours (1), the most common types being cervical, endometrial and ovarian cancer. At more than 604,000 new cases and more than 341,000 deaths in 2020, cervical cancer ranks fourth among women's cancers and seventh overall (2). In 2020, endometrial cancer accounted for over 417,000 new cases and over 97,000 deaths, making it the sixth most frequent cancer in women and the fifteenth most common cancer worldwide (3). Ovarian cancer is the 8th most common cancer in women and the 18th most common cancer overall, with more than 313,000 new cases and more than 207,000 deaths in 2020 (4). The classic methods of treating these diseases are surgery, radiotherapy chemo-

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therapy and different combinations of them, and they are directed against the tumor cell itself (5). This necessitates the search for more and more new and effective therapeutic approaches. Advances in genomic and molecular techniques have led to the introduction of personalized treatment tactics targeting oncogenic pathways rather than the tumor cell itself (5). However, a significant number of patients do not respond to classical or personalized approaches, and this raises the question of what other cellular, local, or systemic characteristics of cancer are not accounted for that may influence cancer progression and limit treatment response (5). Immuno-oncology tries to explain the different mechanisms by which cancer tries to escape from the immune response (6).

One such mechanism is the interaction between the Cluster of Differentiation 47 (CD47) and SIRPα (signal regulatory protein alpha), thus producing an antiphagocytic "don't eat me" signal (7).The transmembrane immunoglobulin CD47, also referred to as integrin-associated protein (IAP), is expressed on the surface of a variety of cells, shielding them from being annihilated by circulating macrophages. When CD47 expression is decreased in aged or diseased cells, macrophages attack those cells (9). Numerous different tumours have demonstrated elevated expression of CD47, which is linked to a bad prognosis (9). As a result, it has been proposed that targeting the CD47 protein may be therapeutically beneficial in some conditions (8).

The aim of this review is to address the role of CD47 in the treatment of gynecological neoplasms. In order to understand this role, the interactions involved in CD47 and its relationship with other immunological cells must be analyzed.

Ligands of CD47

The most researched relationship is that between CD47 and SIRPα. Bidirectional signalling from this contact causes different cell-to-cell reactions, including T-cell activation, promotion of cell-cell fusion, and inhibition of phagocytosis (10-12). Due to CD47's strong affinity for thrombospondin-1 (TSP-1), a secreted glycoprotein involved in angiogenesis and vascular development, nitric oxide signalling in vascular cells is inhibited at several levels by the TSP1-CD47 interaction (13). TSP-1 binding to CD47 influences a number of vital physiological processes, including angiogenesis and inflammation regulation, cell adhesion and migration, and cell proliferation or apoptosis (10). A number of membrane integrins, including αvβ3, a2β1, and aIIbβ3, interact with CD47. Many cellular processes are impacted by CD47/integrin complexes that are produced as a result of these interactions. Number of membrane integrins, including αvβ3, a2β1, and aIIbβ3, interact with CD47. These interactions lead to CD47/integrin complexes, which have an impact on adhesion, spreading, and migration, among other cellular processes (10,14)

CD47 and immune cells

Nearly all immune cells express CD47, albeit the degree of expression varies widely between cell types and pathological states (15). T cell activation and death-inducing mechanisms are among the many cellular processes that are triggered by CD47 signaling (16). Long-lived memory T cell progenitors can live longer when CD47 is expressed on them because it shields them from macrophages (17). Antigen-presenting cells' (APC) and CD4+ T cells' own expression of CD47 can both control the differentiation of these cells. By specifically preventing naïve T cells from developing into Th1 effectors that generate IFN-γ, lymphotoxin-α (LT-α), and TNF-α, CD47 ligation can hinder the immune system's ability to eradicate cancer (18,19).

While CD47 loss does not change the inhibitory function of Treg cells, it does increase Treg cell development and regulate the homeostasis of activated CD103+ Treg cells (20). FoxP3 expression is upregulated in naïve T cells following anti-CD47/anti-TSP-1 therapy (20).

The predominant macrophage checkpoint, CD47, sends a "don't eat me" signal to macrophages (22). The interaction between CD47 and SIRPα modifies the polarization state of macrophages and controls their activity (23). Professional antigen-presenting cells, dendritic cells (DCs), are capable of stimulating naive T lymphocytes. They also provide TSP, which can autocrinally decrease the synthesis of IL-12 and IFN-γ by interacting with CD47 (24,25). The preservation of immunological hemostasis may also be influenced by the interaction between SIRPα on DCs and CD47 expression on T cells (26). Since DCs removal significantly impairs therapeutic efficacy compared to macrophage depletion, DCs are the primary APCs that cross-prime cytotoxic T cells (27).

CD47 blocks the activation of NK cells, and its absence increases their activity and cytotoxicity (28, 29). Anti-CD47 therapy increases the ability of NK cells to destroy tumor cells by enhancing expression of granzyme B and IFN-γ (29). CD47 has therapeutic potential as a checkpoint of NK cells in the tumor microenvironment (30).

CD47 has an important role in the trans-endothelial migration of neutrophils and other leukocytes (31,32). CD47 expressed on myeloid DCs is a critical factor in controlling efficient trafficking through lymphatic and endothelial vessels, seeding in secondary lymphoid organs and participating in T-cell priming (27,33).

CD47 and therapeutic options

The use of checkpoint immunotherapy is growing in popularity and is being used to an increasing number of oncological disorders (34,35). However, not all patients are candidates for this type of treatment, therefore there is a constant need to find new immune checkpoint receptors. Since the innate immune system is the body's initial line of defence against cancer cells, innate checkpoints are becoming more and more attention as viable treatment alternatives (14). The CD47-SIRPα axis is just like this.

The following is the action's mechanism:

- Through a caspase-independent mechanism, CD47 ligation triggers tumour cell death (36,37).
- Anti-CD47 causes tumour cells to be phagocytically taken up by antigen-presenting cells, which then presents the antigen to T cells (38).
- Anti-CD47 abrogates the TSP-1-mediated inhibitory effect against NK cells, but increases their activity and cytotoxicity (29)
- Blockade of CD47 depends on STING (stimulator of interferon genes), which induces a I/II IFN response mediated by dendritic cells and CD8+ T cells (27).
- The CD47/TSP-1 pathway has pleiotropic effects on the immune system and may have therapeutic potential (39,40).

It is currently accepted in the literature that CD47-SIRPα blockade alone is sufficient to induce tumor regression (41), but this may not be entirely sufficient. Additional prophagocytic receptors such as calreticulin, SLAMF7, and macrophage antigen-1 may be involved to enhance the antitumor response (14).

Blockade of CD47-SIRPa as a therapeutic option for the treatment of gynecological neoplasms is still at the experimental level.

Cervical cancer (CC)

In 2019, Li et al experimentally demonstrated that blocking SIRPα in DCs led to increased secretion of cytokines (TNF-α/IL-12/IL-6), IFN-γ from T lymphocytes and in vitro/in vivo observed antitumor activity against CC (42). These results suggest that SIRPα silenced DCs vaccination is a potential therapeutic option against cervical cancer.

Other studies are looking at possible ways to increase the effectiveness of blocking the CD47-SIRPα axis. For example, CD47 has been shown to be associated with programmed death ligand 1 (PD-L1; or CD274, B7-H1), which sends the all-important "don't find me" signal to the adaptive immune system (43). It has been shown that CD47 blockade therapy can activate CD8+ T immune responses to tumors (44), while PD-1 blockade therapy promotes phagocytosis of tumor-associated macrophages (45,46). Xu et al. demonstrated that increased expression of LSD1 (the first discovered histone demethylase) was associated with progression of CRC, and its inhibition increased the therapeutic effect of CD47/PD-L1 blockade therapy in CC (47).

Another study demonstrated that high CD47 expression was associated with increased HIF target gene expression (HIF-1α and HIF-2α are hypoxia-inducible factors) and was associated with worse survival (48). It has been reported that there is high expression of ZEB1 in hypoxic cells of squamous cell carcinoma (49). It has been suggested that a combination regimen using a ZEB1 antagonist with simultaneous blockade of the CD47-SIRPα axis may improve the treatment of most patients with squamous CC (50).

Endometrial cancer (EC)

Yang et al reported that CD47 expression correlated significantly with age, clinical stage, histologic grade, histologic type, menopausal status, and prognosis (51). Expression is increased in the following order in patients with endometrial hyperplasia: simple hyperplasia, complex hyperplasia, and atypical endometrial hyperplasia (51).

Sahin et al reported that CD47 expression levels correlated with tumor grade, had no statistically significant relationship with myometrial invasion and lymphovascular invasion, and concluded that anti-CD47 antibody therapy is a possible alternative for patients with high-grade EC (52).

Another study concluded that CD47 blockade therapy, which can re-educate M2 macrophages by increasing their ability to phagocytose, may be an attractive target for tumor immunotherapy for EC (53).

Ovarian cancer (OC)

There are more reports on the role of CD47 in OC since CD47 was initially identified as a tumor antigen in

human ovarian cancer (54).

Al-Sudani et al. examined the antitumor efficacy of anti-CD47 therapy both alone and in combination, and they found that patients with gynaecological tumours who had high CD47 expression had a decreased immune checkpoint inhibitor (ICI) response and a tendency towards a lower progression-free survival (PFS) (55). Higher CD47 expression correlated negatively with PDL1 and Cytotoxic T-lymphocyte associated protein 4 (CTLA4) expression, as well as cytotoxic T cells and dendritic cells, but positively with TGF-β, BRD4, and CXCR4/CXCL12 expression (55). Based on their results, they concluded that anti-CD47 therapy may help overcome immunotherapy resistance and improve responses to PARP inhibitors in ovarian cancer (55).

A different group similarly found a correlation between lower overall survival (OS) and progression-free survival (PFS) and increased CD47 expression in ovarian cancer (56). They conclude that CD47 has fresh prospects for immunotherapy in patients with ovarian cancer and can be utilised as a possible predictive biomarker (56). According to Liu et al., using anti-CD47 therapy to conventional treatment methods can prevent OC from metastasizing and from reoccurring (57). A full response to therapy is linked to low expression of CD47 (58). And similar findings are reached by other writers (59-63).

Particularly in CC, the function of CD47 expression in gynaecological tumours has not yet been thoroughly understood. Based on the available information, it is evident that the expression levels are correlated with some clinicopathological data in EC, that they are associated with prognosis, OS, and PFS, that they are related to the therapeutic response to standard treatment regimens in OC, and that there may be a therapeutic influence in CC. All of this points to the likelihood that CD47-SIRPα axis blocking is a novel therapeutic approach to influence gynaecological tumours, both on its own and in combination with other ICIs. CD47 is a promising prognostic and predictive marker in these tumours.

Author's contributions

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests

Authors state no conflict of interest.

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Data availability

The authors declare that all related data are available concerning researchers by the corresponding author's email.

REFERENCES

1. https://www.wcrf.org/cancer-trends/worldwide-cancer-data/ (access on 17.02.2024)
2. https://www.wcrf.org/cancer-trends/cervical-cancer-statistics/ (access on 17.02.2024)
3. https://www.wcrf.org/cancer-trends/endometrial-cancer-statistics/ (access on 17.02.2024)
4. https://www.wcrf.org/cancer-trends/ovarian-cancer-statistics/ (access on 17.02.2024)
5. Lee SL, Al-Shamkhani A, Mirnezami A. Immuno-oncology for surgeons. Br J Surg. 2019;106(10):1273-1282.
6. Gallimore A, Tournier C. Immuno-oncology. Essays Biochem. 2023;67(6):903.
7. Cheng L, Li Y, Zhang SB, Teng XD. Molecular pathology of lung cancer: Key to personalized medicine. Zhonghua Bing Li Xue Za Zhi. 2012;41(10):715-20. Chinese
8. Huang CY, Ye ZH, Huang MY, Lu JJ. Regulation of CD47 expression in cancer cells. Transl Oncol. 2020;13(12):100862.
9. Yordanov A, Shivarov V, Kostov S, Ivanova Y, Dimitrova P, Popovska S, et al. Prognostic Utility of CD47 in Cancer of the Uterine Cervix and the Sensitivity of Immunohistochemical Scores. Diagnostics (Basel). 2022;13(1):52.
10. Sick E, Jeanne A, Schneider C, Dedieu S, Takeda K, Martiny L. CD47 update: a multifaceted actor in the tumour microenvironment of potential therapeutic interest. Br J Pharmacol. 2012;167(7): 1415-30.
11. Brown EJ, Frazier WA. Integrin-associated protein (CD47) and its ligands. Trends Cell Biol. 2001;11(3):130-5.
12. Barclay AN. Signal regulatory protein alpha (SIRPalpha)/CD47 interaction and function. Curr Opin Immunol. 2009;21(1):47-52.
13. Isenberg JS, Ridnour LA, Dimitry J, Frazier WA, Wink DA, Roberts DD. CD47 is necessary for inhibition of nitric oxide-stimulated vascular cell responses by thrombospondin-1. J Biol Chem. 2006; 281(36):26069-80.
14. Zhao H, Song S, Ma J, Yan Z, Xie H, Feng Y, et al. CD47 as a promising therapeutic target in oncology. Front Immunol. 2022; 13:757480.
15. Lindberg FP, Gresham HD, Schwarz E, Brown EJ. Molecular cloning of integrin-associated protein: An immunoglobulin family member with multiple membrane-spanning domains implicated in a(v)b3-dependent ligand binding. J Cell Biol. 1993;123(2):485-96.
16. Azcutia V, Routledge M, Williams MR, Newton G, Frazier WA, Manica A, et al. CD47 plays a critical role in T-cell recruitment by regulation of LFA-1 and VLA-4 integrin adhesive functions. Mol Biol Cell. 2013;24(21):3358-68.
17. Van VQ, Raymond M, Baba N, Rubio M, Wakahara K, Susin SA, et al. CD47 high expression on CD4 effectors identifies functional long-lived memory T cell progenitors. J Immunol. 2012;188(9):4249-55.
18. Avice M-N, Rubio M, Sergerie M, Delespesse G, Sarfati M. CD47 ligation selectively inhibits the development of human naive T cells into Th1 effectors. J Immunol. 2000;165(8):4624-31.
19. Bouguermouh S, Van VQ, Martel J, Gautier P, Rubio M, Sarfati M. CD47 expression on T cell is a self-control negative regulator of type 1 immune response. J Immunol. 2008;180(12):8073-82.

20. Rodríguez-Jiménez P, Chicharro P, Llamas-Velasco M, Cibrian D, TrigoTorres L, Vara A, et al. Thrombospondin-1/CD47 interaction regulates Th17 and treg differentiation in psoriasis. Front Immunol. 2019;10:1268.
21. Van VQ, Darwiche J, Raymond M, Lesage S, Bouguermouh S, Rubio M, et al. Cutting edge: CD47 controls the In vivo proliferation and homeostasis of peripheral CD4 + CD25 + Foxp3 + regulatory T cells that express CD103. J Immunol. 2008;181(8):5204-8.
22. Oldenborg PA, Zheleznyak A, Fang YF, Lagenaur CF, Gresham HD, Lindberg FP. Role of CD47 as a marker of self on red blood cells. Science. 2000;288(5473):2051-4.
23. Weiskopf K. Cancer immunotherapy targeting the CD47/SIRPa axis. Eur J Cancer. 2017;76:100-109.
24. Ferrari D, Gorini S, Callegari G, la Sala A. Shaping immune responses through the activation of dendritic cells' P2 receptors. Purinergic Signal. 2007;3(1-2):99-107.
25. Bell BM, Kirk ID, Hiltbrunner S, Gabrielsson S, Bultema JJ. Designer exosomes as next-generation cancer immunotherapy. Nanomedicine. 2016;12(1):163-9.
26. Latour S, Tanaka H, Demeure C, Mateo V, Rubio M, Brown EJ, et al. Bidirectional negative regulation of human T and dendritic cells by CD47 and its cognate receptor signal-regulator protein-a: Down-regulation of IL-12 responsiveness and inhibition of dendritic cell activation. J Immunol. 2001;167(5):2547-54.
27. Liu X, Pu Y, Cron K, Deng L, Kline J, Frazier WA, et al. CD47 blockade triggers T cell–mediated destruction of immunogenic tumors. Nat Med. 2015;21(10):1209-15.
28. Nath PR, Gangaplara A, Pal-Nath D, Mandal A, Maric D, Sipes JM, et al. CD47 expression in natural killer cells regulates homeostasis and modulates immune response to lymphocytic choriomeningitis virus. Front Immunol. 2018;9:2985.
29. Nath PR, Pal-Nath D, Mandal A, Cam MC, Schwartz AL, Roberts DD. Natural killer cell recruitment and activation are regulated by cd47 expression in the tumor microenvironment. Cancer Immunol Res. 2019;7(9):1547-1561.
30. Bald T, Krummel MF, Smyth MJ, Barry KC. The NK cell–cancer cycle: advances and new challenges in NK cell–based immunotherapies. Nat Immunol. 2020;21(8):835-847.
31. Lee Y-T, Ko E-J, Lee Y, Lee Y-N, Bian Z, Liu Y, et al. CD47 plays a role as a negative regulator in inducing protective immune responses to vaccination against influenza virus. J Virol. 2016;90(15):6746-6758.
32. Liu Y, O'Connor MB, Mandell KJ, Zen K, Ullrich A, Bühring H-J, et al. Peptide-mediated inhibition of neutrophil transmigration by blocking CD47 interactions with signal regulatory protein a. J Immunol. 2004; 172(4):2578-85.
33. Van VQ, Lesage S, Bouguermouh S, Gautier P, Rubio M, Levesque M, et al. Expression of the self-marker CD47 on dendritic cells governs their trafficking to secondary lymphoid organs. EMBO J. 2006;25(23):5560-8.
34. Topalian SL, Taube JM, Pardoll DM. Neoadjuvant checkpoint blockade for cancer immunotherapy. Science. 2020;367(6477):eaax0182.
35. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science. 2018;359(6382):1350-1355.
36. Zhao XW, van Beek EM, Schornagel K, van der Maaden H, Van Houdt M, Otten MA, et al. CD47-signal regulatory protein-α (SIRPα) interactions form a barrier for antibody-mediated tumor cell destruction. Proc Natl Acad Sci U S A. 2011;108(45):18342-7.
37. Barkal AA, Weiskopf K, Kao KS, Gordon SR, Rosental B, Yiu YY, et al. Engagement of MHC class I by the inhibitory receptor LILRB1 suppresses macrophages and is a target of cancer immunotherapy. Nat Immunol. 2018;19(1):76-84.
38. Feng R, Zhao H, Xu J, Shen C. CD47: the next checkpoint target for cancer immunotherapy. Crit Rev Oncol Hematol. 2020;152:103014.
39. Gao L, Chen K, Gao Q, Wang X, Sun J, Yang Y-G. CD47 deficiency in tumor stroma promotes tumor progression by enhancing angiogenesis. Oncotarget. 2017;8(14):22406-22413.
40. Jeanne A, Sarazin T, Charlé M, Moali C, Fichel C, Boulagnon-Rombi C, et al. Targeting ovarian carcinoma with TSP-1:CD47 antagonist TAX2 activates antitumor immunity. Cancers (Basel). 2021;13(19): 5019.
41. Liu J, Wang L, Zhao F, Tseng S, Narayanan C, Shura L, et al. Preclinical development of a humanized anti-CD47 antibody with anticancer therapeutic potential. PLoS One. 2015;10(9):e0137345.
42. Li X, Zhou W, Liang Y, Xu C, Xie Z, Liang J, et al. The Immunotherapeutic Effect of SIRPα-Silenced DCs against Cervical Cancer. J Immunol Res. 2020;2020:1705187.
43. Okazaki T, Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application. Int Immunol. 2007;19(7):813-24.
44. Tao H, Qian P, Wang F, Yu H, Guo Y. Targeting CD47 enhances the efficacy of anti-PD-1 and CTLA-4 in an esophageal squamous cell cancer preclinical model. Oncol Res. 2017;25(9):1579-1587.
45. Santoni M, Romagnoli E, Saladino T, Foghini L, Guarino S, Capponi M, et al. Triple negative breast cancer: key role of tumor-associated macrophages in regulating the activity of anti-PD-1/PD-L1 agents. Biochim Biophys Acta Rev Cancer. 2018;1869(1):78-84.
46. Gordon SR, Maute RL, Dulken BW, Hutter G, George BM, McCracken MN, et al. PD-1 expression by tumour-associated macrophages inhibits phagocytosis and tumour immunity. Nature. 2017;545(7655):495-499.
47. Xu S, Wang X, Yang Y, Li Y, Wu S. LSD1 silencing contributes to enhanced efficacy of anti-CD47/PD-L1 immunotherapy in cervical cancer. Cell Death Dis. 2021;12(4):282.
48. Zhang H, Lu H, Xiang L, Bullen JW, Zhang C, Samanta D, et al. HIF-1 regulates CD47 expression in breast cancer cells to promote evasion of phagocytosis and maintenance of cancer stem cells. Proc Natl Acad Sci U S A. 2015;112(45):E6215-23.
49. Chen XJ, Deng YR, Wang ZC, Wei WF, Zhou CF, Zhang YM, et al. Hypoxia-induced ZEB1 promotes cervical cancer progression via CCL8-dependent tumour-associated macrophage recruitment. Cell Death Dis. 2019;10(7):508.
50. Chen XJ, Guo CH, Wang ZC, Yang Y, Pan YH, Liang JY, et al. Hypoxia-induced ZEB1 promotes cervical cancer immune evasion by strengthening the CD47-SIRPα axis. Cell Commun Signal. 2024; 22(1):15.
51. Yang M, Jiang C, Li L, Xing H, Hong L. Expression of CD47 in Endometrial Cancer and Its Clinicopathological Significance. J Oncol. 2022;2022:7188972.
52. Sahin N, Coban G, Unver N, Arici DS, Kilic G, Toluk O. Significance of CD47 expression in endometrial carcinoma. Indian J Pathol Microbiol. 2022;65(4):856-859.
53. Gu S, Ni T, Wang J, Liu Y, Fan Q, Wang Y, et al. CD47 Blockade Inhibits Tumor Progression through Promoting Phagocytosis of Tumor Cells by M2 Polarized Macrophages in Endometrial Cancer. J Immunol Res. 2018;2018:6156757.
54. Poels LG, Peters D, van Megen Y, Vooijs GP, Verheyen RN, Willemen A, et al. Monoclonal antibody against human ovarian tumor-associated antigens. J Natl Cancer Inst. 1986;76(5):781-91.
55. Al-Sudani H, Ni Y, Jones P, Karakilic H, Cui L, Johnson LDS, et al. Targeting CD47-SIRPa axis shows potent preclinical anti-tumor activity as monotherapy and synergizes with PARP inhibition. NPJ Precis Oncol. 2023;7(1):69.
56. Yu L, Ding Y, Wan T, Deng T, Huang H, Liu J. Significance of CD47 and Its Association With Tumor Immune Microenvironment Heterogeneity in Ovarian Cancer. Front Immunol. 2021;12:768115.
57. Liu R, Wei H, Gao P, Yu H, Wang K, Fu Z, et al. CD47 promotes ovarian cancer progression by inhibiting macrophage phagocytosis. Oncotarget. 2017;8(24):39021-39032.
58. Brightwell RM, Grzankowski KS, Lele S, Eng K, Arshad M, Chen H, et al. The CD47 "don't eat me signal" is highly expressed in human ovarian cancer. Gynecol Oncol. 2016;143(2):393-397.
59. Wang CL, Lin MJ, Hsu CY, Lin HY, Tsai HP, Long CY, et al. CD47 promotes cell growth and motility in epithelial ovarian cancer. Biomed Pharmacother. 2019;119:109105.
60. Tian L, Xu B, Teng KY, Song M, Zhu Z, Chen Y, et al. Targeting Fc Receptor-Mediated Effects and the "Don't Eat Me" Signal with an Oncolytic Virus Expressing an Anti-CD47 Antibody to Treat Metastatic Ovarian Cancer. Clin Cancer Res. 2022;28(1):201-214.
61. Li Y, Lu S, Xu Y, Qiu C, Jin C, Wang Y, et al. Overexpression of CD47 predicts poor prognosis and promotes cancer cell invasion in high-grade serous ovarian carcinoma. Am J Transl Res. 2017; 9(6):2901-2910.
62. Tan M, Zhu L, Zhuang H, Hao Y, Gao S, Liu S, et al. Lewis Y antigen modified CD47 is an independent risk factor for poor prognosis and promotes early ovarian cancer metastasis. Am J Cancer Res. 2015; 5(9):2777-87.
63. Masadah R, Ikram D, Riadi R, Tangdiung Y, Nelwan BJ, Ghaznawie M, et al. CD133, CD47, and PD-L1 Expression in Ovarian High-grade Serous Carcinoma and Its Association with Metastatic Disease: A Cross-sectional Study. Asian Pac J Cancer Prev. 2024;25(1):249-255.