Tumor microenvironment manipulates chemoresistance in ovarian cancer (Review)

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Abstract. Ovarian cancer (OC) is the leading cause of mortality among the various types of gynecological cancer, and >75% of the cases are diagnosed at a late stage. Although platinum-based chemotherapy is able to help the majority of patients to achieve remission, the disease frequently recurs and acquires chemoresistance, resulting in high mortality rates. The complexity of OC therapy is not solely governed by the intrinsic characteristics of the OC cells (OCCs) themselves, but is also largely dependent on the dynamic communication between OCCs and various components of their surrounding microenvironment. The present review attempts to describe the mutual interplay between OCCs and their surrounding microenvironment. Tumor-associated macrophages (TAMs) and cancer-associated fibroblasts (CAFs) are the most abundant stromal cell types in OC. Soluble factors derived from CAFs steadily nourish both the OCCs and TAMs, facilitating their proliferation and immune evasion. ATP binding cassette transporters facilitate the extrusion of cytotoxic molecules, eventually promoting cell survival and multidrug resistance. Extracellular vesicles fulfill their role as genetic exchange vectors, transferring cargo from the donor cells to the recipient cells and propagating oncogenic signaling. A greater understanding of the vital roles of the tumor microenvironment will allow researchers to be open to the prospect of developing therapeutic approaches for combating OC chemoresistance.

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Abbreviations: OC, ovarian cancer; OCC, OC cell; TAM, tumor-associated macrophage; CAF, cancer-associated fibroblast; EOC, epithelial OC; TME, tumor microenvironment; ABC, ATP binding cassette; EV, extracellular vesicle; FGF4, fibroblast growth factor 4; IGF2, insulin-like growth factor II; OCSC, OC stem cell; MMP, matrix metalloproteinase; ECM, extracellular matrix; P-gp, P-glycoprotein; MDR, multidrug resistance; MRP1, MDR-associated protein-1; PTX, paclitaxel; MV, microvesicle; miR/miRNA, microRNA; APAF1, apoptotic protease-activating factor-1; EMT, epithelial-mesenchymal transition; DC, dendritic cell; CSF-1, colony stimulating factor-1; PDAC, pancreatic ductal adenocarcinoma

Key words: OC, chemoresistance, microenvironment, CAF, ABC, EV, immune cells

Contents

1. Introduction

Ovarian cancer (OC) has been reported to be the third most common gynecological malignancy worldwide, and the most lethal type of cancer (1). A total of 313,959 newly diagnosed cases and 207,252 associated deaths were reported in 2020 (2). Since OC cells (OCCs) often manifest the disease silently, >75% of cases are diagnosed at the late stage, usually after the tumor has spread throughout the abdomen (3). Currently, the standard treatment for OC comprises maximal cytoreductive surgery followed by platinum-based chemotherapy (4). Although the majority of patients go into clinical remission after conventional chemotherapy, the recurrence rate can be as high as 85% (5). In addition, the overall 5-year survival rate of OC is <50% in numerous countries throughout the world (6).

Almost 90% of ovarian tumors are of the epithelial OC (EOC) type, which is classified into five histological subtypes: Serous tumors (comprising ~80% of EOC), mucinous tumors, endometrioid cancer, ovarian clear cell carcinoma and mixed tumors (7). However, recurrent cases are often chemoresistant,

and therefore, these are associated with a high mortality rate (7). Chemoresistance may be driven by three main factors: Pharmacokinetic factors, the tumor microenvironment (TME) and tumor-specific mechanisms (8). Maintenance therapy with poly(ADP-ribose) polymerase inhibitors, bevacizumab and/or drugs targeting homologous recombination deficiency is becoming more widely used in the treatment of OC (9). Nevertheless, a plethora of studies have focused on the intrinsic characteristics of OCCs, while neglecting the role of the TME (10-13).

The TME consists of the blood and lymphoid vessels, nerves, fibroblasts, extracellular matrix (ECM) proteins, endothelial cells, pericytes and immune cells (14). Essentially, communication between OCCs and various components of the TME has a major impact on chemoresistance (15). It is important to understand how OCCs interact with the surrounding matrix to improve our understanding of tumor cell biology, both during oncogenesis and in terms of how chemoresistance develops. The present review offers a summary of the four most vital aspects: Cancer-associated fibroblasts (CAFs), ATP binding cassette (ABC) transporters, extracellular vesicles (EVs) and immune cells. Considered in their entirety, recovery of chemotherapeutic sensitivity and identification of novel anticancer drug targets are of great significance with respect to the treatment of OC.

2. CAFs

CAFs, a well-recognized abundant stromal cell population in the TME, steadily nourish the tumor cells by secreting soluble factors (16). The soluble factors derived from CAFs undoubtedly provide an important step in the development of CAF-mediated chemoresistance. Fibroblast growth factor 4 (FGF4) and fibroblast-derived insulin-like growth factor II (IGF2) are respectively able to activate the FGF4-FGF4 receptor 2 and IGF2-IGF1 receptor signaling pathways to induce the OC stem cell (OCSC) niche in CAFs (17,18). OCSCs contain all the particular functionalities of the cell subclasses, such as the ability to self-renew and to differentiate (19). Chemotherapeutic agents usually target fast-dividing cells and act in a cell-cycle specific manner, which confers an advantage on the ability of OCSCs to survive due to their slow proliferation rate (20). OCSCs may stay dormant for long periods of time, but they can self-renew at low seeding concentrations and produce more aggressive metastatic progeny (21). CAFs secrete matrix metalloproteinases (MMPs) to degrade matrix collagens, fibronectins and proteoglycans, facilitating TME structural remodeling and promoting matrix contractility (22,23). Unlike a soft TME, such as the greater omentum, which promotes dispersion of the OCCs (24,25), the increased stiffness of the ECM triggers OCC survival and proliferation (26). In addition, increased mechanical stress may lead to the collapse of blood vessels, leading to hypoxia, thereby promoting more aggressive cancer phenotypes and reducing drug delivery (27). Furthermore, the release of glutathione and cysteine by the CAFs contributes towards the depletion of platinum in the nuclei of the adjacent OCCs, thereby imparting resistance to platinum-based chemotherapies (28,29).

In addition to the resident fibroblasts, CAFs may be derived from five alternative sources: Epithelial cells, endothelial cells, mesothelial cells, bone marrow mesenchymal cells and adipose-derived mesenchymal stem cells (30-32). The levels of surface markers, such as α-smooth muscle actin, fibroblast-specific protein 1 and fibroblast activation protein, differ in different CAFs populations (16,33,34). In breast and lung cancer, CD10 and G protein-coupled receptor 77 have been demonstrated to unequivocally define a subset of CAFs that are associated with chemoresistance due to their ABC transporters (35).

However, relevant therapies in OC have been greatly hindered due to a high level of functional heterogeneity and a lack of a specific subset of markers (36,37). One of the most well-characterized examples is provided by anti-stromal therapy, in which it has proven difficult to precisely target CAFs, thereby increasing the risk of ablating vital stromal components required for tissue homeostasis (38). Therefore, there is an urgent need to classify different CAF phenotypes for improved stratification. With the emergence of single-cell technologies, an increasing array of functional assays has become available, and studies on CAFs are entering a critical stage (39,40). Strategies to 'normalize' CAFs (41) or to deprive them of their soluble factors (28,42) may offer feasible methods to complement the existing therapies that target OCCs.

3. ABC transporters

It is well established that the human family of ABC transporters comprises 49 members, which are grouped into 7 distinct subfamilies, termed ABCA through to ABCG (43). In addition to enabling the unidirectional translocation of substrates such as saccharides, lipids, amino acids and proteins, >13 types of ABC transporters are able to permit the extrusion of cytotoxic molecules from cancer cells and reduce the intracellular drug concentration, thereby promoting cell survival and multidrug resistance (MDR) (43,44).

Intrinsically chemoresistant types of cancer (e.g., pancreatic, liver, colon, adrenocortical and kidney cancer) express P-glycoprotein (P-gp; ABCB1) at a high level (44), whereas OC hardly expresses any P-gp at the time of initial presentation (45). The process of acquired chemotherapeutic resistance in OC is often accompanied by a marked overexpression of P-gp, indicating a possible role for P-gp in acquired resistance (45,46). Notably, ascites-induced OC chemoresistance may be mediated by ABC transporters. A previously published study showed that specific MDR-associated protein-1 (MRP1; ABCC1) inhibitors could suppress the ascites-induced resistance to paclitaxel (PTX) in ID8 cells (i.e., a mouse EOC cell line) (47). The expression levels of MRP1 and P-gp were found to be closely associated with the clinical stage and pathological differentiation grade of OC (48,49). Considered together, numerous findings have revealed that ABC transporters are important in facilitating OC drug resistance.

Although a logical approach to overcome MDR would be to inhibit ABC transporters, associated clinical trials that have been conducted have produced disappointing results (50,51). High doses of first-generation P-gp inhibitors (e.g., verapamil) were found to be required to be effective against MDR, resulting in increased levels of toxicity (52). Second-generation inhibitors (e.g., valspodar) have proven to be effective in overcoming the obstacle of high doses, although

they still have poor efficacy due to pharmacokinetics (51). To date, no specific, safe and effective third-generation inhibitors have been approved (53). A multiplicity of ABC transporters may be able to contribute to the acquired MDR of these tumors, providing a plausible explanation to explain how inhibiting only one of these ABC transporters is unlikely to reverse chemoresistance (50,54). Furthermore, the majority of clinical trials that have been performed have been small-scale, randomized and single-institution studies (51,55-57). Due to insufficient inclusion criteria, non-specific patients and inconsistent detection criteria, it has proven to be difficult to differentiate valid from invalid data. In addition to these issues, it may not be possible to regard mass-published cell culture model studies (58) and phase I clinical trials (59-61) with too much optimism, since unexpected results are likely to occur in phase II and III clinical trials.

Certainly, novel approaches, such as photodynamic therapy based on mitochondrial oxidative stress (45) and time-of-flight cytometry for the direct quantitation of platinum (62), have aroused great interest. Further developments in positron emission tomography, fluorescence *in situ* hybridization analysis, RNA sequencing and next-generation sequencing will assist in enabling the selection of a subset of patients for the development of specific ABC transporter inhibitors (63).

4. EVs

EVs, which are classified into exosomes, microvesicles (MVs) and apoptotic bodies, are able to transfer nucleic acids and proteins from donor cells to recipient cells (64,65). MicroRNA (miR/miRNA) fulfills an important role in inducing chemoresistance by targeting various signaling pathways as a major exosomal cargo molecule (66). A particular miRNA that has been widely reported to promote OC chemoresistance is miR-21 (67). Exo-miR-21 released by CAFs induces PTX-resistance in neighboring SKOV3 cells by downregulating apoptotic protease-activating factor-1 (APAF1) (67). APAF1 is able to bind to cytochrome *c* and dATP, which in turn recruit and activate caspases-9 and -3, as well as the apoptotic pathway (68,69). Additionally, exo-miR-98-5p derived from CAFs enhances cisplatin-resistance in OCCs through the downregulation of cyclin-dependent kinase inhibitor 1A, which serves an important role in cell cycle arrest (70).

Exosomal transmission of proteins also has a crucial role in modulating drug resistance in OC (71). Epithelial-mesenchymal transition (EMT) inducers, such as MMPs, annexin A2 and integrin 3, have been found in tumor-derived exosomes, suggesting that exosomes may promote the EMT process in which epithelial cell characteristics are lost and mesenchymal phenotypes are acquired (72,73). A number of different EMT-driven mechanisms that lead to carboplatin and/or PTX resistance have been identified in OC, including β-tubulin variants (taxane-specific resistance), ABC transporter overexpression, changes in the cell cycle, a greater DNA repair capability, anti-apoptotic effects and changes in stress chaperones (74).

Exosomes have been studied extensively in terms of OC chemoresistance, whereas apoptotic bodies and MVs have not been. Previously published studies showed that A2780/PTX-derived MVs could transport bioactive P-gp to chemosensitive A2780 cells *in vitro*, which conferred PTX-resistance to the recipient A2780 cells (69,75,76). The same phenomenon had been demonstrated in breast cancer (77); however, much work needs to be completed to improve our understanding of the role of MVs in OC chemoresistance.

There are four widely accepted potential strategies to overcome the pro-tumorigenic effects of exosomes (69): i) The inhibition of exosomal secretion; ii) the inhibition of the uptake of exosomes by target cells; iii) the promotion of exosomal depletion; and iv) the targeting of exosomal cargo. However, all these strategies remain at the preliminary and experimental stages (69). Notably, exosomes and MVs present an appealing platform for delivering drugs, as they are non-toxic and have low immunogenicity (69). In particular, they are able to transport drugs in a specific and targeted manner (78). Bioengineered exosomes are currently in use for the treatment of several different cancer types, including lung, prostate and pancreatic cancer (79-81). By contrast, the progress made using bioengineered exosomes in OC has been limited. Mesenchymal stem cells with a high proliferative capability have been used to produce large quantities of exosomes for therapeutic purposes (82). However, other challenges, such as how to isolate pure exosomes, how to obtain better loading efficiency and how to accurately deliver the targeted drugs, have to be overcome before the use of exosomes in cancer therapy may be successfully implemented (83).

5. Immune cells

Even though limited numbers of immune cells are able to infiltrate in OC, they exert direct or indirect effects on OC chemoresistance (84). Tumor-associated macrophages (TAMs) are the major population of immune cells that exist in the TME of OC (85), comprising two distinct subsets: Anti-tumorigenic M1-like TAMS and pro-tumorigenic M2-like TAMs (86). A previous study showed that exo-miR223 derived from the M2-like TAMs was effectively internalized by OC cell lines (A2780 and SKOV3 cells), thereby creating a chemoresistant phenotype through activation of the PI3K/AKT signaling pathway (87). In addition to secreting miR-loaded exosomes, in another study, M2-like TAMs were revealed to induce higher expression levels of ABC transporters in A2780 cells (85). Furthermore, TAMs have been shown to occur in close proximity to CAF-populated areas, indicating that a close association may exist between these two cell types (88). A number of previously published studies have established that CAFs are able to actively increase monocyte recruitment and promote their differentiation into M2-like TAMs by secreting multiple soluble factors, including interleukin-6, -8 and -10, and transforming growth factor-β (88,89). More importantly, CAF-induced M2-like TAMs exhibit higher expression levels of programmed cell death protein-1, thereby impairing effector T cell responses and inducing immune suppression of TAMs (90). Reciprocally, M2-like TAMs have been shown to regulate CAF activation as well (86), consequently establishing a positive feedback loop.

Studies that have focused on the influence of other immune cells on OC chemoresistance have been scarce up to the present time. Nevertheless, it should be mentioned that OC-derived EVs have an impact on the adaptive immune

escape process (91). For example, EVs stimulate T cell and NK cell proliferation, as well as inhibiting their functional activation (92,93). FAS ligand and TNF-related apoptosis-inducing ligand expressed by OC-derived EVs were shown to inhibit dendritic cell (DC) activation by inducing apoptosis (94). In brief, EVs assist OCCs in acquiring chemoresistance through immune suppression and immune evasion.

Strategies to block macrophage recruitment have been successfully developed (95). It is well established that colony stimulating factor-1 (CSF-1) and chemokine C-C motif ligand 2 are macrophage chemoattractants (96). Anti-CSF-1 receptor agents have been shown to prevent the recruitment of M2-like TAMs to tumor areas in pancreatic ductal adenocarcinoma (PDAC) models (97). However, CSF-1 receptor is not exclusively expressed by M2-like TAMs (98). Other immune cells, including M1-like TAMs and DCs, would be affected too, leading to complex interactions (98). By contrast, repolarizing M2-like TAMs back into the M1-like phenotype appears to be the more attractive option. In the PDAC model, the combination of anti-CD40 antibody and gemcitabine has been demonstrated to repolarize M2-like TAMs back into the M1-like phenotype, leading to increased sensitivity to gemcitabine and a reduced tumor burden (95). However, further clinical trials are required in a range of solid tumors. Additionally, the mechanism through which TAMs interact with CAFs has not been fully investigated to date (86). Future studies are required to delineate the precise mechanisms underlying CAF-TAM interactions in the TME in order to make further advances on the current cancer-targeted therapies.

6. Conclusion

Low survival rates in patients with OC are considered to mainly result from a late diagnosis, disease recurrence and chemoresistance. Specifically, chemoresistance is emerging as a major hurdle in OC treatment. Rather than focusing on the isolated impact of OCCs, the present review attempted to encompass the dynamic interplay between the TME and OCCs.

The soluble factors derived from CAFs not only induce formation of the OCSC niche, but also increase the stiffness of the ECM, which promotes the development of more aggressive and drug-resistant cancer phenotypes (17,18,22,23). ABC transporters are responsible for the extrusion of cytotoxic molecules from the OCCs and for reducing the intracellular drug concentration, eventually promoting cell survival and MDR (43,44). Since exosomes are used as genetic exchange vectors in the TME, exosomal cargoes activate signaling pathways in recipient cells, thereby facilitating cell proliferation and the EMT process, and inhibiting apoptosis (67,73). In addition, OCCs acquire chemoresistance through immune suppression and immune evasion (90).

Extensive crosstalk occurs among these components in the TME. Soluble factors secreted by CAFs and P-gp proteins can be released in the form of exosomes (70,75). TAMs may secrete EVs and express ABC transporters as well (85,87). TAMs are found close to the CAF-populated areas, and they engage in complex bidirectional interactions with CAFs (88).

The current review briefly presents the most up-to-date roles of the TME in OC chemoresistance and summarizes current research gaps in TME-targeted therapy. Although the role of the TME in fostering OC chemoresistance is becoming more recognized, research into this topic is just beginning and further work is required to advance current TME-targeted OC therapies.

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QLZ, JSD and YMW conducted the literature search and wrote the manuscript. FXX and LSH supervised the project and provided critical revisions. All authors read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

References

1. Miller KD, Nogueira L, Mariotto AB, Rowland JH, Yabroff KR, Alfano CM, Jemal A, Kramer JL and Siegel RL: Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin 69: 363-385, 2019.
2. Elshami M, Yaseen A, Alser M, Al-Slaibi I, Jabr H, Ubaiat S, Tuffaha A, Khader S, Khraishi R, Jaber I, *et al*: Knowledge of ovarian cancer symptoms among women in Palestine: A national cross-sectional study. BMC Public Health 21: 1992, 2021.
3. Baldwin LA, Huang B, Miller RW, Tucker T, Goodrich ST, Podzielinski I, DeSimone CP, Ueland FR, van Nagell JR and Seamon LG: Ten-year relative survival for epithelial ovarian cancer. Obstet Gynecol 120: 612-618, 2012.
4. De Andrade WP, Da Conceicao Braga L, Goncales NG, Silva LM and Da Silva Filho AL: HSPA1A, HSPA1L and TRAP1 heat shock genes may be associated with prognosis in ovarian epithelial cancer. Oncol Lett 19: 359-367, 2020.
5. Zhu H, Zou X, Lin S, Hu X and Gao J: Effects of naringin on reversing cisplatin resistance and the Wnt/β-catenin pathway in human ovarian cancer SKOV3/CDDP cells. J Int Med Res 48: 300060519887869, 2020.
6. Fu J, Shang Y, Qian Z, Hou J, Yan F, Liu G, Dehua L and Tian X: Chimeric Antigen receptor-T (CAR-T) cells targeting Epithelial cell adhesion molecule (EpCAM) can inhibit tumor growth in ovarian cancer mouse model. J Vet Med Sci 83: 241-247, 2021.
7. Colombo PE, Fabbro M, Theillet C, Bibeau F, Rouanet P and Ray-Coquard I: Sensitivity and resistance to treatment in the primary management of epithelial ovarian cancer. Crit Rev Oncol Hematol 89: 207-216, 2014.

8. Elzek MA and Rodland KD: Proteomics of ovarian cancer: Functional insights and clinical applications. Cancer Metastasis Rev 34: 83-96, 2015.
9. Kuroki L and Guntupalli SR: Treatment of epithelial ovarian cancer. BMJ 371: m3773, 2020.
10. Wang J, Da C, Su Y, Song R and Bai Z: MKNK2 enhances chemoresistance of ovarian cancer by suppressing autophagy via miR-125b. Biochem Biophys Res Commun 556: 31-38, 2021.
11. Muhanmode Y, Wen MK, Maitinuri A and Shen G: Curcumin and resveratrol inhibit chemoresistance in cisplatin-resistant epithelial ovarian cancer cells via targeting P13K pathway. Hum Exp Toxicol 40 (12_suppl): S861-S868, 2021.
12. Feng X, Bai X, Ni J, Wasinger VC, Beretov J, Zhu Y, Graham P and Li Y: CHTOP in chemoresistant epithelial ovarian cancer: A novel and potential therapeutic target. Front Oncol 9: 557, 2019.
13. Hu K, Yao L, Xu Z, Yan Y and Li J: Prognostic value and therapeutic potential of CBX family members in ovarian cancer. Front Cell Dev Biol 10: 832354, 2022.
14. Hansen JM, Coleman RL and Sood AK: Targeting the tumour microenvironment in ovarian cancer. Eur J Cancer 56: 131-143, 2016.
15. Worzfeld T, Pogge von Strandmann E, Huber M, Adhikary T, Wagner U, Reinartz S and Muller R: The unique molecular and cellular microenvironment of ovarian cancer. Front Oncol 7: 24, 2017.
16. Jena BC, Das CK, Bharadwaj D and Mandal M: Cancer associated fibroblast mediated chemoresistance: A paradigm shift in understanding the mechanism of tumor progression. Biochim Biophys Acta Rev Cancer 1874: 188416, 2020.
17. Kalluri R: The biology and function of fibroblasts in cancer. Nat Rev Cancer 16: 582-598, 2016.
18. Yasuda K, Torigoe T, Mariya T, Asano T, Kuroda T, Matsuzaki J, Ikeda K, Yamauchi M, Emori M, Asanuma H, *et al*: Fibroblasts induce expression of FGF4 in ovarian cancer stem-like cells/cancer-initiating cells and upregulate their tumor initiation capacity. Lab Invest 94: 1355-1369, 2014.
19. Ayen A, Jimenez Martinez Y, Marchal JA and Boulaiz H: Recent progress in gene therapy for ovarian cancer. Int J Mol Sci 19: 1930, 2018.
20. Deng J, Wang L, Chen H, Hao J, Ni J, Chang L, Duan W, Graham P and Li Y: Targeting epithelial-mesenchymal transition and cancer stem cells for chemoresistant ovarian cancer. Oncotarget 7: 55771-55788, 2016.
21. McGinity CL, Palmieri EM, Somasundaram V, Bhattacharyya DD, Ridnour LA, Cheng RYS, Ryan AE, Glynn SA, Thomas DD, Miranda KM, *et al*: Nitric oxide modulates metabolic processes in the tumor immune microenvironment. Int J Mol Sci 22: 7068, 2021.
22. Ishii G, Ochiai A and Neri S: Phenotypic and functional heterogeneity of cancer-associated fibroblast within the tumor microenvironment. Adv Drug Deliv Rev 99(Pt B): 186-196, 2016.
23. Leask A: A centralized communication network: Recent insights into the role of the cancer associated fibroblast in the development of drug resistance in tumors. Semin Cell Dev Biol 101: 111-114, 2020.
24. Chen RR, Yung MMH, Xuan Y, Zhan S, Leung LL, Liang RR, Leung THY, Yang H, Xu D, Sharma R, *et al*: Targeting of lipid metabolism with a metabolic inhibitor cocktail eradicates peritoneal metastases in ovarian cancer cells. Commun Biol 2: 281, 2019.
25. Naffar-Abu Amara S, Kuiken HJ, Selfors LM, Butler T, Leung ML, Leung CT, Kuhn EP, Kolarova T, Hage C, Ganesh K, *et al*: Transient commensal clonal interactions can drive tumor metastasis. Nat Commun 11: 5799, 2020.
26. He C, Wang L, Li L and Zhu G: Extracellular vesicle-orchestrated crosstalk between cancer-associated fibroblasts and tumors. Transl Oncol 14: 101231, 2021.
27. Sahai E, Astsaturov I, Cukierman E, DeNardo DG, Egeblad M, Evans RM, Fearon D, Greten FR, Hingorani SR, Hunter T, *et al*: A framework for advancing our understanding of cancer-associated fibroblasts. Nat Rev Cancer 20: 174-186, 2020.
28. Wang W, Kryczek I, Dostal L, Lin H, Tan L, Zhao L, Lu F, Wei S, Maj T, Peng D, *et al*: Effector T cells abrogate stroma-mediated chemoresistance in ovarian cancer. Cell 165: 1092-1105, 2016.
29. Dasari S, Fang Y and Mitra AK: Cancer associated fibroblasts: Naughty neighbors that drive ovarian cancer progression. Cancers (Basel) 10: 406, 2018.
30. Liu T, Zhou L, Li D, Andl T and Zhang Y: Cancer-associated fibroblasts build and secure the tumor microenvironment. Front Cell Dev Biol 7: 60, 2019.
31. Rynne-Vidal A, Au-Yeung CL, Jimenez-Heffernan JA, Perez-Lozano ML, Cremades-Jimeno L, Barcena C, Cristobal-Garcia I, Fernandez-Chacon C, Yeung TL, Mok SC, *et al*: Mesothelial-to-mesenchymal transition as a possible therapeutic target in peritoneal metastasis of ovarian cancer. J Pathol 242: 140-151, 2017.
32. Bu L, Baba H, Yasuda T, Uchihara T and Ishimoto T: Functional diversity of cancer-associated fibroblasts in modulating drug resistance. Cancer Sci 111: 3468-3477, 2020.
33. Sun Q, Zhang B, Hu Q, Qin Y, Xu W, Liu W, Yu X and Xu J: The impact of cancer-associated fibroblasts on major hallmarks of pancreatic cancer. Theranostics 8: 5072-5087, 2018.
34. Huang L, Xu AM, Liu S, Liu W and Li TJ: Cancer-associated fibroblasts in digestive tumors. World J Gastroenterol 20: 17804-17818, 2014.
35. Su S, Chen J, Yao H, Liu J, Yu S, Lao L, Wang M, Luo M, Xing Y, Chen F, *et al*: CD10(+)GPR77(+) cancer-associated fibroblasts promote cancer formation and chemoresistance by sustaining cancer stemness. Cell 172: 841-856.e16, 2018.
36. Cummings M, Freer C and Orsi NM: Targeting the tumour microenvironment in platinum-resistant ovarian cancer. Semin Cancer Biol 77: 3-28, 2021.
37. Chen X and Song E: Turning foes to friends: Targeting cancer-associated fibroblasts. Nat Rev Drug Discov 18: 99-115, 2019.
38. Ozdemir BC, Pentcheva-Hoang T, Carstens JL, Zheng X, Wu CC, Simpson TR, Laklai H, Sugimoto H, Kahlert C, Novitskiy SV, *et al*: Depletion of carcinoma-associated fibroblasts and fibrosis induces immunosuppression and accelerates pancreas cancer with reduced survival. Cancer Cell 25: 719-734, 2014.
39. Dominguez CX, Muller S, Keerthivasan S, Koeppen H, Hung J, Gierke S, Breart B, Foreman O, Bainbridge TW, Castiglioni A, *et al*: Single-Cell RNA sequencing reveals stromal evolution into LRRC15^{+} myofibroblasts as a determinant of patient response to cancer immunotherapy. Cancer Discov 10: 232-253, 2020.
40. Kieffer Y, Hocine HR, Gentric G, Pelon F, Bernard C, Bourachot B, Lameiras S, Albergante L, Bonneau C, Guyard A, *et al*: Single-Cell analysis reveals fibroblast clusters linked to immunotherapy resistance in cancer. Cancer Discov 10: 1330-1351, 2020.
41. Sherman MH, Yu RT, Engle DD, Ding N, Atkins AR, Tiriac H, Collisson EA, Connor F, Van Dyke T, Kozlov S, *et al*: Vitamin D receptor-mediated stromal reprogramming suppresses pancreatitis and enhances pancreatic cancer therapy. Cell 159: 80-93, 2014.
42. Duluc C, Moatassim-Billah S, Chalabi-Dchar M, Perraud A, Samain R, Breibach F, Gayral M, Cordelier P, Delisle MB, Bousquet-Dubouch MP, *et al*: Pharmacological targeting of the protein synthesis mTOR/4E-BP1 pathway in cancer-associated fibroblasts abrogates pancreatic tumour chemoresistance. EMBO Mol Med 7: 735-753, 2015.
43. Bustos-Cruz RH, Martinez LR, Garcia JC, Barreto GE and Suarez F: New ABCC2 rs3740066 and rs2273697 polymorphisms identified in a healthy colombian cohort. Pharmaceutics 10: 93, 2018.
44. Gottesman MM and Pastan IH: The role of multidrug resistance efflux pumps in cancer: Revisiting a JNCI publication exploring expression of the MDR1 (P-glycoprotein) gene. J Natl Cancer Inst 107: djv222, 2015.
45. Baglo Y, Sorrin AJ, Pu X, Liu C, Reader J, Roque DM and Huang HC: Evolutionary dynamics of cancer multidrug resistance in response to olaparib and photodynamic therapy. Transl Oncol 14: 101198, 2021.
46. Vaidyanathan A, Sawers L, Gannon AL, Chakravarty P, Scott AL, Bray SE, Ferguson MJ and Smith G: ABCB1 (MDR1) induction defines a common resistance mechanism in paclitaxel- and olaparib-resistant ovarian cancer cells. Br J Cancer 115: 431-441, 2016.
47. Mo L, Pospichalova V, Huang Z, Murphy SK, Payne S, Wang F, Kennedy M, Cianciolo GJ, Bryja V, Pizzo SV and Bachelder RE: Ascites increases expression/function of multidrug resistance proteins in ovarian cancer cells. PLoS One 10: e0131579, 2015.
48. Bagnoli M, Beretta GL, Gatti L, Pilotti S, Alberti P, Tarantino E, Barbareschi M, Canevari S, Mezzanzanica D and Perego P: Clinicopathological impact of ABCC1/MRP1 and ABCC4/MRP4 in epithelial ovarian carcinoma. Biomed Res Int 2013: 143202, 2013.

49. Jia Y, Sung S, Gao X and Cui XM: Expression levels of TUBB3, ERCC1 and P-gp in ovarian cancer tissues and adjacent normal tissues and their clinical significance. J BUON 23: 1390-1395, 2018.
50. Ween MP, Armstrong MA, Oehler MK and Ricciardelli C: The role of ABC transporters in ovarian cancer progression and chemoresistance. Crit Rev Oncol Hematol 96: 220-256, 2015.
51. Robey RW, Pluchino KM, Hall MD, Fojo AT, Bates SE and Gottesman MM: Revisiting the role of ABC transporters in multidrug-resistant cancer. Nat Rev Cancer 18: 452-464, 2018.
52. Teng YN, Wang CCN, Liao WC, Lan YH and Hung CC: Caffeic acid attenuates multi-drug resistance in cancer cells by inhibiting efflux function of human P-glycoprotein. Molecules 25: 247, 2020.
53. Guo X, To KKW, Chen Z, Wang X, Zhang J, Luo M, Wang F, Yan S and Fu L: Dacomitinib potentiates the efficacy of conventional chemotherapeutic agents via inhibiting the drug efflux function of ABCG2 in vitro and in vivo. J Exp Clin Cancer Res 37: 31, 2018.
54. Shaffer BC, Gillet JP, Patel C, Baer MR, Bates SE and Gottesman MM: Drug resistance: Still a daunting challenge to the successful treatment of AML. Drug Resist Updat 15: 62-69, 2012.
55. Tachibana M, Papadopoulos KP, Strickler JH, Puzanov I, Gajee R, Wang Y and Zahir H: Evaluation of the pharmacokinetic drug interaction potential of tivantinib (ARQ 197) using cocktail probes in patients with advanced solid tumours. Br J Clin Pharmacol 84: 112-121, 2018.
56. Zhu T, Howieson C, Wojtkowski T, Garg JP, Han D, Fisniku O and Keirns J: The effect of verapamil, a P-glycoprotein inhibitor, on the pharmacokinetics of peficitinib, an orally administered, once-daily JAK inhibitor. Clin Pharmacol Drug Dev 6: 548-555, 2017.
57. Fox E, Widemann BC, Pastakia D, Chen CC, Yang SX, Cole D and Balis FM: Pharmacokinetic and pharmacodynamic study of tariquidar (XR9576), a P-glycoprotein inhibitor, in combination with doxorubicin, vinorelbine, or docetaxel in children and adolescents with refractory solid tumors. Cancer Chemother Pharmacol 76: 1273-1283, 2015.
58. Patel A, Li TW, Anreddy N, Wang DS, Sodani K, Gadhia S, Kathawala R, Yang DH, Cheng C and Chen ZS: Suppression of ABCG2 mediated MDR in vitro and in vivo by a novel inhibitor of ABCG2 drug transport. Pharmacol Res 121: 184-193, 2017.
59. Gupta P, Zhang YK, Zhang XY, Wang YJ, Lu KW, Hall T, Peng R, Yang DH, Xie N and Chen ZS: Voruciclib, a Potent CDK4/6 inhibitor, antagonizes ABCB1 and ABCG2-mediated multi-drug resistance in cancer cells. Cell Physiol Biochem 45: 1515-1528, 2018.
60. Grande E, Giovannini M, Marriere E, Pultar P, Quinlan M, Chen X, Rahmanzadeh G, Curigliano G and Cui X: Effect of capmatinib on the pharmacokinetics of digoxin and rosuvastatin administered as a 2-drug cocktail in patients with MET-dysregulated advanced solid tumours: A phase I, multicentre, open-label, single-sequence drug-drug interaction study. Br J Clin Pharmacol 87: 2867-2878, 2021.
61. Chen R, Herrera AF, Hou J, Chen L, Wu J, Guo Y, Synold TW, Ngo VN, Puverel S, Mei M, *et al*: Inhibition of MDR1 overcomes resistance to brentuximab vedotin in hodgkin lymphoma. Clin Cancer Res 26: 1034-1044, 2020.
62. Comsa E, Nguyen KA, Loghin F, Boumendjel A, Peuchmaur M, Andrieu T and Falson P: Ovarian cancer cells cisplatin sensitization agents selected by mass cytometry target ABCC2 inhibition. Future Med Chem 10: 1349-1360, 2018.
63. Goebel J, Chmielewski J and Hrycyna CA: The roles of the human ATP-binding cassette transporters P-glycoprotein and ABCG2 in multidrug resistance in cancer and at endogenous sites: Future opportunities for structure-based drug design of inhibitors. Cancer Drug Resist 4: 784-804, 2021.
64. Butera G, Pacchiana R and Donadelli M: Autocrine mechanisms of cancer chemoresistance. Semin Cell Dev Biol 78: 3-12, 2018.
65. Luo R, Liu M, Yang Q, Cheng H, Yang H, Li M, Bai X, Wang Y, Zhang H, Wang S, *et al*: Emerging diagnostic potential of tumor-derived exosomes. J Cancer 12: 5035-5045, 2021.
66. Law ZJ, Khoo XH, Lim PT, Goh BH, Ming LC, Lee WL and Goh HP: Extracellular vesicle-mediated chemoresistance in oral squamous cell carcinoma. Front Mol Biosci 8: 629888, 2021.
67. Tang Z, Li D, Hou S and Zhu X: The cancer exosomes: Clinical implications, applications and challenges. Int J Cancer 146: 2946-2959, 2020.
68. Au Yeung CL, Co NN, Tsuruga T, Yeung TL, Kwan SY, Leung CS, Li Y, Lu ES, Kwan K, Wong KK, *et al*: Exosomal transfer of stroma-derived miR21 confers paclitaxel resistance in ovarian cancer cells through targeting APAF1. Nat Commun 7: 11150, 2016.
69. Milman N, Ginini L and Gil Z: Exosomes and their role in tumorigenesis and anticancer drug resistance. Drug Resist Updat 45: 1-12, 2019.
70. Santos P and Almeida F: Role of exosomal miRNAs and the tumor microenvironment in drug resistance. Cells 9: 1450, 2020.
71. Eguchi T, Taha EA, Calderwood SK and Ono K: A novel model of cancer drug resistance: Oncosomal release of cytotoxic and antibody-based drugs. Biology (Basel) 9: 47, 2020.
72. Han X, Zhen S, Ye Z, Lu J, Wang L, Li P, Li J, Zheng X, Li H, Chen W, *et al*: A Feedback loop between miR-30a/c-5p and DNMT1 mediates cisplatin resistance in ovarian cancer cells. Cell Physiol Biochem 41: 973-986, 2017.
73. Yu S, Cao H, Shen B and Feng J: Tumor-derived exosomes in cancer progression and treatment failure. Oncotarget 6: 37151-37168, 2015.
74. Cao Y, Shen T, Zhang C, Zhang QH and Zhang ZQ: MiR-125a-5p inhibits EMT of ovarian cancer cells by regulating TAZ/EGFR signaling pathway. Eur Rev Med Pharmacol Sci 23: 8249-8256, 2019.
75. Zhang FF, Zhu YF, Zhao QN, Yang DT, Dong YP, Jiang L, Xing WX, Li XY, Xing H, Shi M, *et al*: Microvesicles mediate transfer of P-glycoprotein to paclitaxel-sensitive A2780 human ovarian cancer cells, conferring paclitaxel-resistance. Eur J Pharmacol 738: 83-90, 2014.
76. Wan Z, Gao X, Dong Y, Zhao Y, Chen X, Yang G and Liu L: Exosome-mediated cell-cell communication in tumor progression. Am J Cancer Res 8: 1661-1673, 2018.
77. Lv MM, Zhu XY, Chen WX, Zhong SL, Hu Q, Ma TF, Zhang J, Chen L, Tang JH and Zhao JH: Exosomes mediate drug resistance transfer in MCF-7 breast cancer cells and a probable mechanism is delivery of P-glycoprotein. Tumour Biol 35: 10773-10779, 2014.
78. Mashouri L, Yousefi H, Aref AR, Ahadi AM, Molaei F and Alahari SK: Exosomes: Composition, biogenesis, and mechanisms in cancer metastasis and drug resistance. Mol Cancer 18: 75, 2019.
79. Kim MS, Haney MJ, Zhao Y, Yuan D, Deygen I, Klyachko NL, Kabanov AV and Batrakova EV: Engineering macrophage-derived exosomes for targeted paclitaxel delivery to pulmonary metastases: In vitro and in vivo evaluations. Nanomedicine 14: 195-204, 2018.
80. Saari H, Lazaro-Ibanez E, Viitala T, Vuorimaa-Laukkanen E, Siljander P and Yliperttula M: Microvesicle- and exosome-mediated drug delivery enhances the cytotoxicity of Paclitaxel in autologous prostate cancer cells. J Control Release 220(Pt B): 727-737, 2015.
81. Binenbaum Y, Fridman E, Yaari Z, Milman N, Schroeder A, Ben David G, Shlomi T and Gil Z: Transfer of miRNA in macrophage-derived exosomes induces drug resistance in pancreatic adenocarcinoma. Cancer Res 78: 5287-5299, 2018.
82. Rashid MH, Borin TF, Ara R, Alptekin A, Liu Y and Arbab AS: Generation of novel diagnostic and therapeutic exosomes to detect and deplete protumorigenic M2 macrophages. Adv Ther (Weinh) 3: 1900209, 2020.
83. Sinha D, Roy S, Saha P, Chatterjee N and Bishayee A: Trends in research on exosomes in cancer progression and anticancer therapy. Cancers (Basel) 13: 326, 2021.
84. Majidpoor J and Mortezaee K: The efficacy of PD-1/PD-L1 blockade in cold cancers and future perspectives. Clin Immunol 226: 108707, 2021.
85. Nowak M and Klink M: The role of tumor-associated macrophages in the progression and chemoresistance of ovarian cancer. Cells 9: 1299, 2020.
86. Mao X, Xu J, Wang W, Liang C, Hua J, Liu J, Zhang B, Meng Q, Yu X and Shi S: Crosstalk between cancer-associated fibroblasts and immune cells in the tumor microenvironment: New findings and future perspectives. Mol Cancer 20: 131, 2021.
87. Zhu X, Shen H, Yin X, Yang M, Wei H, Chen Q, Feng F, Liu Y, Xu W and Li Y: Macrophages derived exosomes deliver miR-223 to epithelial ovarian cancer cells to elicit a chemoresistant phenotype. J Exp Clin Cancer Res 38: 81, 2019.
88. Liu T, Han C, Wang S, Fang P, Ma Z, Xu L and Yin R: Cancer-associated fibroblasts: An emerging target of anti-cancer immunotherapy. J Hematol Oncol 12: 86, 2019.

89. An Y, Liu F, Chen Y and Yang Q: Crosstalk between cancer-associated fibroblasts and immune cells in cancer. J Cell Mol Med 24: 13-24, 2020.
90. Gok Yavuz B, Gunaydin G, Gedik ME, Kosemehmetoglu K, Karakoc D, Ozgur F and Guc D: Cancer associated fibroblasts sculpt tumour microenvironment by recruiting monocytes and inducing immunosuppressive PD-1^{+} TAMs. Sci Rep 9: 3172, 2019.
91. Whiteside TL: Tumor-derived exosomes and their role in tumor-induced immune suppression. Vaccines (Basel) 4: 35, 2016.
92. Cai X, Caballero-Benitez A, Gewe MM, Jenkins IC, Drescher CW, Strong RK, Spies T and Groh V: Control of tumor initiation by NKG2D naturally expressed on ovarian cancer cells. Neoplasia 19: 471-482, 2017.
93. Shenoy GN, Loyall J, Berenson CS, Kelleher RJ Jr, Iyer V, Balu-Iyer SV, Odunsi K and Bankert RB: Sialic acid-dependent inhibition of T cells by exosomal ganglioside GD3 in ovarian tumor microenvironments. J Immunol 201: 3750-3758, 2018.
94. Tian W, Lei N, Zhou J, Chen M, Guo R, Qin B, Li Y and Chang L: Extracellular vesicles in ovarian cancer chemoresistance, metastasis, and immune evasion. Cell Death Dis 13: 64, 2022.
95. Ireland LV and Mielgo A: Macrophages and fibroblasts, key players in cancer chemoresistance. Front Cell Dev Biol 6: 131, 2018.
96. Balta E, Wabnitz GH and Samstag Y: Hijacked immune cells in the tumor microenvironment: Molecular mechanisms of immunosuppression and cues to improve T cell-based immunotherapy of solid tumors. Int J Mol Sci 22: 5736, 2021.
97. Mitchem JB, Brennan DJ, Knolhoff BL, Belt BA, Zhu Y, Sanford DE, Belaygorod L, Carpenter D, Collins L, Piwnica-Worms D, *et al*: Targeting tumor-infiltrating macrophages decreases tumor-initiating cells, relieves immunosuppression, and improves chemotherapeutic responses. Cancer Res 73: 1128-1141, 2013.
98. Cannarile MA, Weisser M, Jacob W, Jegg AM, Ries CH and Ruttinger D: Colony-stimulating factor 1 receptor (CSF1R) inhibitors in cancer therapy. J Immunother Cancer 5: 53, 2017.