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The Role of Inflammasomes in Ovarian Cancer

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Abstract: Ovarian cancer is a leading cause of gynecological cancer-related deaths in women worldwide, mainly because of its late diagnosis. In many cases, at the time of diagnosis, the cancer cells are chemoresistant and invasive. Early detection of the disease is crucial for a clinically satisfactory outcome, treatment planning, and a better prognosis. The development of new strategies for early detection may contribute to improving overall survival in patients. Inflammation is an established factor in carcinogenesis, and protein complexes named inflammasomes, along with their components and subproducts, such as interleukins and other molecules, have been explored as promising potential targets for the detection and management of ovarian cancer. This chapter provides an overview of the role of inflammasomes in ovarian cancer.

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INTRODUCTION

Ovarian cancer is the seventh most common malignancy in women and is a major cause of gynecological cancer-related deaths (1). Ovarian cancer incidence increases with age and is usually diagnosed in the sixth decade of life (1–3). Due to the lack of specific signs and symptoms, ovarian cancer is usually diagnosed late, and peritoneal and distant metastases are common at diagnosis (2, 4, 5). Epithelial ovarian cancer (EOC) accounts for approximately 90% of all ovarian malignancies (6–8). EOC is traditionally classified into the following four main subtypes based on the differentiation of the epithelial components: serous, clear cell, mucinous, and endometrioid. Serous tumors represent over 70% of all diagnosed EOC cases, while endometrioid, mucinous, and clear cell tumors represent about 10% or less each (9, 10). EOCs are heterogeneous neoplasms, which were initially considered to be derived from the ovarian epithelium. However, it has been found that there are numerous similarities between ovarian cancer cells and epithelial cells from extra-ovarian sites. EOCs are subclassified into type I and type II tumors (11). In short, type I tumors are commonly low-grade, with a high frequency of mutations in the Ras signaling pathway. They generally lack mutations in both *p53* and *BRCA* and show a relatively normal karyotype. In addition, they are usually poorly responsive to platinum-based therapy (cisplatin). Type II EOCs are typically high-grade, invasive tumors. They present wild-type *Ras*, *BRCA* dysfunction, and *p53* mutations. Type II tumors also exhibit changes in the DNA copy number and are responsive to platinum derivatives (12). Regardless of its heterogeneity, the standard treatment for ovarian cancer includes cytoreductive surgery followed by platinum (cisplatin and carboplatin) and taxane (paclitaxel and docetaxel)-based chemotherapy (13). Despite the treatment's initial success, over 70% of patients show recurrence and chemoresistance (3, 14) resulting in aggressive and potentially lethal disease (3, 14, 15).

There is an urgent need for novel markers and therapeutic strategies for ovarian cancer (10). In this context, inflammation and inflammasomes have attracted the attention of researchers in almost all diseases, including ovarian cancer. In a nutshell, inflammasomes are cytosolic multiprotein oligomers of the innate immune system that induce inflammation in response to infection or host-cell derived molecules, for example, molecules from cancer cells (16, 17) They mainly regulate the activation of caspase-1 (interleukin-1 converting enzyme). Once activated and assembled, inflammasomes promote proteolytic cleavage, maturation, and secretion of various pro-inflammatory cytokines such as interleukin 1β (IL-1β) and interleukin 18 (IL-18), and the cleavage of gasdermins (GSDM), a protein family that executes cell death and inflammation (18). Proteolytic cleavage releases the N-terminal fragments of these molecules. The released N-terminals insert into the cell membrane, forming large oligomeric pores, causing an imbalance of cellular homeostasis, and the induction of an

inflammatory form of cell death called pyroptosis (18). This chapter provides a snapshot of the current understanding of the role of inflammasomes in ovarian cancer.

INFLAMMATION AND INFLAMMASOMES IN OVARIAN CANCER

Inflammation is one of the events that promote initiation, development, progression, and chemoresistance in ovarian cancer (19, 20). The inflammatory pathways involved in ovulation may lead to ovarian cancer (21). Nowak and colleagues (22) analyzed the serological and the tumoral microenvironment of ovarian cancer patients along with samples of benign ovarian tumor patients. They observed that, in advanced stages of the disease, interleukins 6, 8 and 10 were significantly overexpressed compared to early-stage disease. Interleukins are pro-inflammatory cytokines released during pyroptosis (23). First, PRR (pattern recognition receptor) is stimulated in response to a stimulus (infection or host-derived molecule), which then activates the transcription factor nuclear factor-κB (NF-κB). This results in pro-interleukins and inflammasome expression (24).

Inflammasomes are protein complexes formed by the nod-like receptor family (NLR) and comprise examples such as NLRP1, NLRP3 and NLRC4. Moreover, these complexes are formed by a pyrin domain (PYD) that binds to the NLR protein. Additionally, there is a caspase activation and recruitment domain known as CARD that is responsible for the binding of the complex to a caspase molecule. Finally, CARD and caspase, together, form the adapter protein (ASC) (17, 25). Inflammasome repositioning to the mitochondria, reactive oxygen species (ROS), mitochondrial DNA, cardiolipin, potassium efflux, and lysosome cathepsin are examples of signals for inflammasome assembly (26). After assembly, the caspase molecule binds to a specific site where its cleavage and consequent activation occur. Caspase cleaves pro-interleukin and GSDM, releasing the N-terminal portion, which binds to the cell membrane, forming pores that characterize pyroptosis (27, 28). This mechanism is crucial for cancer cell survival (29). IL-1β and IL-18 stand out for their participation in malignant progression and the occurrence of metastasis in various tumor types, such as pancreatic, breast, ovarian, and melanoma (30, 31).

Interleukins and cathepsins

Interleukin 18 (IL-18) is a cytokine responsible for the maturation of natural killer (NK) and T cells (32). This cytokine plays a fundamental role in antitumor immunity (33), which requires its maturation through proteolytic cleavage, mediated by caspase 1 (34). It is known that healthy ovarian epithelial cells secrete the active form of IL-18. However, ovarian cancer cell lines secrete the inactive form, either by inactivating caspase 1 or by mutations related to its proteolytic function (35). Orengo *et al.* (36) found high concentrations of pro-IL-18 in the ascites and serum of ovarian cancer patients. Furthermore, IL-18BP, an endogenous inhibitor of IL-18, has been reported to be overexpressed in patients with the disease (37). Uppendahl *et al.* (38) highlighted the importance of IL-18 in

short-term cytokine-induced memory-like NK cell activation (CIML NK) in ovarian cancer cellular models. CIML NK was inefficient in inducing cell death within one day, but it was successful in eliminating cancer cells after seven days of exposure to cytokines. Accordingly, a phase I clinical trial has demonstrated the importance of IL-18 as a possible alternative therapy, since it confirmed that combinations of doxorubicin and IL-18 were tolerable without attenuating the effects of IL-18 (39).

Inflammation plays a key role in the development of ovarian cancer (40). *BRCA1* gene is involved in ovarian cancer susceptibility, it can incite inflammation, and mutant *BRCA1* expression in normal ovarian cell line significantly increases interleukin 1β (IL-1β) protein expression (30, 41). It is noteworthy that IL-1β is also responsible for the inflammasome assembly initiation since it stimulates its expression through the NF-κB pathway. Stem cells have anti-inflammatory activity due to their ability to promote tissue repair by paracrine action (42, 43). Kalamegam *et al.* (44) had mixed human ovarian cancer cell lines with human Wharton's jelly stem cells lysate or conditioned medium from these stem cells and showed that both inhibited the proliferation of ovarian cancer cells through the downregulation of *IL-1*β expression while increasing IL-1β receptor antagonist (*IL-1RA*) synthesis. In contrast, Li *et al.* demonstrated that the increased expression of inflammasome elements, such as pro-caspase 1, caspase 1, pro-IL-1β, IL-1β, pro-IL-18, and IL-18, significantly attenuated proliferation, migration, and invasion of OVCA A2780 cells (45). Luborsky *et al.* (46) observed that, when compared to normal tissues, ovarian tumors have a high expression of IL-1β, IL-18, and caspase 1.

Interleukin 8 (IL-8) can stimulate metastasis and is associated with poor prognosis in ovarian cancer (47, 48). Interleukin 10 (IL-10) is another inflammatory cytokine that is overexpressed in ovarian cancer and prevents excessive inflammation in normal tissues (49). However, IL-10 can cause immunosuppression by inhibiting the expression of major histocompatibility complex (MHC) molecules, which leads to antigen presenting cells malfunctioning and help cancer cell survival. Furthermore, IL-10 can facilitate metastasis and stimulate the expression of anti-apoptotic and pro-inflammatory genes (50, 51).

Cathepsins D, K and L are overexpressed in malignant ovarian cancer indicating their relationship with invasiveness, proliferation, and migration (52–56); the inhibition of cathepsin L reversed paclitaxel chemoresistance in SKOV3 ovarian cancer cells (57).

NLR family protein 3 containing pyrin domain (NLRP3)

There are many types of inflammasomes that vary according to their function. The nucleotide-binding domain leucine-rich repeat-containing (NLRs) inflammasomes were first described in 2002 (58). Among these, it is worthwhile to highlight NLRP3, NLRP2, NLRP1, and NLRC4 (59). The NLR family protein 3 containing pyrin domain (NLRP3), shown in Figure 1, is the best characterized inflammasome (60, 61). Higher NLRP3 expression was identified in ovarian cancer tissues from 46 patients and in ovarian tumor cell lines when compared to normal peritumoral tissues from these patients and normal ovarian cells (62). A comparison of NLRP3 expression in pan-cancerous and normal tissues using data from The Cancer Genome Atlas Program showed higher NLRP3 expression in ovarian cancer and indicated worse overall survival (63). Genes such as *NLRP3, IL-1B, and IL-18* were

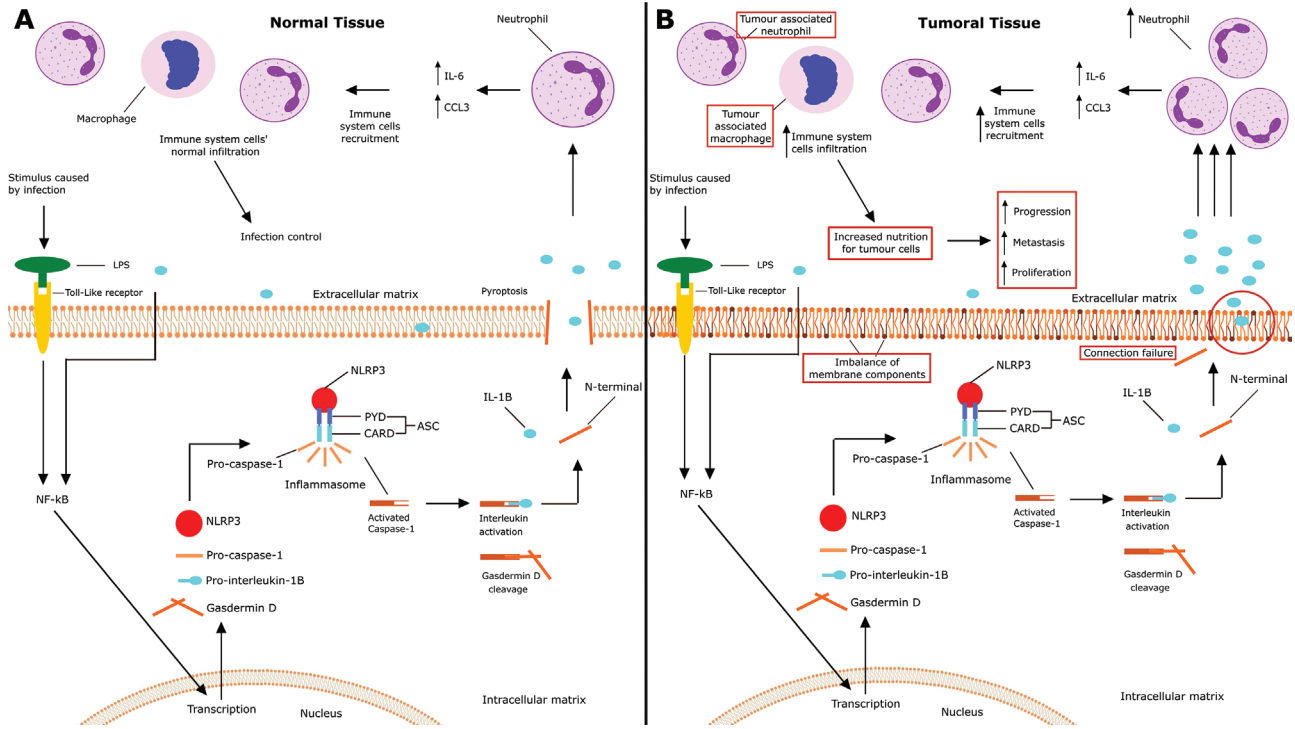

Figure 1 Comparison of NLRP3 inflammasome activation in normal tissue and tumor tissue. A, Demonstration of the pathway in a normal cell. Stimuli caused by infection and IL-1β induce the expression of NLRP3 inflammasome components, gasdermin D, pro-IL-1β, and pro-caspase 1. The NLRP3 inflammasome oligomerization enables the activation of the caspase 1 enzyme responsible for cleaving the pro-IL-1β. The cell secret IL-1β, inducing immune system cell recruitment and infiltration, such as neutrophils that secrete IL-6 and C-C Motif Chemokine Ligand 3 (CCL3). Caspase 1 cleaves gasdermin D and the N-terminal portion is responsible for the formation of pores in the membrane and induction of pyroptosis. This may not occur in the tumor cell because of alterations in tumor cell membrane that make it difficult for the N-terminal connection to membrane lipids. **B,** Inflammasome activation in a tumor cell causes imbalance of components in the membrane and therefore pyroptosis induction fails. In this case, the recruitment and infiltration of immune system cells occur on a larger scale, increasing nutrition for tumor cells and favoring tumor progression, proliferation, and metastasis.

identified in ovarian carcinoma samples using public microarray data. The association between genes and patients' survival showed that high expression of AIM2 and NLRP3 were significantly correlated with low survival disease progression-free (64). However, this association is still unclear, as Luborsky *et al.* (46) observed that the NLRP3 inflammasome was not significantly overexpressed in ovarian cancer, while other components of this inflammasome's pathway were overexpressed.

Treatment with carboplatin increased NLRP3 inflammasome activation in macrophages by caspase 3 and GSDM E (65). In the same study, NLRP3 was found in samples from carboplatin-treated ovarian cancer patients, demonstrating the importance of this inflammasome in ovarian carcinogenesis and possibly chemoresistance (65). Thus, it can be inferred that the NLRP3 inflammasome overactivation, rather than its overexpression, would be associated with carcinogenesis. An inverse relationship has been reported between miR-22 (microRNA 22), an endogenous inhibitor of NLRP3, and the NLRP3 inflammasome. It was also observed that miR-22 was downregulated in SKOV3 ovarian cancer cells. The same group reported that *NLRP3* inhibition by miR-22 and the inhibition of PI3K/AKT pathway decreased cell proliferation and mesenchymal-epithelial transition (66).

Absent in melanoma 2 (AIM2)

Absent in melanoma 2 (AIM2) inflammasome assembly occurs in the presence of cytosolic DNA (67). Lu *et al.* (68) have shown that it can auto-oligomerize. It should be noted that ASC protein phosphorylation at threonine Y60 and Y137 is important for AIM2 assembly (69). AIM2 drives pro-IL-18 and pro-IL-1β proteolytic cleavage without relying on NLRP3 and/or TLR (Toll-like receptor) stimuli (17, 67). AIM2 is a good predictor of efficacy of antiangiogenic therapies, as observed in patients treated with bevacizumab (70). AIM2 is involved in the malignant transformation of endometriosis to clear cell and endometrioid ovarian carcinoma (64, 71). This inflammasome has a high prognostic significance in several histological subtypes of ovarian cancer because overexpression of AIM2 has been reported to worsen progression-free survival of patients (70). These studies point to the significance of AIM2 as a biomarker for ovarian cancer and requires further exploration.

GSDM

GSDM is an essential component for pyroptosis to occur because after its cleavage at the N-terminal domain, pores start to form in the cell membrane. GSDM A is commonly expressed in epithelial tissues, and it is upregulated in ovarian cancer (72). GSDM C and D are usually expressed in organs of the digestive system, skin, vagina, and bladder. They are also expressed in some cancers (73). GSDM C and D are upregulated in serous ovarian cancer and thought to be indicators of poor prognosis (74–76). GSDM D is expressed in gastrointestinal tissues (75), but it has also been reported to be overexpressed in serous ovarian cancer (74). Another crucial discovery was that GSDM D may be cleaved by serine proteases in neutrophils (77). This pathway

is necessary for the formation of neuroendocrine tumors (NETs) that facilitate the development of metastasis (78). To be activated, GSDM D mainly needs caspase 1, but may also be cleaved by caspase 11 (77, 79). These caspases are found at low levels in high-grade serous ovarian cancer (74). GDSM E is known to be a tumor suppressor molecule because of its antitumoral properties (80). This characteristic may be attributed to its ability to decrease the appearance of tumor-associated immune cells, such as tumor-associated macrophages (81).

Although there is an expression of these components, pyroptosis might not occur since the formation of pores in the cell membrane does not necessarily lead to cell death. The mechanisms behind cell membrane repair, or inefficient pyroptosis, are still unclear (79). It has been shown that the imbalance of phosphatidylinositide and cholesterol in the cell membrane makes the insertion of the GSDM N-terminal domain in the cell membrane difficult, thus hindering the formation of pores. Given that this imbalance is common in cancers (82), including ovarian cancer, the hypothesis is that there is a greater difficulty in pore formation, because of the higher levels of phosphatidylinositide and cholesterol in cell membrane, which makes the cancer cells viable (83). Cholesterol metabolism is altered in ovarian cancer (84). Thus, pyroptosis, impaired by metabolic alterations, plays a crucial role in the overall survival of ovarian cancer cells.

CONCLUSION

Currently, there is an increasing interest in understanding the relationship between ovarian cancer and inflammasomes. Available evidence is contradictory with some inflammasomes such as NLRP3, IL-1β, IL-18, IL-8, IL-10, AIM2, and cathepsin being associated with the development and progression of ovarian cancer, while the overexpression of others such as pro-caspase-1, caspase-1, pro-IL-1β, IL-1β, pro-IL-18, and IL-18 attenuating proliferation, migration, and invasion of ovarian cancer cells. The mechanisms by which these molecules aggravate or attenuate the development of ovarian cancer are not clear. Despite the existing gaps, the inflammatory pathway demonstrates its impacts, and hence the manipulation of these pathways emerges as potential therapeutic targets. To this end, blocking components of the NLRP3 pathway, or the use of IL-1 receptor antagonists, has produced promising experimental results. Further studies will enable deciphering the role of inflammasomes and their therapeutic potential in ovarian cancer.

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REFERENCES

1. American Cancer Society. Key Statistics for Ovarian Cancer, 2022. Available in: https://www.cancer.org/cancer/ovarian-cancer/about/key-statistics.html. Access on January 14th, 2022.
2. Morgan Jr RJ, Alvarez RD, Armstrong DK, Boston B, Burger RA. Chen L-M, et al. Epithelial ovarian cancer. J Natl Compr Canc Netw. 2011;9(1):82–113. https://doi.org/10.6004/jnccn.2011.0008
3. Paes MF, Daltoé RD, Madeira KP, Rezende LCD, Sirtoli GM, Herlinger AL, et al. A retrospective analysis of clinicopathological and prognostic characteristics of ovarian tumors in the State of Espírito Santo, Brazil. J Ovarian Res. 2011;4:14. Published 2011 Aug 9. https://doi.org/10.1186/1757-2215-4-14
4. Rossing MA, Wicklund KG, Cushing-Haugen KL, Weiss NS. Predictive value of symptoms for early detection of ovarian cancer. J Natl Cancer Inst. 2010;102(4):222–229. https://doi.org/10.1093/jnci/djp500
5. Ghoneuma A, Almousaa S, Warrena B, Abdulfattahab AY, Shuac J, Abouelfadlad H, et al. Exploring the clinical value of tumor microenvironment in platinum-resistant ovarian cancer. Semin Cancer Biol. 2021;77:83–98. https://doi.org/10.1016/j.semcancer.2020.12.024
6. Romero I, Bast RC Jr. Minireview: human ovarian cancer: biology, current management, and paths to personalizing therapy. Endocrinology. 2012;153(4):1593–1602. https://doi.org/10.1210/en.2011-2123
7. Bowtell DD, Böhm S, Ahmed AA, Aspuria P-J, Bast Jr RC, Beral V, et al. Rethinking ovarian cancer II: reducing mortality from high-grade serous ovarian cancer. Nat Rev Cancer. 2015;15(11):668–679. https://doi.org/10.1038/nrc4019
8. Lisio MA, Fu L, Goyeneche A, Gao ZH, Telleria C. High-Grade Serous Ovarian Cancer: Basic Sciences, Clinical and Therapeutic Standpoints. Int J Mol Sci. 2019;20(4):952. Published 2019 Feb 22. https://doi.org/10.3390/ijms20040952
9. Jelovac D, Armstrong DK. Recent progress in the diagnosis and treatment of ovarian cancer. CA Cancer J Clin. 2011;61(3):183–203. https://doi.org/10.3322/caac.20113
10. Berek JS, Crum C, Friedlander M. Cancer of the ovary, fallopian tube, and peritoneum. Int J Gynaecol Obstet. 2012;119 Suppl 2:S118-S129. https://doi.org/10.1016/S0020-7292(12)60025-3
11. Vang R, Shih IeM, Kurman RJ. Ovarian low-grade and high-grade serous carcinoma: pathogenesis, clinicopathologic and molecular biologic features, and diagnostic problems. Adv Anat Pathol. 2009;16(5):267–282. https://doi.org/10.1097/PAP.0b013e3181b4fffa
12. Bowtell DD. The genesis and evolution of high-grade serous ovarian cancer. Nat Rev Cancer. 2010;10(11):803–808. https://doi.org/10.1038/nrc2946
13. Cristea M, Han E, Salmon L, Morgan RJ. Practical considerations in ovarian cancer chemotherapy. Ther Adv Med Oncol. 2010;2(3):175–187. https://doi.org/10.1177/1758834010361333
14. Ledermann JA, Raja FA, Fotopoulou C, Gonzalez-Martin A, Colombo N, Sessa C et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi24–32. https://doi.org/10.1093/annonc/mdt333
15. Sherman-Baust CA, Weeraratna AT, Rangel LBA, Pizer ES, Cho KR, Schwartz DR, et al. Remodeling of the extracellular matrix through overexpression of collagen VI contributes to cisplatin resistance in ovarian cancer cells. Cancer Cell. 2003;3(4):377–386. https://doi.org/10.1016/S1535-6108(03)00058-8
16. Mariathasan S, Newton K, Monack DM, Vucic D, French DM, Lee WP, et al. Differential activation of the inflammasome by caspase-1 adaptors ASC and Ipaf. Nature. 430 (6996): 213–218.https://doi.org/10.1038/nature02664
17. Broz P, Dixit VM. Inflammasomes: mechanism of assembly, regulation and signalling. Nat Rev Immunol. 2016;16(7):407–420. https://doi.org/10.1038/nri.2016.58
18. Broz P, Pelegrín P, Shao F. The gasdermins, a protein family executing cell death and inflammation. Nature Revi Immunol. 2020; 20:143–157 https://doi.org/10.1038/s41577-019-0228-2
19. Jia D, Nagaoka Y, Katsumata M, Orsulic S. Inflammation is a key contributor to ovarian cancer cell seeding. Sci Rep. 2018;8(1):12394. https://doi.org/10.1038/s41598-018-30261-8
20. Kisielewski R, Tołwińska A, Mazurek A, Laudański P. Inflammation and ovariancancer--current views. Ginekol Pol. 2013;84(4):293–297. https://doi.org/10.17772/gp/1579

21. Landen CN Jr, Birrer MJ, Sood AK. Early events in the pathogenesis of epithelial ovarian cancer. J Clin Oncol. 2008;26(6):995–1005. https://doi.org/10.1200/JCO.2006.07.9970
22. Nowak M, Glowacka E, Szpakowski M, Szyllo K, Malinowski A, Kulig A, et al. Proinflammatory and immunosuppressive serum, ascites and cyst fluid cytokines in patients with early and advanced ovarian cancer and benign ovarian tumors. Neuro Endocrinol Lett. 2010;31(3):375–383.
23. Yi YS. Regulatory Roles of Flavonoids on Inflammasome Activation during Inflammatory Responses. Mol Nutr Food Res. 2018;62(13):e1800147. https://doi.org/10.1002/mnfr.201800147
24. Lamkanfi M, Dixit VM. Mechanisms and functions of inflammasomes. Cell. 2014;157(5):1013–1022. https://doi.org/10.1016/j.cell.2014.04.007
25. Latz E, Xiao TS, Stutz A. Activation and regulation of the inflammasomes. Nat Rev Immunol. 2013;13(6):397–411. https://doi.org/10.1038/nri3452
26. Guo H, Callaway JB, Ting JP. Inflammasomes: mechanism of action, role in disease, and therapeutics. Nat Med. 2015;21(7):677–687. https://doi.org/10.1038/nm.3893
27. Yerramothu P, Vijay AK, Willcox MDP. Inflammasomes, the eye and anti-inflammasome therapy. Eye (Lond). 2018;32(3):491–505. https://doi.org/10.1038/eye.2017.241
28. Spel L, Martinon F. Inflammasomes contributing to inflammation in arthritis. Immunol Rev. 2020;294(1):48–62. https://doi.org/10.1111/imr.12839
29. Fanga Y, Tianb S, Pana Y, Li W, Wang Q, Tang Y, et al. Pyroptosis: A new frontier in cancer. Biomed Pharmacother. 2020;121:109595. https://doi.org/10.1016/j.biopha.2019.109595
30. Woolery KT, Mohamed M, Linger RJ, Dobrinski KP, Roman J, Kruk PA. BRCA1 185delAG Mutation Enhances Interleukin-1β Expression in Ovarian Surface Epithelial Cells. Biomed Res Int. 2015;2015:652017. https://doi.org/10.1155/2015/652017
31. Dagenais M, Dupaul-Chicoine J, Douglas T, Champagne C, Morizot A, Saleh M. The Interleukin (IL)-1R1 pathway is a critical negative regulator of PyMT-mediated mammary tumorigenesis and pulmonary metastasis. Oncoimmunology. 2017;6(3):e1287247. https://doi.org/10.1080/2162402X.2017.1287247
32. Takeda K, Tsutsui H, Yoshimoto T, et al. Defective NK cell activity and Th1 response in IL-18-deficient mice. Immunity. 1998;8(3):383–390. https://doi.org/10.1016/S1074-7613(00)80543-9
33. Oka N, Markova T, Tsuzuki K, et al. IL-12 regulates the expansion, phenotype, and function of murine NK cells activated by IL-15 and IL-18. Cancer Immunol Immunother. 2020;69(9):1699–1712. https://doi.org/10.1007/s00262-020-02553-4
34. Ghayur T, Banerjee S, Hugunin M, et al. Caspase-1 processes IFN-gamma-inducing factor and regulates LPS-induced IFN-gamma production. Nature. 1997;386(6625):619–623. https://doi.org/10.1038/386619a0
35. Wang ZY, Gaggero A, Rubartelli A, et al. Expression of interleukin-18 in human ovarian carcinoma and normal ovarian epithelium: evidence for defective processing in tumor cells. Int J Cancer. 2002;98(6):873–878. https://doi.org/10.1002/ijc.10268
36. Orengo AM, Fabbi M, Miglietta L, et al. Interleukin (IL)-18, a biomarker of human ovarian carcinoma, is predominantly released as biologically inactive precursor. Int J Cancer. 2011;129(5):1116–1125. https://doi.org/10.1002/ijc.25757
37. Carbotti G, Barisione G, Orengo AM, et al. The IL-18 antagonist IL-18-binding protein is produced in the human ovarian cancer microenvironment. Clin Cancer Res. 2013;19(17):4611–4620. https://doi.org/10.1158/1078-0432.CCR-13-0568
38. Uppendahl LD, Felices M, Bendzick L, et al. Cytokine-induced memory-like natural killer cells have enhanced function, proliferation, and in vivo expansion against ovarian cancer cells. Gynecol Oncol. 2019;153(1):149–157. https://doi.org/10.1016/j.ygyno.2019.01.006
39. Simpkins F, Flores A, Chu C, et al. Chemoimmunotherapy using pegylated liposomal Doxorubicin and interleukin-18 in recurrent ovarian cancer: a phase I dose-escalation study. Cancer Immunol Res. 2013;1(3):168–178. https://doi.org/10.1158/2326-6066.CIR-13-0098
40. Macciò A, Madeddu C. Inflammation and ovarian cancer. Cytokine. 2012;58(2):133–147. https://doi.org/10.1016/j.cyto.2012.01.015
41. Liao Y, Tu C, Song X, Cai L. Case report: Analysis of BRCA1 and BRCA2 gene mutations in a hereditary ovarian cancer family. J Assist Reprod Genet. 2020;37(6):1489–1495. https://doi.org/10.1007/s10815-020-01783-w

42. Ulivi V, Tasso R, Cancedda R, Descalzi F. Mesenchymal stem cell paracrine activity is modulated by platelet lysate: induction of an inflammatory response and secretion of factors maintaining macrophages in a proinflammatory phenotype. Stem Cells Dev. 2014;23(16):1858–1869. https://doi.org/10.1089/scd.2013.0567
43. Tasso R, Ulivi V, Reverberi D, Lo Sicco C, Descalzi F, Cancedda R. In vivo implanted bone marrow-derived mesenchymal stem cells trigger a cascade of cellular events leading to the formation of an ectopic bone regenerative niche. Stem Cells Dev. 2013;22(24):3178–3191. https://doi.org/10.1089/scd.2013.0313
44. Kalamegam G, Sait KHW, Anfinan N, et al. Cytokines secreted by human Wharton's jelly stem cells inhibit the proliferation of ovarian cancer (OVCAR3) cells in vitro. Oncol Lett. 2019;17(5):4521–4531. https://doi.org/10.3892/ol.2019.10094
45. Li J, Zhou L, Jiang H, Lin L, Li Y. Inhibition of FOSL2 aggravates the apoptosis of ovarian cancer cells by promoting the formation of inflammasomes. Genes Genomics. 2022;44(1):29–38. https://doi.org/10.1007/s13258-021-01152-6
46. Luborsky J, Barua A, Edassery S, Bahr JM, Edassery SL. Inflammasome expression is higher in ovarian tumors than in normal ovary. PLoS One. 2020;15(1):e0227081.https://doi.org/10.1371/journal.pone.0227081
47. Thongchot S, Jamjuntra P, Therasakvichya S, et al. Interleukin-8 released by cancer-associated fibroblasts attenuates the autophagy and promotes the migration of ovarian cancer cells. Int J Oncol. 2021;58(5):14. https://doi.org/10.3892/ijo.2021.5194
48. Rodrigues ISS, Martins-Filho A, Micheli DC, et al. IL-6 and IL-8 as Prognostic Factors in Peritoneal Fluid of Ovarian Cancer. Immunol Invest. 2020;49(5):510–521. https://doi.org/10.1080/08820139.2019.1691222
49. Mustea, A., Könsgen, D., Braicu, E. I., Pirvulescu, C., Sun, P., Sofroni, D., Lichtenegger, W., & Sehouli, J. (2006). Expression of IL-10 in patients with ovarian carcinoma. Anticancer research, 26(2C), 1715–1718.
50. Sato T, Terai M, Tamura Y, Alexeev V, Mastrangelo MJ, Selvan SR. Interleukin 10 in the tumor microenvironment: a target for anticancer immunotherapy. Immunol Res. 2011;51(2–3):170–182. https://doi.org/10.1007/s12026-011-8262-6
51. Batchu RB, Gruzdyn OV, Kolli BK, et al. IL-10 Signaling in the Tumor Microenvironment of Ovarian Cancer. Adv Exp Med Biol. 2021;1290:51–65. https://doi.org/10.1007/978-3-030-55617-4_3
52. Pranjol MZ, Gutowski N, Hannemann M, Whatmore J. The Potential Role of the Proteases Cathepsin D and Cathepsin L in the Progression and Metastasis of Epithelial Ovarian Cancer. Biomolecules. 2015;5(4):3260–3279. Published 2015 Nov 20. https://doi.org/10.3390/biom5043260
53. Chai Y, Wu W, Zhou C, Zhou J. The potential prognostic value of cathepsin D protein in serous ovarian cancer. Arch Gynecol Obstet. 2012;286(2):465–471. https://doi.org/10.1007/s00404-012-2318-2
54. Xu H, Ma Y, Zhang Y, et al. Identification of Cathepsin K in the Peritoneal Metastasis of Ovarian Carcinoma Using In-silico, Gene Expression Analysis. J Cancer. 2016;7(6):722–729.https://doi.org/10.7150/jca.14277
55. Zhang L, Wei L, Shen G, et al. Cathepsin L is involved in proliferation and invasion of ovarian cancer cells. Mol Med Rep. 2015;11(1):468–474. https://doi.org/10.3892/mmr.2014.2706
56. Sui H, Shi C, Yan Z, Wu M. Overexpression of Cathepsin L is associated with chemoresistance and invasion of epithelial ovarian cancer. Oncotarget. 2016;7(29):45995–46001. https://doi.org/10.18632/oncotarget.10276
57. Zhang H, Zhang L, Wei L, et al. Knockdown of cathepsin L sensitizes ovarian cancer cells to chemotherapy. Oncol Lett. 2016;11(6):4235–4239.https://doi.org/10.3892/ol.2016.4494
58. Martinon F, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. Mol Cell. 2002;10(2):417–426. https://doi.org/10.1016/S1097-2765(02)00599-3
59. Yang J, Liu Z, Xiao TS. Post-translational regulation of inflammasomes. Cell Mol Immunol. 2017;14(1):65–79. https://doi.org/10.1038/cmi.2016.29
60. Shao BZ, Xu ZQ, Han BZ, Su DF, Liu C. NLRP3 inflammasome and its inhibitors: a review. Front Pharmacol. 2015;6:262. Published 2015 Nov 5. https://doi.org/10.3389/fphar.2015.00262
61. Inoue M, Shinohara ML. The role of interferon-β in the treatment of multiple sclerosis and experimental autoimmune encephalomyelitis - in the perspective of inflammasomes. Immunology. 2013; 139(1), 11–18. https://doi.org/10.1111/imm.12081

62. Wu H, Liu J, Zhang Y, Li Q, Wang Q, Gu Z. miR-22 suppresses cell viability and EMT of ovarian cancer cells via NLRP3 and inhibits PI3K/AKT signaling pathway. Clin Transl Oncol. 2021;23(2):257–264. https://doi.org/10.1007/s12094-020-02413-8
63. Ding Y, Yan Y, Dong Y, Xu J, Su W, Shi W, et al. NLRP3 promotes immune escape by regulating immune checkpoints: A pan-cancer analysis. Int Immunopharmacol. 2022;104:108512. https://doi.org/10.1016/j.intimp.2021.108512
64. Chang CM, Wang ML, Lu KH, Yang YP, Juang CM, Wang PH, et al. (2017). Integrating the dysregulated inflammasome-based molecular functionome in the malignant transformation of endometriosis-associated ovarian carcinoma. Oncotarget. 2017; 9(3), 3704–3726. https://doi.org/10.18632/oncotarget.23364
65. Heath O, Berlato C, Maniati E, et al. Chemotherapy Induces Tumor-Associated Macrophages that Aid Adaptive Immune Responses in Ovarian Cancer. Cancer Immunol Res. 2021;9(6):665–681. https://doi.org/10.1158/2326-6066.CIR-20-0968
66. Wu TC, Xu K, Martinek J, Young RR, Banchereau R, George J. et al. IL 1 receptor antagonist controls transcriptional signature of inflammation in patients with metastatic breast cancer. Cancer research. 2018: 78(18):5243–5258. https://doi.org/10.1158/0008-5472.CAN-18-0413
67. Hornung V, Ablasser A, Charrel-Dennis M, et al. AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC. Nature. 2009;458(7237):514–518. https://doi.org/10.1038/nature07725
68. Lu A, Kabaleeswaran V, Fu T, Magupalli VG, Wu H. Crystal structure of the F27G AIM2 PYD mutant and similarities of its self-association to DED/DED interactions. J Mol Biol. 2014;426(7):1420–1427. https://doi.org/10.1016/j.jmb.2013.12.029
69. Mambwe B, Neo K, Javanmard Khameneh H, et al. Tyrosine Dephosphorylation of ASC Modulates the Activation of the NLRP3 and AIM2 Inflammasomes. Front Immunol. 2019;10:1556. https://doi.org/10.3389/fimmu.2019.01556
70. Hsu PC, Chao TK, Chou YC, et al. AIM2 Inflammasome in Tumor Cells as a Biomarker for Predicting the Treatment Response to Antiangiogenic Therapy in Epithelial Ovarian Cancer Patients. J Clin Med. 2021;10(19):4529. https://doi.org/10.3390/jcm10194529
71. Liu C, Huang X, Su H. The role of the inflammasome and its related pathways in ovarian cancer. Clin Transl Oncol. 2022 Aug;24(8):1470–1477. https://doi.org/10.1007/s12094-022-02805-y
72. Ye Y, Dai Q, Qi H. A novel defined pyroptosis-related gene signature for predicting the prognosis of ovarian cancer. Cell Death Discov. 2021;7(1):71. https://doi.org/10.1038/s41420-021-00451-x
73. Zou J, Zheng Y, Huang Y, Tang D, Kang R, Chen R. The Versatile Gasdermin Family: Their Function and Roles in Diseases. Front Immunol. 2021;12:751533. https://doi.org/10.3389/fimmu.2021.751533
74. Liu T, Hou M, Li M, et al. Pyroptosis: A Developing Foreland of Ovarian Cancer Treatment. Front Oncol. 2022;12:828303. https://doi.org/10.3389/fonc.2022.828303
75. Saeki N, Kuwahara Y, Sasaki H, Satoh H, Shiroishi T. Gasdermin (Gsdm) localizing to mouse Chromosome 11 is predominantly expressed in upper gastrointestinal tract but significantly suppressed in human gastric cancer cells. Mamm Genome. 2000;11(9):718–724. https://doi.org/10.1007/s003350010138
76. Berkel C, Cacan E. Differential Expression and Copy Number Variation of Gasdermin (GSDM) Family Members, Pore-Forming Proteins in Pyroptosis, in Normal and Malignant Serous Ovarian Tissue. Inflammation. 2021;44(6):2203–2216. https://doi.org/10.1007/s10753-021-01493-0
77. Pandeya A, Li L, Li Z, Wei Y. Gasdermin D (GSDMD) as a new target for the treatment of infection. Medchemcomm. 2019;10(5):660–667. Published 2019 Apr 4. https://doi.org/10.1039/C9MD00059C
78. Kaltenmeier C, Simmons RL, Tohme S, Yazdani HO. Neutrophil Extracellular Traps (NETs) in Cancer Metastasis. Cancers (Basel). 2021;13(23):6131. https://doi.org/10.3390/cancers13236131
79. Orning P, Lien E, Fitzgerald KA. Gasdermins and their role in immunity and inflammation. J Exp Med. 2019;216(11):2453–2465. https://doi.org/10.1084/jem.20190545
80. De Schutter E, Croes L, Ibrahim J, et al. GSDME and its role in cancer: From behind the scenes to the front of the stage. Int J Cancer. 2021;148(12):2872–2883. https://doi.org/10.1002/ijc.33390
81. Zhang Z, Zhang Y, Xia S, et al. Gasdermin E suppresses tumour growth by activating anti-tumour immunity. Nature. 2020;579(7799):415–420. https://doi.org/10.1038/s41586-020-2071-9

82. Szlasa W, Zendran I, Zalesińska A, Tarek M, Kulbacka J. Lipid composition of the cancer cell membrane. J Bioenerg Biomembr. 2020;52(5):321–342. https://doi.org/10.1007/s10863-020-09846-4
83. Mulvihill E, Sborgi L, Mari SA, Pfreundschuh M, Hiller S, Müller DJ. Mechanism of membrane pore formation by human gasdermin-D. EMBO J. 2018;37(14):e98321. https://doi.org/10.15252/embj.201798321
84. He J, Siu MKY, Ngan HYS, Chan KKL. Aberrant Cholesterol Metabolism in Ovarian Cancer: Identification of Novel Therapeutic Targets. Front Oncol. 2021;11:738177. https://doi.org/10.3389/fonc.2021.738177