The new prospectives of statins in combination therapies for ovarian cancer based on connections of mechanisms

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Abstract

Epithelial ovarian cancer is a disease with the highest mortality rate among gynecological tumors. After years of studies, despite targeted drugs and immunotherapies have been developing, their therapeutic effects are still not ideal. Statins, as lipid-lowering medicines, have many findings beyond expectation in the fight against cancer, and have shown promisingly positive results in clinical trials. Actually, statins cannot be used as a monotherapy to achieve complete remission due to its efficacy established, but for its great potential lying in effects about synergism and sensibilization with other drugs, and even the reduction of side effects of anti-cancer treatment. This review summarizes the evidence and potential of combining statins with first-line chemotherapy, bevacizumab, PARP inhibitors and immunotherapy drugs in the pharmacotherapy of ovarian cancer, and proposes hypothesises about new combination therapies based on the current mechanisms and theories, to provide a new perspective to further experimental research and clinical trials.

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Abstract

Epithelial ovarian cancer is a disease with the highest mortality rate among gynecological tumors. After years of studies, despite targeted drugs and immunotherapies have been developing, their therapeutic effects are still not ideal. Statins, as lipid-lowering medicines, have many findings beyond expectation in the fight against cancer, and have shown promisingly positive results in clinical trials. Actually, statins cannot be used as a monotherapy to achieve complete remission due to its efficacy established, but for its great potential lying in effects about synergism and sensibilization with other drugs, and even the reduction of side effects of anti-cancer treatment. This review summarizes the evidence and potential of combining statins with first-line chemotherapy, bevacizumab, PARP inhibitors and immunotherapy drugs in the pharmacotherapy of ovarian cancer, and proposes hypothesises about new combination therapies based on the current mechanisms and theories, to provide a new perspective to further experimental research and clinical trials.

Key words: Statins; Ovarian cancer; Combination therapy

Introduction

With the highest mortality rate among gynecologic cancers, ovarian cancer (OC) is the third most common gynecological tumor in the world. Based on the source of OC, epithelial cancers (EOC) are the most common subtype, accounting for 90% of all case, devided by tumor cytohistology into serous, endometrioid, mucinous, clear cell, and the rest being rarer subtypes or unspecified[1]. Among these cytohistologic subtypes, serous carcinoma consistently has the highest incidence and lowest 5-year survival rate of patients[2]. The high mortality rate is related to the declining effectiveness of pharmacological therapies besides late diagnosis and lack of early detection of the disease[3].

Generally, combination platinum derivatives with taxane is recognized as the first-line pharmacological therapy, but it often ends up with disease recurrence and the acquisition of platinum resistance defined as progression occurring within 6 months after the last dose of platinum-based therapy. There is also about 20% of patients are primary platinum refractory, who have progression within 4 weeks of platinum-based treatment[4].

In recent years, targeted therapy and immunotherapy have provided a new direction for the treatment of EOC. Bevacizumab has shown positive results in standard chemotherapy, even in platinum-resistant relapsed disease[5]. PARP inhibitors, such as olaparib, niraparib and rucaparib, are managed to do good to patients whose tomors with a BRCA1 and/or BRCA2 mutation (BRCAm) or homologous recombination deficiency (HRD)[6]. Unfortunately, their clinical efficacy is still limited[7], and many subsequent novel therapies have no positive clinical outcome, such as Ofra-vec (an gene agent to inhibit angiogenesis and tumor response)[8], Lurbinectedin (carcinogenic transcription inhibitors)[9]. Therefore, developing new treatment options and identifying biomarker oriented strategies is still critical to personalize treatment for EOC patients.

Actually, the area of combination regimens remain active. Comparison with exploring new drugs with enormous costs, it seems like a good idea to make statins as complementary drugs of pharmacological therapies mentioned above. Statins, as old medicines, have great potential anti-tumor effects, while reducing the costs borne by patients.

Statins, originally used as a class of lipid-lowering drugs by inhibiting enzyme hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase (HMGCR) in the rate-limiting step in cholesterol hepatic biosynthesis, in the treatment and prevention of cardiovascular diseases[10]. However, it has received increasing attention due to its anti-inflammatory, antiproliferative, anti-invasive, radiosensitive, radioprotective and immune-activating[11]effects, which has gone far beyond its lipid-lowering effects. Massive efforts have been made to determine their utility in cancer prevention, as well as their potential use in combination therapies for treatment of certain malignancie. Currently, prospective studies and retrospective studies had been reported that statins improved OC prognosis[12]. Its treatment effect is intensely associated with some factors about the type (lipophilic or hydrophilic), dose (high or low), usage of statin use (continuous statin users or post-diagnostic statin users), subtype of ovarian cancer tissue (Serous, endometrioid, clear cell or mucinous OC), grades of serous OC (high-grade or low-grade)[12],[13]. Some biomarkers has been found to identify patients who will respond to statin treatment[13], but have not been practiced in clinic. Even though we found that statins could not achieve the target effect of complete remission, their greater potential lies in acting as adjuncts to other drugs to achieve synergistic and sensitizing effects, which still exists lots of room to explore.

This review summarizes the mechanism based on characteristics of ovarian cancer associated with statins, and displays the existing evidence from the preclinical studies involving statins combining with other promising agents for treatment of EOC (**Figure 1**), also puts forward hypothesis of new treatment options based on the existing theoretical research to expect to get attention in practical application.

Mechanisms based on characteristics of ovarian cancerconnecting with statins

2.1 Lipid Metabolism

Ovarian cancer is unique in abdominal implantation, a way of metastasis compared with other epithelial malignancies, and the most common site of metastasis is the omentum rich in fat. Omental adipocytes can secrete adipokines to promote the selective orientation of cancer cells[14]. Then, ECO cells interact with and convert them into "cancer-associated adipocytes"[15], absorbing them to meet their demands for energy. Mukherjee A et al.[15] report that adipocytes can support requirements of ovarian cancer cells through the reprogramming of glucose metabolism. In addition, cholesterol levels in tumor cells were elevated compared to normal cells, and OC cells rely more on uptake of exogenous lipids and cholesterol[16]. De Wolf et al. found the up-regulation of HMGCR in ECO, compared with normal ovarian epithelial cells[17]. Interestingly, in platinum-resistant ovarian cancer cells, HUANG X Y, et al. discover the up-regulation of low-density lipoprotein receptor (LDLR) expression and down-regulation of HMGCR expression[18]. The factors inscribed into changes in the two drug targets is necessary to be further studied. In addition, high cholesterol levels in tumor cells is associated with platinum resistance in ovarian cancer[19], possibly due to preventing the entrence of platinum by reduction of the permeability and fluidity of the cell membranes of cancer cells.

These studies suggest that lipid metabolism plays an important role in the metastasis and drug resistance of ovarian cancer, and statins has great potential in anti-ovarian cancer because it inhibits HMGCR in the mevalonate pathway (MVAP) to reduce the production of cholesterol.

While Criscuolo,D.et al. declared that statins in OC cells would induce platinum resistance by stimulating exogenous cholesterol to increase intake due to inhibition of endogenous cholesterol synthesis in the MVAP, the conclution exists some paradox theoretically[19]. Because it was based on the study of HUANG X Y, et al. [18] about the up-regulation of low-density lipoprotein receptor (LDLR) expression and down-regulation of HMGCR expression in platinum-resistant ovarian cancer cell, which merely indicated that platinum-resistant cells have increased uptake intensity of exogenous cholesterol. If statins would increase intracellular cholesterol by activating more LDLRs, the speed should be faster than that of its inhibition of endogenous cholesterol synthesis, then the result would contradict their lipid-lowering effects and anticancer results in clinic. Hence, the key may be the reconstruction of balance of endogenous and exogenous cholesterol synthesis, and the main strategy for this problem should focus on two aspects, decreasing endogenous cholesterol synthesis and reducing the concentration of exogenous cholesterol or targeting LDL receptors. In addition, statins can re-polarize tumor-associated macrophages (TAM) via reducting cholesterol to increase tumor necrosis factor (TNF)-α, but to decrease transforming growth factor (TGF)-β, which suppresses epithelial-to-mesenchymal transition (EMT) (a biological process by epithelial cells losing their cellular identity and acquiring a mesenchymal phenotype, involving cancer metastasis)[20]. Moreover, combination of cholesterol and its G protein-coupled receptor (GPCR) can activate the Hedgehog (HH) pathway that has been proved an extraordinary promotion for the development of EOC[21]. Statins is confirmed to reduce proliferation of medulloblastoma cells by reduction of cholesterol systhesis to inhibit HH pathway[22], but whether statins fighting against ovarian cancer by the mechanism is necessary to establish further.

2.2 MVAP beyond cholesterol systhesis

In addition to cholesterol biosynthesis, the MVAP is a crucial metabolic pathway for numerous cellular activities[23], and HMGCR on which is a drug target of statins. In EOC, HMGCR is also established as a metabolic oncogene, improving tumor development, and commonly seen in OC cells with the TP53 mutation[24]. Thus the inhibition of statins for it should achieve a good anti-ovarian cancer effect in theory. Meanwhile, statins decreases the production of farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP) by inhibiting HMGCR[25], which effect guanosine-triphosphate hydrolase (GTPases), such as Ras and Rho, that participate in proliferation, migration and cell invasion[26], and then farnesylation is unable to complete, which can make the protein non-polar to achieve cell membrane anchoring. Indeed, MVAP can also restrain EMT without cholesterol. Kato S.et al. demonstrated that statins revamped the stemness and EMT marker expression patterns (both in mRNA and protein levels) in ovarian cancer by the MVAP inactivating of the Hippo/YAP/Rho pathway[27]. Therefore, statin can restrict the proliferation and metastasis of EOC. Moreover, the results after knocking out the hydroxymethylglutaryl (HMG) metabolic target were similar to those of statins, further confirming that statins can inhibit ovarian cancer progression

through the MVAP[28].

2.3Voltage-dependent anion channel 1 (VDAC1)

The mitochondrial porins, called voltage dependent anionic channels (VDAC) plays a main role in selective permeability, which contributes to constant exchange of metabolites and ions with the cytoplasm through the external mitochondrial membrane (MOM)[29]. Among VDAC isoforms in mammals, namely VDAC1, VDAC2, and VDAC3, VDAC1 is the most characteristic one, serving as an essential gate for metabolites in the MOM (ATP/ADP, NAD+/NADH, Krebs cycle's intermediates, cholesterol and glutamate), and taking part in cholesterol distribution and in fatty acid transport across the MOM, meanwhile, modulating the flow of small ions (Cl-, K+, Na+, and Ca2+)[30]. What's more, it is acknowledged as a regulator of apoptosis. Under the stimulation of apoptosis, VDAC1 interacts with the pro-apoptotic protein Bax to form a channel that promotes the release of cytochrome c (CYT c) to the cytoplasm to activate apoptosis[31].

It is found that VDAC1 is upregulated in OC cell lines but not in normal cell line and has been proved as a gene related positively with statin response in OC cells[32]. Meanwhile, VDAC1 can be regulated by statins, which binds to hexokinase (HK), the rate-limiting enzyme of glycolysisIt, to play a role in the interconnection between mitochondrial respiration and the regulation of glycolysis, likely to be a potential therapeutic target in OC[33].

2.4 The PI3K/AKT/ mTOR signal pathway

The control of cell survival, growth, proliferation, angiogenesis, transcription, translation, and metabolism is largely dependent on the PI3K/AKT/mTOR signaling pathway[34]. It is overexpressed in 45% of high-grade serous ovarian cancer (HGSOC) and can promote OC cells proliferation and anti-apoptosis[35]. The study of J. Huang, L and co-workers implies a close connection of specific genetic aberrations in OC cell lines with siRNA targeting components in the PI3K/AKT/mTOR signaling pathway[36]. The PI3K/Akt/mTOR signaling pathway also activates sterol regulatory element binding protein (SREBPs) transcription to promote cholesterol uptake and synthesis to meet the needs of cancer cells[37]. Exactly, statins have a link with this pathway, which are observed that act on cancer cells can inhibit PI3K/AKT activation to promote the expression of PTEN[38]. And they can depend on mTOR to inhibit Akt phosphorylation and nuclear translocation, then to sensitize p53-deficient cells to cytostatic drugs in hepatocellular carcinoma HepG2 cells and non-small cell lung cancer cells[39]. Moreover, Stine et al. point out that simvastatin blocks the PI3K/AKT pathway in SKOV3 and HEY cellst to increase the active oxygen level to cause DNA damage and to reduce the vascular endothelial growth factor (VEGF) expression, to induce endoplasmic reticulum (ER) stress, having an anti-proliferation and metastasis effect on ovarian cancer[40].

The synergies of statins and antitumor therapies in OC

3.1 Paclitaxel and platinum

Paclitaxel and platinum are well-known anticancer agents, the former by interfering with spindle formation to promote tubulin polymerization and to block mitosis at the metaphase-anaphase transition[41], the latter binding to DNA by the formation of intra-stranded and inter-stranded crosslinks to kill tumor cells as main mechanism. Cisplatin, carboplatin, and oxaliplatin, as platinum-based anticancer drugs, with remarkable therapeutic effects, are widely used in the clinic.

Statins combined with cisplatin can arrest cell cycle and induce premature apoptosis, with accompanied dysregulation of Ras pathway proteins, finally resulting in synergistic reduction in ovarian cancer cell proliferation[42]. Robinson,E.et al. found that if simvastatin was administered together with either carboplatin or paclitaxel, additive effects were seen in the inhibition of autophagosome trafficking in human ovarian cancer cell lines; however, when simvastatin was given before carboplatin, strong antagonism was observed[43]. Actually, the plasma concentration of statin obtained in this context is inadequate to counteract the effect of carboplatin, implying that this is not a significant issue[43]. It also remind us that would be better to study how to increase the concentration of statins in the ovaries.

There have also been many experimental studies of statins combined with paclitaxel or platinum-based drugs for other cancers. The simvastatin's combination with paclitaxel remarkably augments efficacy in cellular system and xenograft mouse model of cervical cancer by by depleting GGPP, inhibiting prenylation, decreasing GTPases activities[44]. Lovastatin can sensitize cells to paclitaxel and dampen metastatic spread by depleting caveolin-1 or inhibiting MVAP from destroying lipid rafts, then decreasing the metastatic-potential and chemoresistance in CD133 Hipancreatic tumor initiating cells[45]. Combination therapy of low-dose paclitaxel and fluvastatin reduced cell viability and induced apoptosis by forming DNA fragmentation in primary meningioma cell culture[46]. It is discovered that combined action of lovastatin and paclitaxel resulted in upgraded mitosin levels and that lovastatin changed the association of mitosin with condensed chromosomes, in the human leukemia K562 and HL-60 cell lines[47].

What's more, with regard to drug resistence, it was revealed that simvastatin can inhibit FAK signaling pathway to resensitize the drug-resistant cancer cells to paclitaxel, by destroying lipid rafts, cholesterol-rich domains, and suppressing integrin-β3 and focal adhesion formation[48].

In terms of drug side effects, rosuvastatin and duloxetine bring down mechanical allodynia and thermal hyperalgesia in mice treated with paclitaxel.[49] Simvastatin and rosuvastatin may have a protective effect against cisplatin-induced kidney and liver damage via amelioration of lipid peroxidation as well as due to improvement of kidney and liver function, and lipid-lowering effects in rats[50]. These potential beneficial results imply a bonus to protect normal organs for statins except for anti-cancer effects.

3.2 Bevacizumab

Bevacizumab is a monoclonal antibody to inhibit VEGF. By linking with VEGF-A, bevacizumab obstructs the link between VEGF-A and VEGFR, thus preventing the VEGF signalling pathways that stimulate neovascularization[51]. It prolongs progression free survival (PFS) when added to first-line chemotherapy, and to platinum-sensitive disease. Bevacizumab has also shown activity in platinum-resistant ovarian cancer (PROC). Early treatment of PROC with a combination of bevacizumab and chemotherapy allows most patients to benefit from anti-angiogenic therapy[52].

The investigation of the relationship between statins and angiogenesis has been done, and interestingly, the effects of HMG-CoA reductase inhibition on angiogenesis is biphasic dose-dependent, proangiogenic at low therapeutic concentrations but reversed by GGPP at high, which is related with alterations in VEGF signaling and endothelial apoptosis[53]. Even though low-dose statins may have a little effect on angiogenesis or tumor growth, they are still thought to increase the sensitivity of cancer cells to signalling chemotherapy[54]. This may explain why some clinical studies favor low-dose, continuous statin therapy over short-dose, high-dose statin therapy, but this does not lead to more complete and valid conclusions[55].

Therefore, theoretically, it can be inferred that bevacizumab and statins have a certain synergistic effect on anti-cancer. In a study of Lee et al., statins (simvastatin, lovastatin, atorvastatin, and pravastatin) in combination with bevacizumab directly suppress angiogenic mediators, such as angiopoietin2, binding immunoglobulin protein (BiP), and Hsp90a, to reduce the cell viability, migration, invasion, and tube formation of human umbilical vein endothelial cell. The synergy of bevacizumab with simvastatin obviously weakens the growth and metastases of xenograft tumours in contrast to with bevacizumab alone[56]. Although there is a lack of relevant studies on the treatment of ovarian cancer by statin combined with bevacizumab, the above theories and studies imply the potential of this combination therapy as a new research direction.

3.3 Poly ADP-ribose polymeraseb (PARP) inhibitors (PARP-is)

PARP-is became the first targeted treatment for HGSOC, selectively active for women with double-strand DNA break repair (BRCA) mutations and/or a homologous recombination (HR) deficiency (HRD) phenotype up to 50% of cases[57]. Mostly, PARP inhibitors eliminate selectively cancer cells through DNA damage accumulation, after block the single-strand DNA break repair process in BRCA1/2 and/or HRD cancer cells, while unaffecting normal cells with an intact double-strand DNA break repair system[57]. With further clinical trials of olaparib, niraparib and rucaparib, they usually cause a good initial response, and treatment

landscape hasn't been limited to a subgroup of women with relapsed ovarian cancer, which has shifted to the first-line maintenance therapy setting[60], but many patients develop resistance to PARP-is and appear disease progression or relapse of tumor cells[57].

According to the experimental and clinical results on PARP-is activating AKT under oxidative stress conditions[61], it emphasizes Akt activation that is critical in the cytoprotective properties of PARP1 inhibition, which can undermine the cellular inhibitory effect of PARP1 inhibitor on cancers carrying BRCA mutations. Reports about the increase of PARP-is' cytotoxicity by Akt inhibitor support this notion[62]. As experimental evidences in vitro and in vivo indicate that inhibition of PARP1 can activate the cytoprotective PI3K-Akt pathway, which induce mitochondrial protection and apoptosis resistance that contribute to the limitation of cytostatic efficacy in PARP-is therapy[63].

Actually, many studies on the anti-cancer mechanism of statins have proved that they are inhibitors of AKT, that is, they reduce the phosphorylation of AKT to inhibit the proliferation of cancer cells[64]. A study indicates that statin-induced inhibition of Akt phosphorylatio can sensitize cells to cytostatic drugs. This mechanism appears to occur only in cancer cells, whereas in normal cells statins activate the AKT pathway for cell protection. To a certain extent, the overlapping results of these studies suggest that statins may counteract parp inhibitor resistance through AKT signaling pathway, and the potential as a new combination therapy for ovarian cancer, which needs to be confirmed in further experiments and clinical trials.

3.4 Immunotherapy

3.4.1 Anti-PD1/PD-L1

Programmed death ligand 1 (PD-L1) is the main ligand of programmed death receptor 1 (PD1) on T cells. The combination between the two strongly inhibits T cell receptor (TCR) signaling and CD80/CD28 co-stimulation leads to tumors evading detection tumors evade detection[66]. Many tumors take advantage of this negative immunomodulatory mechanism by upregulating the expression of PD-L1, thus benefiting their survival[67]. OC is usuallly regarded as a "cold tumor", for the reduced infiltration by immune cells, especially CD8+ T cells[68]. Clinical trial results show the low efficacy of anti-PD1 /PD-L1 monotherapy[69]. Therefore, EOC has been establish to be immunogenic, but no immunotherapy has been approved to date. To improve the anti-PD1 /PD-L1 response rate, multiple treatment strategies are currently being investigated. Notably, it has indicated that statins lead to better clinical outcomes in malignant pleural mesothelioma (MPM) and advanced non-small cell lung cancer (NSCLC) patients treated with nivolumab, a PD1-targeting antibody, suggesting that statins with immune checkpoint inhibitors are promising for combination cancer therapy.[11,70][] Otherwise, phosphorylated and activatedβ-catenin-S552 through AKT can supress statin-mediated PD-L1 in lung cancer and melanoma cells[72]. Statins combinating with anti-PD-1 antibody could strengthen the efficacy of immunotherapy for head and neck squamous cell carcinoma (HNSCC) and the effect of cisplatin to struggle with it by inducing calreticulin exposure and ER stress in a cancer-specific manner and promote HNSCC cell death[73]. And statins are also confirmed to activate tumor-specific CD8+ T cells and antigen-presenting cells to increase their numbers in the tumor tissues[74]. Meanwhile, as the MVAP inhibitors, statins are robust for synergizing with anti-PD-1 antibodies in multiple mouse cancer models[11]. It indicates that statins are likely to have a synergistic effect with anti-PD1/PD-L1, this new combination therapy of ovarian cancer can be validated in basic experiments before further designing reasonable clinical trials.

3.4.2 Tumor vaccines

Tumor vaccines, as a form of active immunotherapy, work by providing tumor-associated antigens and activation signals to stimulate endogenous tumor-specific T cells[75]. If a vaccine can turn ovarian cancer into an immunogenic hot tumor, that is generating a lot of tumor-specific immune cells, then checkpoint inhibitors may produce a better response rate in combination therapy[76]. There is a challenge for cancer vaccines, to identify the appropriate immune adjuvant that has an ability of non-antigenic molecules[77] to induce robust immune responses for the efficacy of vaccines for cancer[78].

Statins should be viewed as a rational vaccine adjuvant. Xia Y et al. report that lipophilic statin inhibits the geranylgeranylation of small GTPases, such as Rab5 in antigen-presenting cells (APC), inducing both Th1 and cytolytic T cell responses, which of effect are scarce in clinical adjuvants. It also can delay endosomal antigen entry into degradative lysosomes, that is manipulation of endocytic maturation without overt inflammatory signals, thus enhancing antigen presentation[11]. Furthermore, statins have been established to make myeloid cells sensitive to external stimuli like lipopolysaccharide (LPS) and to produce cytokines, and it with IL-2 co-stimulation also activate human NK cells[78]. A study in clinic is reported that simvastatin treatment induces autoantibodies against oxLDL increasing, with an expansion of CD8+ T cells found[79]. This means that statins may be used as an adjuvant in tumor vaccines to melt the "coldness" of ovarian cancer by increasing infiltration by CD8+ T cells, providing a new view of combination therapy.

Outlook

At present, a mass of clinical studies and experiments have confirmed the anti-cancer effect of statins in OC. According to the results of many mechanism studies, it can be inferred that statins still have great potential in the field of anti-OC, but due to the limitations of indications of statins usage and routine treatment regimen in clinic for clinical trial design, prospective studies are still few. In this review, we found that there are relatively many studies on the combination of statins with paclitaxel and platinum drugs, while studies on the combination of statins with such promising drugs like bevacizumab, PARP is, anti-PD/PD-1 and tumor vaccines in the treatment of ovarian cancer are scarce. In Figures 1, we summarize the systematic connection of mechanisms about statins associating with treatment of EOC. Meanwhile, it is also critical to study how to increase the concentration of statins in the ovaries, rather than the plasma concentration, for practical application and efficacy. With researches deepened on statins in the fields of immunotherapy and other fields, statins have shown a surprising side, which suggests the necessity of conducting experimental studies on the combination of statins with the medicines above to provide evidence and confidence for clinical trials, so as to look forward to entering the clinical trial stage as soon as possible.

Conflicts of interest

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References

1. Torre LA, Trabert B, DeSantis CE, Miller KD, Samimi G, Runowicz CD, Gaudet MM, Jemal A, Siegel RL. Ovarian cancer statistics, 2018. CA Cancer J Clin. 2018 Jul;68(4):284-296.
2. Coburn SB, Bray F, Sherman ME, Trabert B. International patterns and trends in ovarian cancer incidence, overall and by histologic subtype. Int J Cancer. 2017 Jun 1;140(11):2451-2460.
3. Zhu JW, Charkhchi P, Akbari MR. Potential clinical utility of liquid biopsies in ovarian cancer. Mol Cancer. 2022 May 11;21(1):114.
4. Colombo N, Sessa C, du Bois A, Ledermann J, McCluggage WG, McNeish I, Morice P, Pignata S, Ray-Coquard I, Vergote I, Baert T, Belaroussi I, Dashora A, Olbrecht S, Planchamp F, Querleu D; ESMO-ESGO Ovarian Cancer Consensus Conference Working Group. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease+. Ann Oncol. 2019 May 1;30(5):672-705.
5. Oza AM, Cook AD, Pfisterer J, Embleton A, Ledermann JA, Pujade-Lauraine E, Kristensen G, Carey MS, Beale P, Cervantes A, Park-Simon TW, Rustin G, Joly F, Mirza MR, Plante M, Quinn M, Poveda A, Jayson GC, Stark D, Swart AM, Farrelly L, Kaplan R, Parmar MK, Perren TJ; ICON7 trial investigators. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. Lancet Oncol. 2015 Aug;16(8):928-36.
6. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature. 2011 Jun 29;474(7353):609-15. doi: 10.1038/nature10166. Erratum in: Nature. 2012 Oct

11;490(7419):298.
7. Richardson DL, Eskander RN, O'Malley DM. Advances in Ovarian Cancer Care and Unmet Treatment Needs for Patients With Platinum Resistance: A Narrative Review. JAMA Oncol. 2023 Jun 1;9(6):851-859.
8. VBL Therapeutics. VBL announces top-line data from phase 3 OVAL trial of Ofra-Vec in patients with platinum-resistant ovarian cancer. Accessed September 15, 2023.
9. Gaillard S, Oaknin A, Ray-Coquard I, et al. Lurbinectedin versus pegylated liposomal doxorubicin or topotecan in patients with platinum-resistant ovarian cancer: a multicenter, randomized, controlled, open-label phase 3 study (CORAIL). Gynecol Oncol.2021;163(2):237-245.
10. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG; PROSPER study group. PROspective Study of Pravastatin in the Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet. 2002 Nov 23;360(9346):1623-30.
11. Xia Y, Xie Y, Yu Z, Xiao H, Jiang G, Zhou X, Yang Y, Li X, Zhao M, Li L, Zheng M, Han S, Zong Z, Meng X, Deng H, Ye H, Fa Y, Wu H, Oldfield E, Hu X, Liu W, Shi Y, Zhang Y. The Mevalonate Pathway Is a Druggable Target for Vaccine Adjuvant Discovery. Cell. 2018 Nov 1;175(4):1059-1073.e21.
12. Wang Q, Zhi Z, Han H, Zhao Q, Wang X, Cao S, Zhao J. Statin use improves the prognosis of ovarian cancer: An updated and comprehensive meta-analysis. Oncol Lett. 2022 Dec 23;25(2):65.
13. Kobayashi Y, Takeda T, Kunitomi H, Chiwaki F, Komatsu M, Nagai S, Nogami Y, Tsuji K, Masuda K, Ogiwara H, Sasaki H, Banno K, Aoki D. Response Predictive Markers and Synergistic Agents for Drug Repositioning of Statins in Ovarian Cancer. Pharmaceuticals (Basel). 2022 Jan 21;15(2):124.
14. Nieman, K. M. et al. Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth. Nat. Med.2011;17, 1498–1503.
15. Mukherjee A, Bezwada D, Greco F, Zandbergen M, Shen T, Chiang CY, Tasdemir M, Fahrmann J, Grapov D, La Frano MR, Vu HS, Faubert B, Newman JW, McDonnell LA, Nezi L, Fiehn O, DeBerardinis RJ, Lengyel E. Adipocytes reprogram cancer cell metabolism by diverting glucose towards glycerol-3-phosphate thereby promoting metastasis. Nat Metab. 2023 Sep;5(9):1563-1577.
16. Zhang Y, Wang Y, Zhao G, Orsulic S, Matei D. Metabolic dependencies and targets in ovarian cancer. Pharmacol Ther. 2023 May;245:108413.
17. de Wolf E, Abdullah MI, Jones SM, Menezes K, Moss DM, Drijfhout FP, Hart SR, Hoskins C, Stronach EA, Richardson A. Dietary geranylgeraniol can limit the activity of pitavastatin as a potential treatment for drug-resistant ovarian cancer. Sci Rep. 2017 Jul 14;7(1):5410.
18. Huang X, Wei X, Qiao S, Zhang X, Li R, Hu S, Mao H, Liu P. Low Density Lipoprotein Receptor (LDLR) and 3-Hydroxy-3-Methylglutaryl Coenzyme a Reductase (HMGCR) Expression are Associated with Platinum-Resistance and Prognosis in Ovarian Carcinoma Patients. Cancer Manag Res. 2021 Dec 6;13:9015-9024.
19. Criscuolo D, Avolio R, Calice G, Laezza C, Paladino S, Navarra G, Maddalena F, Crispo F, Pagano C, Bifulco M, Landriscina M, Matassa DS, Esposito F. Cholesterol Homeostasis Modulates Platinum Sensitivity in Human Ovarian Cancer. Cells. 2020 Mar 30;9(4):828.
20. Georgakopoulos-Soares I, Chartoumpekis DV, Kyriazopoulou V, Zaravinos A. EMT Factors and Metabolic Pathways in Cancer. Front Oncol. 2020 Apr 7;10:499.
21. Huang P, Nedelcu D, Watanabe M, Jao C, Kim Y, Liu J, Salic A. Cellular Cholesterol Directly Activates Smoothened in Hedgehog Signaling. Cell. 2016 Aug 25;166(5):1176-1187.
22. Gordon RE, Zhang L, Peri S, Kuo YM, Du F, Egleston BL, Ng JMY, Andrews AJ, Astsaturov I, Curran T, et al. Statins synergize with hedgehog pathway inhibitors for treatment of medulloblastoma. Clin Cancer Res. 2018;24(6):1375–88.
23. Huang P, Nedelcu D, Watanabe M, Jao C, Kim Y, Liu J, Salic A. Cellular Cholesterol Directly Activates Smoothened in Hedgehog Signaling. Cell. 2016 Aug 25;166(5):1176-1187.
24. Freed-Pastor W, Prives C. Targeting mutant p53 through the mevalonate pathway. Nat Cell Biol. 2016 Oct 27;18(11):1122-1124.

25. Wang M, Casey PJ. Protein prenylation: unique fats make their mark on biology. Nat Rev Mol Cell Biol. 2016 Feb;17(2):110-22.
26. Cordle A, Koenigsknecht-Talboo J, Wilkinson B, Limpert A, Landreth G. Mechanisms of statin-mediated inhibition of small G-protein function. J Biol Chem. 2005 Oct 7;280(40):34202-9.
27. Kato S, Liberona MF, Cerda-Infante J, Sánchez M, Henríquez J, Bizama C, Bravo ML, Gonzalez P, Gejman R, Brañes J, García K, Ibañez C, Owen GI, Roa JC, Montecinos V, Cuello MA. Simvastatin interferes with cancer 'stem-cell' plasticity reducing metastasis in ovarian cancer. Endocr Relat Cancer. 2018 Oct;25(10):821-836.
28. Yarmolinsky J, Bull CJ, Vincent EE, Robinson J, Walther A, Smith GD, Lewis SJ, Relton CL, Martin RM. Association Between Genetically Proxied Inhibition of HMG-CoA Reductase and Epithelial Ovarian Cancer. JAMA. 2020 Feb 18;323(7):646-655.
29. Shoshan-Barmatz V, De Pinto V, Zweckstetter M, Raviv Z, Keinan N, Arbel N. VDAC, a multi-functional mitochondrial protein regulating cell life and death. Mol Aspects Med. 2010 Jun;31(3):227-85.
30. Campbell AM, Chan SH. Mitochondrial membrane cholesterol, the voltage dependent anion channel (VDAC), and the Warburg effect. J Bioenerg Biomembr. 2008 Jun;40(3):193-7.
31. Magrì A, Reina S, De Pinto V. VDAC1 as Pharmacological Target in Cancer and Neurodegeneration: Focus on Its Role in Apoptosis. Front Chem. 2018 Apr 6;6:108.
32. Kobayashi Y, Takeda T, Kunitomi H, Chiwaki F, Komatsu M, Nagai S, Nogami Y, Tsuji K, Masuda K, Ogiwara H, Sasaki H, Banno K, Aoki D. Response Predictive Markers and Synergistic Agents for Drug Repositioning of Statins in Ovarian Cancer. Pharmaceuticals (Basel). 2022 Jan 21;15(2):124.
33. Lipper CH, Stofleth JT, Bai F, Sohn YS, Roy S, Mittler R, Nechushtai R, Onuchic JN, Jennings PA. Redox-dependent gating of VDAC by mitoNEET. Proc Natl Acad Sci U S A. 2019 Oct 1;116(40):19924-19929.
34. Carnero A, Blanco-Aparicio C, Renner O, Link W, Leal JF. The PTEN/PI3K/AKT signalling pathway in cancer, therapeutic implications. Curr Cancer Drug Targets. 2008 May;8(3):187-98.
35. Gasparri ML, Bardhi E, Ruscito I, Papadia A, Farooqi AA, Marchetti C, Bogani G, Ceccacci I, Mueller MD, Benedetti Panici P. PI3K/AKT/mTOR Pathway in Ovarian Cancer Treatment: Are We on the Right Track? Geburtshilfe Frauenheilkd. 2017 Oct;77(10):1095-1103.
36. Huang J, Zhang L, Greshock J, Colligon TA, Wang Y, Ward R, Katsaros D, Lassus H, Butzow R, Godwin AK, Testa JR, Nathanson KL, Gimotty PA, Coukos G, Weber BL, Degenhardt Y. Frequent genetic abnormalities of the PI3K/AKT pathway in primary ovarian cancer predict patient outcome. Genes Chromosomes Cancer. 2011 Aug;50(8):606-18.
37. Deng CF, Zhu N, Zhao TJ, Li HF, Gu J, Liao DF, Qin L. Involvement of LDL and ox-LDL in Cancer Development and Its Therapeutical Potential. Front Oncol. 2022 Feb 16;12:803473.
38. Miraglia E, Högberg J, Stenius U. Statins exhibit anticancer effects through modifications of the pAkt signaling pathway. Int J Oncol. 2012 Mar;40(3):867-75.
39. Roudier E, Mistafa O, Stenius U. Statins induce mammalian target of rapamycin (mTOR)-mediated inhibition of Akt signaling and sensitize p53-deficient cells to cytostatic drugs. Mol Cancer Ther. 2006 Nov;5(11):2706-15.
40. Stine JE, Guo H, Sheng X, Han X, Schointuch MN, Gilliam TP, Gehrig PA, Zhou C, Bae-Jump VL. The HMG-CoA reductase inhibitor, simvastatin, exhibits anti-metastatic and anti-tumorigenic effects in ovarian cancer. Oncotarget. 2016 Jan 5;7(1):946-60.
41. Zhu L, Chen L. Progress in research on paclitaxel and tumor immunotherapy. Cell Mol Biol Lett. 2019 Jun 13;24:40.
42. Hu D, Yang C, Lok CN, Xing F, Lee PY, Fung YME, Jiang H, Che CM. An Antitumor Bis(N-Heterocyclic Carbene)Platinum(II) Complex That Engages Asparagine Synthetase as an Anticancer Target. Angew Chem Int Ed Engl. 2019 Aug 5;58(32):10914-10918.
43. Robinson E, Nandi M, Wilkinson LL, Arrowsmith DM, Curtis AD, Richardson A. Preclinical evaluation of statins as a treatment for ovarian cancer. Gynecol Oncol. 2013 May;129(2):417-24.
44. Pan Q, Xu J, Ma L. Simvastatin enhances chemotherapy in cervical cancer via inhibition of multiple

prenylation-dependent GTPases-regulated pathways. Fundam Clin Pharmacol. 2020 Feb;34(1):32-40.
45. Gupta VK, Sharma NS, Kesh K, Dauer P, Nomura A, Giri B, Dudeja V, Banerjee S, Bhattacharya S, Saluja A, Banerjee S. Metastasis and chemoresistance in CD133 expressing pancreatic cancer cells are dependent on their lipid raft integrity. Cancer Lett. 2018 Dec 28;439:101-112.
46. Tichomirowa MA, Theodoropoulou M, Daly AF, Yassouridis A, Hansen S, Lu J, Lange M, Goldbrunner RH, Stalla GK, Renner U. Toll-like receptor-4 is expressed in meningiomas and mediates the antiproliferative action of paclitaxel. Int J Cancer. 2008 Oct 15;123(8):1956-63.
47. Holstein SA, Hohl RJ. Synergistic interaction of lovastatin and paclitaxel in human cancer cells. Mol Cancer Ther. 2001 Dec;1(2):141-9.
48. Jin H, He Y, Zhao P, Hu Y, Tao J, Chen J, Huang Y. Targeting lipid metabolism to overcome EMT-associated drug resistance via integrin β3/FAK pathway and tumor-associated macrophage repolarization using legumain-activatable delivery. Theranostics. 2019 Jan 1;9(1):265-278.
49. Lobos N, Lux S, Zepeda RJ, Pelissier T, Marcos JL, Bustos-Quevedo G, Hernández A, Constandil L. Rosuvastatin Synergistically Enhances the Antinociceptive Efficacy of Duloxetine in Paclitaxel-Induced Neuropathic Pain in Mice. Int J Mol Sci. 2023 May 6;24(9):8359.
50. Maheshwari RA, Sailor GU, Patel L, Balaraman R. Amelioration of cisplatin-induced nephrotoxicity by statins. Indian J Pharmacol. 2013 Jul-Aug;45(4):354-8.
51. Garcia J, Hurwitz HI, Sandler AB, Miles D, Coleman RL, Deurloo R, Chinot OL. Bevacizumab (Avastin®) in cancer treatment: A review of 15 years of clinical experience and future outlook. Cancer Treat Rev. 2020 Jun;86:102017.
52. Bamias A, Gibbs E, Khoon Lee C, Davies L, Dimopoulos M, Zagouri F, Veillard AS, Kosse J, Santaballa A, Mirza MR, Tabaro G, Vergote I, Bloemendal H, Lykka M, Floquet A, Gebski V, Pujade-Lauraine E. Bevacizumab with or after chemotherapy for platinum-resistant recurrent ovarian cancer: exploratory analyses of the AURELIA trial. Ann Oncol. 2017 Aug 1;28(8):1842-1848.
53. Weis M, Heeschen C, Glassford AJ, Cooke JP. Statins have biphasic effects on angiogenesis. Circulation. 2002 Feb 12;105(6):739-45.
54. Baines AT, Xu D, Der CJ. Inhibition of Ras for cancer treatment: the search continues. Future Med Chem. 2011 Oct;3(14):1787-808.
55. Hus M, Grzasko N, Szostek M, Pluta A, Helbig G, Woszczyk D, Adamczyk-Cioch M, Jawniak D, Legiec W, Morawska M, Kozinska J, Waciński P, Dmoszynska A. Thalidomide, dexamethasone and lovastatin with autologous stem cell transplantation as a salvage immunomodulatory therapy in patients with relapsed and refractory multiple myeloma. Ann Hematol. 2011 Oct;90(10):1161-6.
56. Lee SJ, Lee I, Lee J, Park C, Kang WK. Statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, potentiate the anti-angiogenic effects of bevacizumab by suppressing angiopoietin2, BiP, and Hsp90α in human colorectal cancer. Br J Cancer. 2014 Jul 29;111(3):497-505.
57. Cordani N, Bianchi T, Ammoni LC, Cortinovis DL, Cazzaniga ME, Lissoni AA, Landoni F, Canova S. An Overview of PARP Resistance in Ovarian Cancer from a Molecular and Clinical Perspective. Int J Mol Sci. 2023 Jul 25;24(15):11890.
58. Wu J, Starr S. Low-fidelity compensatory backup alternative DNA repair pathways may unify current carcinogenesis theories. Future Oncol. 2014 May;10(7):1239-53.
59. Matulonis UA. The rapid evolution of PARP inhibitor therapy for advanced ovarian cancer: Lessons being learned and new questions emerging from phase 3 trial long-term outcome data. Gynecol Oncol. 2022 Dec;167(3):401-403.
60. O'Malley DM, Krivak TC, Kabil N, Munley J, Moore KN. PARP Inhibitors in Ovarian Cancer: A Review. Target Oncol. 2023 Jul;18(4):471-503.
61. Tapodi A, Bognar Z, Szabo C, Gallyas F, Sumegi B, Hocsak E. PARP inhibition induces Akt-mediated cytoprotective effects through the formation of a mitochondria-targeted phospho-ATM-NEMO-Akt-mTOR signalosome. Biochem Pharmacol. 2019 Apr;162:98-108.
62. Szanto A, Hellebrand EE, Bognar Z, Tucsek Z, Szabo A, Gallyas F Jr, Sumegi B, Varbiro G. PARP-1 inhibition-induced activation of PI-3-kinase-Akt pathway promotes resistance to taxol. Biochem Pharmacol. 2009 Apr 15;77(8):1348-57.

63. Gallyas F Jr, Sumegi B, Szabo C. Role of Akt Activation in PARP Inhibitor Resistance in Cancer. Cancers (Basel). 2020 Feb 25;12(3):532.
64. Beckwitt CH, Shiraha K, Wells A. Lipophilic statins limit cancer cell growth and survival, via involvement of Akt signaling. PLoS One. 2018 May 15;13(5):e0197422.
65. Dimmeler S, Aicher A, Vasa M, Mildner-Rihm C, Adler K, Tiemann M, Rütten H, Fichtlscherer S, Martin H, Zeiher AM. HMG-CoA reductase inhibitors (statins) increase endothelial progenitor cells via the PI 3-kinase/Akt pathway. J Clin Invest. 2001 Aug;108(3):391-7.
66. Arasanz H, Gato-Cañas M, Zuazo M, Ibañez-Vea M, Breckpot K, Kochan G, Escors D. PD1 signal transduction pathways in T cells. Oncotarget. 2017 Apr 19;8(31):51936-51945.
67. Kythreotou A, Siddique A, Mauri FA, Bower M, Pinato DJ. PD-L1. J Clin Pathol. 2018 Mar;71(3):189-194.
68. Chen DS, Mellman I. Elements of cancer immunity and the cancer-immune set point. Nature. 2017 Jan 18;541(7637):321-330.
69. Matulonis UA, Shapira-Frommer R, Santin AD, Lisyanskaya AS, Pignata S, Vergote I, Raspagliesi F, Sonke GS, Birrer M, Provencher DM, Sehouli J, Colombo N, González-Martín A, Oaknin A, Ottevanger PB, Rudaitis V, Katchar K, Wu H, Keefe S, Ruman J, Ledermann JA. Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: results from the phase II KEYNOTE-100 study. Ann Oncol. 2019 Jul 1;30(7):1080-1087.
70. Cantini L, Pecci F, Hurkmans DP, Belderbos RA, Lanese A, Copparoni C, Aerts S, Cornelissen R, Dumoulin DW, Fiordoliva I, Rinaldi S, Aerts JGJV, Berardi R. High-intensity statins are associated with improved clinical activity of PD-1 inhibitors in malignant pleural mesothelioma and advanced non-small cell lung cancer patients. Eur J Cancer. 2021 Feb;144:41-48.
71. Omori M, Okuma Y, Hakozaki T, Hosomi Y. Statins improve survival in patients previously treated with nivolumab for advanced non-small cell lung cancer: An observational study. Mol Clin Oncol. 2019 Jan;10(1):137-143.
72. Lim WJ, Lee M, Oh Y, Fang XQ, Lee S, Lim CH, Park J, Lim JH. Statins Decrease Programmed Death-Ligand 1 (PD-L1) by Inhibiting AKT and β-Catenin Signaling. Cells. 2021 Sep 20;10(9):2488.
73. Kansal V, Burnham AJ, Kinney BLC, Saba NF, Paulos C, Lesinski GB, Buchwald ZS, Schmitt NC. Statin drugs enhance responses to immune checkpoint blockade in head and neck cancer models. J Immunother Cancer. 2023 Jan;11(1):e005940.
74. Kwon M, Nam GH, Jung H, Kim SA, Kim S, Choi Y, Lee YS, Cho HJ, Kim IS. Statin in combination with cisplatin makes favorable tumor-immune microenvironment for immunotherapy of head and neck squamous cell carcinoma. Cancer Lett. 2021 Dec 1;522:198-210.
75. Voelker R. Pursuing an Effective Ovarian Cancer Vaccine. JAMA. 2018 Sep 4;320(9):858-860.
76. Di Pasquale A, Preiss S, Tavares Da Silva F, Garçon N. Vaccine Adjuvants: from 1920 to 2015 and Beyond. Vaccines (Basel). 2015 Apr 16;3(2):320-43.
77. Akula MK, Shi M, Jiang Z, Foster CE, Miao D, Li AS, Zhang X, Gavin RM, Forde SD, Germain G, Carpenter S, Rosadini CV, Gritsman K, Chae JJ, Hampton R, Silverman N, Gravallese EM, Kagan JC, Fitzgerald KA, Kastner DL, Golenbock DT, Bergo MO, Wang D. Control of the innate immune response by the mevalonate pathway. Nat Immunol. 2016 Aug;17(8):922-9.
78. Gruenbacher G, Gander H, Nussbaumer O, Nussbaumer W, Rahm A, Thurnher M. IL-2 costimulation enables statin-mediated activation of human NK cells, preferentially through a mechanism involving CD56+ dendritic cells. Cancer Res. 2010 Dec 1;70(23):9611-20.
79. Gonçalves I, Cherfan P, Söderberg I, Nordin Fredrikson G, Jonasson L. Effects of simvastatin on circulating autoantibodies to oxidized LDL antigens: relation with immune stimulation markers. Autoimmunity. 2009 Mar;42(3):203-8.

Figure

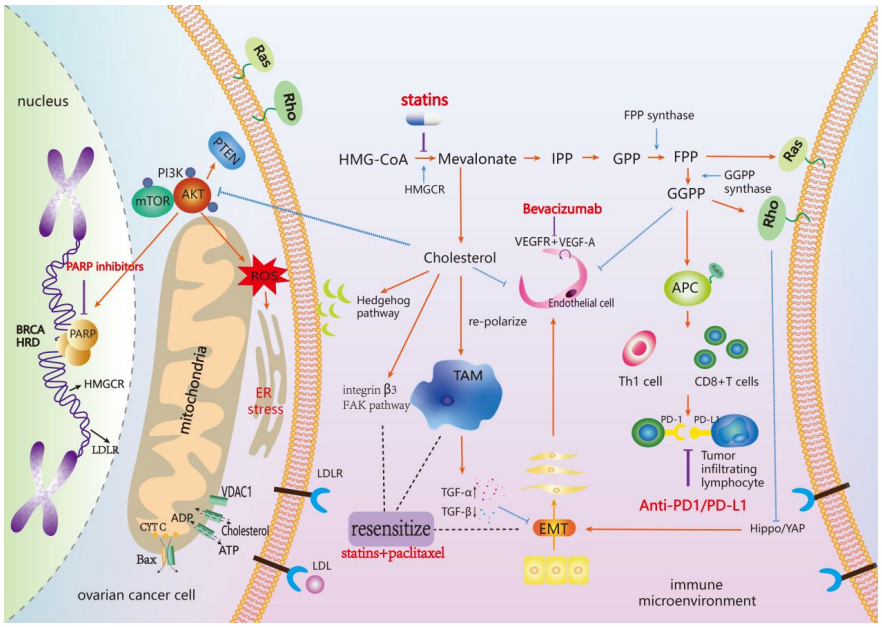

Fig. 1. Systematic connection of mechanisms about statins associating with treatment of EOC. - denotes induction; [?]denotes inhibition.