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Microbial infection, inflammation and epithelial ovarian cancer (Review)

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Abstract. Ovarian cancer is the most common, and life-threatening, type of female gynecological cancer. The etiology of ovarian cancer remains unclear, and there are currently no effective screening or treatment methods for the disease. Microbial infection serves a marked function in inducing carcinogenesis. A number of studies have identified pelvic inflammatory disease as a risk factor for epithelial ovarian cancer. Thus, it is hypothesized that microbial infection may contribute to ovarian cancer. In the present review, the microorganisms that have been identified to be associated with ovarian cancer and the underlying molecular mechanisms involved are discussed. Infection-induced chronic inflammation is considered an important process for carcinogenesis, cancer progression and metastasis. Therefore, the pathological process and associated inflammatory factors are reviewed in the present paper.

Contents

1. Introduction

Ovarian cancer is the most life-threatening type of gynecological cancer in females. According to Cancer Statistics (1), there were an estimated 22,440 novel cases of ovarian cancer in 2017. In addition, the number of ovarian cancer-associated mortalities was 14,080, which was the fifth most common cause of cancer-associated mortality in American females (1). Epithelial ovarian cancer (EOC) is the most common histological type of ovarian cancer, with ~75% cases of ovarian cancer diagnosed at an advanced stage (FIGO stages III-IV) and the overall survival rate of EOC ranging between 15 and 30% for the last 20 years (2). The exact cause of ovarian cancer remains unclear; however, a number of associated risk factors have been identified. Ovulation-associated factors including pregnancy frequency, breastfeeding, early menarche, late menopause and the use of the oral contraceptive pill were all associated with EOC. In addition, hereditary factors served an important function in the development of ovarian cancer, with females who had a family history of ovarian cancer, personal history of breast cancer or alteration in breast cancer early onset (BRCA)1 or BRCA2 genes contributed to an increased risk of EOC. Furthermore, inflammation was a risk factor of EOC, and females who have experienced pelvic inflammatory disease (PID), endometriosis or frequent exposure to talc and asbestos were identified to exhibit an increased risk of ovarian cancer (3). Lin *et al* identified that females with an episode of clinically apparent PID exhibited a 1.9-fold increase in the development of EOC, whereas females who had experienced ≥5 episodes of PID exhibited a 2.5-fold increased risk. In addition, patients with PID aged ≤35 years were at an increased risk of developing ovarian cancer compared with the control population during 1-3 years of follow-up (4). In early 1995, a case-control study, including 450 females with ovarian cancer and 564 controls, revealed that 23.1% of cases and 18.1% of controls had PID and, adjusted for age, smoking, country of birth, parity, duration of oral contraceptive use and abortion, the odds ratio was 1.53 [95% confidence interval (CI), 1.10-2.13; P=0.012] (5). Furthermore, females with recurrent PID presented an increased risk (odds ratio, 1.88; 95% CI, 1.13-3.12; P=0.014), which suggested that PID may increase the risk of developing ovarian cancer (5). In a Chinese study conducted in 1989, PID was associated with an increased risk of inducing ovarian cancer (odds ratio, 3.0; 95% CI, 0.30-30.2) (6).

Malignancies are hypothesized to be partially initiated by microbial infections and >15% of malignancies may be attributed to infections (7). According to the International Agency for Research on Cancer (IARC), 6 viruses and 1 bacterium are certified as causes of cancer, which are human papillomavirus

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(HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), Epstein-Barr virus (EBV), human T-lymphotropic virus 1 and Kaposi's sarcoma-associated herpes virus, and *Helicobacter pylori*, respectively. Persistent infections induce chronic inflammation which may cause successive inflammatory reactions, thus dysregulated innate or adaptive immune responses may be pro-tumorigenic (8). In the present review, studies of microorganisms that may induce ovarian carcinogenesis are summarized and the underlying molecular mechanisms that link chronic inflammation to ovarian cancer are examined.

2. Ovarian carcinogenesis and microorganisms

Chlamydia trachomatis. *C. trachomatis* is one of the most common types of bacteria that cause sexually transmitted infections (STIs). In the USA, almost 4 million cases of *C. trachomatis* infections occur each year; however, only 25% of those cases were diagnosed and treated (9). *C. trachomatis* an obligate intracellular bacterium with a unique life cycle involving stages of infective extracellular elementary body (EB) and non-infective intracellular reticulate body (RB) (10). Unlike the majority of bacteria, *C. trachomatis* intracellular and, unlike viruses, *C. trachomatis* possesses DNA and RNA (11). When a host is infected with *C. trachomatis*, the host exhibits a long asymptomatic period, since the host immune response fails to control infection. According to Molano *et al* (12), ~46, 18 and 6% of *C. trachomatis* infections were persistent for 1, 2 and 4 years of follow-up, respectively, as determined using plasmid polymerase chain reaction, without consideration of serotypes. After 4 years of follow-up, 94% of females who had a *C. trachomatis* infection were healthy (13). During a period of infection, the innate and adaptive immune system are stimulated to fight against infection. The innate immune system initiates more rapid and primitive responses to infection, compared with that of the adaptive immune system, and includes surface defenses, cytokine elaboration, complement activation and phagocytic responses (14). The innate immune response begins by the binding of pathogen-associated molecular patterns (PAMPs) to cell receptors, activating nuclear factor-κB (NF-κB) which subsequently binds to specific DNA sequences in the nucleus, inducing the production of pro-inflammatory cytokines (14,15). In addition, the natural antimicrobial peptides (NAPs) and pattern recognition Toll-like receptors (TLRs) are key mediators of the innate immune system. Secretory leukocyte protease inhibitor (SLPI) and elafin are potential NAPs; an oviductal epithelial cell line infected with *C. trachomatis* increased the expression level of elafin (16). TLRs are typically expressed in epithelial cells; previous studies have identified that *Chlamydia* activated TLR3 in murine reproductive tract epithelial cells and TLR2 is critical for *Chlamydia*-mediated host cell activation and pathology (17,18). The host immune system-stimulated production of pro- or anti-inflammatory cytokines are considered to be important factors in determining the disease outcomes. For instance, interferon (IFN)-γ, interleukin (IL)-6, IL-8, IL-10, IL-12, neutrophils or macrophages serve protective or destructive roles in *C. trachomatis* infection, PID or infertility (19). Persistent inflammation and the subsequent tissue damage or inhibition of apoptosis of host cells contribute to carcinogenesis following *Chlamydia* infection (20). According to Shanmughapriya *et al* (21), 80% of ovarian cancer cases were identified as positive for *Chlamydia*; however, none of the controls were determined to be positive. Additionally, a previous seroepidemiological study identified a positive association between plasma *C. trachomatis* immunoglobulin (Ig)G and ovarian tumors (22). Owing to the hypothesis of the tubal origin of epithelial ovarian cancer, Carvalho and Carvalho (23) identified that primary tubal cancer, induced by *C. trachomatis* fimbrial infection, may be an origin of serous ovarian carcinoma; however, additional study was required. Acute *C. trachomatis* infection activated the paracrine Wnt signaling pathway, which led to profound disruption of the fallopian tube epithelial structure and function that facilitated the dissemination of damage beyond that of infected cells (24). Furthermore, heat shock protein 60 (HSP60) is an immune protein that induces immune responses. HSP60, synthesized during *C. trachomatis* infection, is markedly conserved in evolution and possesses common antigenic epitopes (25). Exogenous HSP60 from microbes may stimulate the immune response in humans and additionally reacts with the endogenous chaperonin (26). The accumulation of exogenous chlamydial HSP60 in the cytoplasm of active replicating eukaryotic cells may interfere with the regulation of the apoptotic pathway (27). In addition, overexpression of HSP60 induced tumor viability and metastasis (28,29). Furthermore, the concentrations of IgG antibodies against HSP60/65 was increased in ovarian cancer serum, compared with the controls, and HSP60 expression in ovarian cancer tissues was visibly increased compared with normal ovarian tissues (30,31).

Mycoplasma genitalium. *M. genitalium* is a microbe that causes STIs in males and females, and it is >30 years since it was initially isolated from males with non-gonococcal urethritis (32). *M. genitalium* belongs to the mollicutes class and is the smallest self-replicating organism consisting of 580 kb and 485 genes (33,34). The prevalence rate of *M. genitalium* in females is decreased compared with that of *C. trachomatis*. According to Manhart *et al* (35), the genital prevalence rates of *M. genitalium*, *Neisseria gonorrhoeae* and *C. trachomatis* were ~1, 0.4 and 4.2%, respectively. Infection of *M. genitalium* was associated with non-gonococcal urethritis, bacterial vaginosis and vaginitis, cervicitis, PID and infertility in females (36). The role served by *M. genitalium*in ovarian cancer is controversial. According to Idahl *et al* (22), serum *M. genitalium* IgG antibodies were markedly increased in ovarian malignancies or benign tumors compared with that in controls. However, in another study, *M. genitalium* was not identified in ovarian tumor tissues (37). According to Chan *et al* (38), mycoplasmas were detected in 59.3% of the malignant ovarian cancer specimens. In contrast, Quirk *et al* (39) identified *Mycoplasma* DNA in only 6 (13%) of the 46 ovarian tumor DNA samples, which failed to determine an association between ovarian cancer and *Mycoplasma*. *M. genitalium* was positive in a number of additional types of malignancy, BPH-1 cells, after 19 weeks of co-culture with *M. genitalium*, exhibited anchorage-independent viability and the migration and invasion ability was markedly increased; the infected BPH-1 cells were also found to be tumorigenic in nude mice (40). In addition, cervical, vaginal and prostatic epithelial cells secreted a number of inflammatory cytokines following infection with *M. genitalium* including IL-6 and

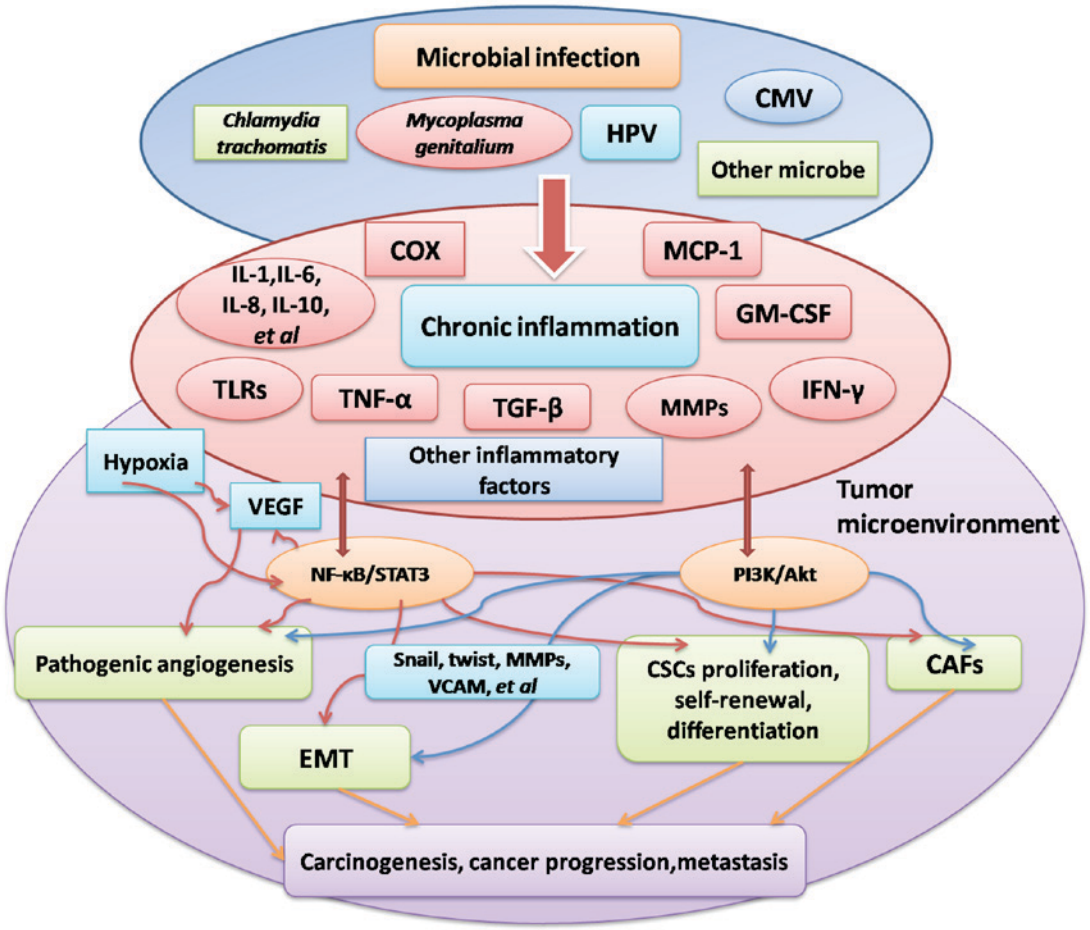

Figure 1. Inflammatory factors and signaling pathways in cancer induced by microbial infection. CMV, cytomegalovirus; HPV, human papillomavirus; COX, cyclooxygenase; MCP-1, monocyte chemotactic protein 1; GM-CSF, granulocyte/macrophage colony-stimulating factor; IL, interleukin; TLR, Toll-like receptor; TNF-α, tumor necrosis factor α; MMP, matrix metalloproteinase; IFN-γ, interferon-γ; VEGF, vascular endothelial growth factor; NF-κB, nuclear factor-κB; STAT3, signal transducer and activator of transcription 3; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; Twist, Twist-related protein 1; VCAM, vascular cell adhesion protein; EMT, epithelial-mesenchymal transition; CSC, cancer stem cell; CAF, cancer-associated fibroblast.

IL-8 (41,42). Furthermore, *Mycoplasma* infection served an oncogenic function in cultured mouse embryo cells (43). The pathophysiology process of *M. genitalium* infection included adherence to epithelial cells, cell invasion, production of toxins and immunological responses (36). These processes were associated with PID and tubal factor infertility. *M. genitalium* infection traversed from the lower genital tract to upper genital tract, which caused persistent inflammation in the fallopian tubes and ovaries (44). According to Baczynska *et al* (45) and Crum *et al* (46), *M. genitalium* and *Mycoplasma hominis* caused swelling of the tubal epithelial cilia, through production of a toxin or metabolism products, which was consistent with previous studies that ovarian cancer originated from the fallopian tube epithelium. As aforementioned, the immunological response serves an essential function in *M. genitalium* infection. Persistent *M. genitalium* infection enhanced endocervical epithelial cells secretion of IL-6, IL-8, granulocyte colony-stimulating factor, granulocyte/macrophage colony-stimulating factor (GM-CSF) and monocyte chemotactic protein (MCP)-1, and increased the sensitivity to TLR agonists. This suggested that infected subjects may be hyper-responsive to exogenous innate immune stimulation induced by STIs, or to other STIs including bacterial vaginosis (47). Furthermore, a previous study demonstrated that following inoculation with *M. genitalium* of 3D endocervical epithelial cells for 48 h, host defense and inflammation-associated genes were activated (48). Pro-inflammatory cytokines including IL-6, IL-7, IL-8, MCP-1 and GM-CSF were secreted following *M. genitalium* infection (48).

Human papillomavirus (HPV). HPV is one of the most common types of sexually transmitted virus in the world. In the USA, the overall HPV prevalence was 26.8% in females aged between 14 and 59 years; however, in females aged between 20 and 24 years, the HPV prevalence rate was ≤44.8% (49). In China, a pooled analysis of 17 population-based studies, including 30,207 females, identified the HPV prevalence to be 17.7% (50). Furthermore, a province-wide study was conducted in Ningbo province which identified 185 of 1,373 females aged between 22 and 64 years (13.5%) as HPV-positive and the prevalence rates were 13.8, 8.8 and 7.9% in Shenzhen, Xinjiang and Chaozhou, respectively (51-54). The papillomavirus family is heterogeneous and highly species-specific. Over 200 HPV genotypes have been identified and these are subdivided into three broad categories, depending on their oncogenic potential. High-risk HPV types include HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, HPV-68 andHPV-73. HPV-16

and HPV-18 are the most common types of HPV identified in malignancies (55). In addition, HPV was demonstrated to be positive in a number of types of malignancy. According to Tang *et al* (56), HPV was detected in 96.6% of cervical carcinomas, in 14.1% of head and neck squamous cell carcinomas, and in bladder urothelial carcinoma and lung squamous cell carcinoma. Whether HPV infection, *C. trachomatis* or *M. genitalium* are associated with ovarian cancer is debated. A previous meta-analysis, summarizing 24 primary studies from 11 countries on 3 continents, contained information on HPV and ovarian cancer and included 880 subjects (57). This study identified an association between HPV infection and ovarian cancer, as HPV prevalence in patients with ovarian cancer was demonstrated to be 17.5%. In Saudi patients, an increased proportion of HPV-16 and HPV-18 was observed in 42.9 and 26.2% ovarian cancer tissues, respectively (58). In addition, previous studies identified that increased-risk HPV DNA may be determined in ovarian serous carcinomas and present in females at a high risk of developing EOC (including females with ≥2 first-degree relatives with ovarian or breast cancer or females with mutations in BRCA1 or BRCA2 genes) (59,60). However, a study from Iraq identified that HPV-16 existed in only 9.67% of malignant ovarian epithelial tumors, which suggested that HPV infection served a relatively minor function in the pathogenesis of ovarian cancer (61).

HPV replicates and assembles exclusively in the nucleus, and initially establishes infection in undifferentiated and actively proliferating cells in the basal layer of epithelium cells. During carcinogenic progression, the HPV genome typically integrates into a host cell chromosome, and the viral oncoproteins E6 and E7 induce cell immortalization and transformation (62). E6 and E7 inactivate two cellular tumor suppressor proteins: p53 and retinoblastoma protein (63). HPV-16 E7 increased the retention of γ-H2A histone family, member X (a marker for cellular response to DNA damage) and decreased sublethal DNA damage repair in head and neck cancer cells. The results of this study suggested that E7 expression markedly delayed radiation-induced DNA damage repair in head and neck normal epithelial cells, and head and neck cancer cells (64). In addition, HPV E6/E7 were identified to increase the intracellular expression of the oncogenic microRNA 17-92 cluster and decrease the expression of the anti-proliferative p21 gene in HPV-positive cancer cells (65). According to Gregoire *et al* (66), introduction of HPV-16 E6/E7 genes into human ovarian surface epithelial (HOSE) cells may extend the lifespan and induce malignant transformation of these cells.

Cytomegalovirus (CMV). CMV infection is rarely associated with ovarian cancer. Shanmughapriya *et al* (21) identified ~50% of ovarian cancers to be CMV-positive, of which 80 and 20% were invasive and borderline tumors, respectively. As discussed in a review (67), 10 studies have described CMV oophoritis, which demonstrated that CMV infection may cause an underlying malignancy or immunosuppressive status. In addition, the aforementioned review identified steroid therapy as a strong risk factor for CMV reactivation (67). Furthermore, CMV infection was revealed to contribute to a number of types of malignancy including those of brain, breast, colon, cervical andprostate (68-72). CMV is not a typical oncogenic virus, but it is described as an oncomodulation virus (73). CMV proteins may control the cell cycle, inhibit apoptosis and induce telomerase activity, angiogenesis and cellular migration (74). A previous study identified that human HCMV binds to epithelial growth factor receptor and integrins αvβ3 and α2β1 to induce an angiogenic response to human mammary epithelial cells (75). CMV IL-10 is an HCMV UL111A gene product that has 27% sequence identity with IL-10; CMV IL-10 could bind the IL-10 receptor expressed by MCF-7 breast cancer cells to promote proliferation of MCF-7 cells (76). In addition, mouse CMV infection was identified to enhance glioblastoma cell viability through signal transducer and activator of transcription STAT3 activation, whereas the STAT3 inhibitor prevented the HCMV stimulation in human glioblastoma neurosphere growth (*in vitro* and *in vivo)* (77).

3. Inflammation and ovarian carcinogenesis

Inflammation is a biological response to disrupted tissue homeostasis and possesses four essential factors including inducers, sensors, inflammatory mediators and target tissues (78). Microbial infection is one of the most common types of inducer which promotes inflammatory responses; other inducers include autoimmune diseases and agnogenic inflammatory diseases (79). Inflammatory sensors include macrophages, dendritic cells, mast cells, T cells, B cells, fibrocytes and endothelial cells. Inflammation is mediated by immune cells as an immediate defense in response to infection or injury by noxious stimuli. Innate immune cells, including neutrophils, mast cells and macrophages, exhibit receptors that signal the activation and production of an array of biologically active proteins and defense molecules, in response to detrimental substances and damaged or altered self-molecules (80). Inflammatory mediators including inflammatory cytokines, chemokines, growth factors, reactive oxygen and nitrogen species and cytokines, secreted by inflammatory cells, cause genomic alterations in the epithelium and subsequent cancer initiation. Chronic infections are responsible for 15% of malignancies worldwide (81,82). For example, GM-CSF/IFN-γ-and GM-CSF/IL-3/IFN-γ-deficient mice were administered with acute and chronic inflammatory reactions in a number of organs, particularly in the lungs, soft tissues, lymph nodes, ovaries, adrenal glands and the liver. A previous study indicated that the cause of cancer formation in these mice was bacterial, presumably due to the creation of a persistent inflammatory response (83). There have been notable studies which identified that factors associated with immune responses may alter the pathogenesis and initiation of ovarian cancer, through genetic and protein analysis (84). According to Curiel *et al* (85), regulatory T (Treg) cells served a substantial role in ovarian cancers, and blocking Treg cell migration or function may aid ovarian cancer therapy. Furthermore, Treg cells were associated with an increased risk of mortality and decreased survival time. C-C motif chemokine 22, produced by the tumor microenvironment, was suggested to be a mediator of Treg cells and tumors (85). According to Block *et al* (86), pro-inflammatory factor NF-κB-associated single-nucleotide polymorphisms were associated with the overall survival time of patients with ovarian cancer. A case-control study, including 7,776 cases and 11,843 controls, revealed that regular use of non-steroidal anti-inflammatory drugs, including aspirin, decreased the risk of ovarian cancer (87).

Inflammation-activated angiogenesis and carcinogenesis. Inflammation-induced angiogenesis is associated with a number of pathophysiological processes including tumor viability, wound healing and ovulation. The process of angiogenesis is regulated by angiogenic cytokines and growth factors secreted by inflammatory cells. Inflammation and hypoxia are two primary types of angiogenesis inducers. Vascular endothelial growth factor (VEGF), induced by chronic inflammation, serves functions in tumor angiogenesis, viability and metastasis, and targeting VEGF to inhibit angiogenesis may prevent cancer progression (88,89). The NF-κB pathway, critical for pro-inflammatory gene expression, is considered to exhibit a function in angiogenesis of tumor and inflamed tissues, and the NF-κB-inducing kinase may be a therapeutic target in chronic inflammatory diseases and tumor neoangiogenesis (90). Hypoxia, when tissues lack oxygen, induces angiogenesis and inflammation, and hypoxia-inducible factor (HIF)-1 activation is well-known as an adaptive strategy to hypoxia and consists of two subunits: HIF-1α and HIF-1β. HIF-1 activates transcription of genes encoding angiogenic growth factors, including VEGF, angiopoietin (ANGPT)1, ANGPT2 and platelet-derived growth factor, which are secreted by hypoxic cells and stimulate epithelial cells, resulting in angiogenesis (91). Angiogenesis has been identified as a necessary process for oncogenesis and subsequent tumor growth. Exosomes, extracted from high-grade ovarian cancer cells, induce angiogenesis, and activating transcription factor 2 and metastasis-associated 1 may serve a key function in exosomal enhancement of tumor development (92). In addition, angiogenesis is associated with the formation of malignant ascites in ovarian cancer (93). Anti-angiogenesis therapy is regarded as a novel effective therapeutic strategy for ovarian cancer and a number of clinical trials have validated angiogenesis as a target in ovarian cancer, through the addition of VEGF pathway inhibitors, including the monoclonal anti-VEGF antibody bevacizumab. A previous meta-analysis, including 12 studies, demonstrated that the incorporation of anti-angiogenesis therapy was markedly associated with an improved clinical outcome (94,95). Microbial infection which induces angiogenesis serves a vital function in tumorigenesis. According to Li *et al* (96), lung cancer cells which overexpress HPV-16 E6 and E7 oncoproteins markedly stimulate capillary tube formation of human umbilical vein endothelial cells *in vitro* and increase tumor angiogenesis, HIF-1α and VEGF proteins *in vitro* and *in vivo*. HCMV infection is present in >90% of glioblastoma multiforme (GBM) and HCMV viral protein pp71 induced the production of stem cell factor (SCF), an important pro-angiogenic factor in GBM. Furthermore, the secretion of SCF stimulated by pp71 requires the activation of the NF-κB signaling pathway (97).

Inflammation-activated epithelial-mesenchymal transition and carcinogenesis. Epithelial-mesenchymal transition (EMT) is a biological process where epithelial cells lose their planar and apical-basal polarity and cell-cell adhesion, and gain migratory and invasive properties to become mesenchymal stem cells. EMT was first recognized as a feature of embryogenesis and it additionally occurs in wound healing, organ fibrosis, cancer progression and cancer metastasis (98). EMT is characterized primarily by the loss of epithelial (E-)cadherin and a number of transcription factors have been identified to repress E-cadherin. Zinc finger protein SNAI1 (Snail), zinc finger E-box-binding homeobox (ZEB), E2A immunoglobulin-enhancer binding factor (E47) and Krüppel-like factor 8 bound to and repressed the activity of the E-cadherin promoter; whereas Twist-related protein 1 (Twist) and FOXC2 were common factors that repressed E-cadherin transcription indirectly. Furthermore, a previous study demonstrated that EMT was utilized by cancer cells to enhance aggressiveness by acquiring chemoresistance and stem-cell-like properties and escaping from host immunity (99). Snail was upregulated in ovarian cancer and was identified to be positively associated with the expression of fibronectin and neuralcadherin, but was negatively associated with the expression of E-cadherin and β-catenin (100). Oncogene high-mobility group AT-Hook 2 was revealed to be a EMT-associated gene that was overexpressed in OSE cell lines and assisted in the understanding of the tumorigenesis of ovarian serous carcinoma (101). In addition, EMT is associated with ovarian cancer which is resistant to conventional chemotherapy. A previous study identified EMT genes, including Snail, zinc finger protein SNAI2 (Slug), Twist2 and Zeb2, upregulated in cisplatin-resistant ovarian cancer cell lines; however, following knockdown of the Snail and Slug genes, the EMT phenotype was reversed and drug sensitivity was restored (102). Inflammatory factors tumor necrosis factor-α, transforming growth factor (TGF)-β1 and IL-6 induced EMT in inflammatory breast cancer cells, through the NF-κB and STAT3 signaling pathways (103). Microbes including *Helicobacter*, *Mycoplasma hyorhinis*, *Citrobacter rodentium*, EBV and HCV were reported to induce EMT (104-108). The components and products of bacteria are considered to serve functions in the induction of EMT. Li *et al* (109) identified that lipopolysaccharide (LPS) promoted invasion and metastasis of liver hepatocellular carcinoma HepG2 cells and downregulated the expression of E-cadherin, suggesting that TLR4 may involve the process of EMT. Furthermore, LPS was demonstrated to decrease E-cadherin expression in intrahepatic biliary epithelial cells (HIBEpiCs) and increased the mesenchymal markers S100 calcium-binding protein A1 and sterile α motif. In addition, it was hypothesized that LPS induced EMT of HIBEpiCs, through the TGF-β1/Smad2/3 signaling pathway (110). Flagellin and muramyl dipeptides are two bacterial products that maybe associated with EMT. A previous study revealed that flagellin induced EMT by activating NF-κB and mitogen-activated protein kinase (MAPK), but failed to increase the level of Snail in A549 adenocarcinomic human alveolar basal epithelial cells and BEAS-2B human bronchial epithelial cells (111). Muramyl dipeptides were considered to activate nucleotide-binding oligomerization domain-like receptors (NOD) and subsequently recruit receptor-interacting serine/threonine kinase 2, a kinase required for NOD-mediated NF-κB and MAPK activation (112). A previous study revealed that EBV induced EMT of human corneal epithelial cells through activation of phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) and extracellular-signal-regulated kinase (ERK) signaling pathways (113). The EBV latent membrane protein 1 (LMP1) and 2A (LMP2A) are involved in EMT; it was first identified that LMP1 induced EMT via Twist in nasopharyngeal carcinoma

tissues. Furthermore, LMP1 in lung epithelium predisposed cells to undergo EMT by enhancing signaling through the ERK signaling pathway and the interaction with TGF-β1 may also stimulate EMT (114,115). In addition, HCV induces EMT: HCV core protein repressed E-cadherin expression by upregulating E12/E47 to induce EMT. In cholangiocarcinoma, HCV has been shown to induce EMT, promoting carcinoma progression through a mechanism dependent on the lysyloxidase-like 2 signaling pathway (116).

Inflammation-activated cancer stem cells (CSCs) and carcinogenesis. CSCs are defined as cells that possess the capacity of self-renewal, cancer viability, metastasis, recurrence and they are not sensitive to radio- and chemotherapy. CSCs exist in a number of types of cancer, including ovarian, breast, colon, prostate and leukemia. Bapat *et al* (117) were the first to isolate ovarian CSCs from ascites of patients with ovarian cancer, 19 of which were spontaneously immortalized and two cell lines were characterized with CSCs that presented the specific markers of stem cells including Nestin, octamer-binding transcription factor 4 and Nanog. Additional biomarkers of ovarian CSCs include aldehyde dehydrogenases, cluster of differentiation (CD)44, CD133, CD24, epithelial cell adhesion molecule, CD117, lymphocyte antigen 6 complex, locus A and leucine-rich repeat-containing G-protein-coupled receptor 5 (118). CSCs interact with, and are regulated by, a number of signaling pathways and cytokines inthe tumor microenvironment. Inflammatory cytokines, including IL-1, IL-6 and IL-8, activate the STAT3/NF-κB signaling pathway in tumor and stromal cells, which stimulates cytokine production and self-renewal of CSCs. The positive-feedback loops contribute to the interactions between chronic inflammation and cancer (119). NF-κB is a primary source of pro-inflammatory cytokines and a previous study demonstrated that NF-κB inhibitors may induce cell death in ovarian CSCs, which prevented cancer recurrence and chemoresistance (120). In addition, TLRs that respond to PAMPs served an important function in EOC stem cells and TLR2, TLR4, TLR5 and TLR9 recognize primarily bacterial products, whereas TLR3 and TLR8 recognize viral components. A previous study identified the TLR2-myeloid differentiation primary response gene 88 (MyD88)-NF-κB signaling pathway as being able to promote tumor repair and enhance self-renewal in $CD44^+/MyD88^+$ EOC stem cells (121). IL-17, secreted by T helper 17 cells and macrophages in the tumor microenvironment, binds to IL-17 receptor, overexpressed in ovarian $CD133^+$ cancer stem-like cells, and subsequently increased the tumorigenic potential and self-renewal, through the NF-κB and p38 MAPK signaling pathway *in vitro* and *in vivo* (122). Cell viability of ovarian cancer cells was markedly increased following co-culture with carcinoma-associated mesenchymal stem cells (CA-MSCs), which existed in the tumor microenvironment and protected ovarian cancer cells from carboplatin-induced viability inhibition and apoptosis. Furthermore, phosphorylation of Akt and X-linked inhibitor of apoptosis protein served an important function in stimulating CA-MSC-secreted factors which protect ovarian cancers from carboplatin-induced apoptosis (123).

Inflammation-activated cancer-associated fibroblasts and carcinogenesis. The tumor microenvironment is composed of distinct cellular and structural factors, including the vasculature, immune-associated cells, fibroblasts and extracellular matrix. Cancer-associated fibroblasts (CAFs) exhibit a function in tumor-stroma crosstalk. Fibroblasts are involved in tissue repair, the inflammatory response, human tumorigenesis and metastasis. EBV infection was suggested to induce myofibroblast activation in scleroderma (SSc) fibroblasts and the profibroblast-associated factors, including TGF-β1, endothelin 1, SMA as well as TGF β-regulated genes such as early growth response 1, plasminogen activator inhibitor-1, cartilage oligomeric matrix protein and basement membrane-zone genes coding for collagen IV, were up-regulated in SSc fibroblasts (124). LPS of bacteria directly induces lung fibroblast viability by activating TLR4 signaling, and TLR4-induced activation of the PI3K-Aktsignaling pathway and downregulation of phosphatase and tensin homolog served a function in the process (125). In ovarian cancer, CAFs upregulated the expression of the pro-inflammatory factors IL-6, cyclooxygenase-2 and the chemokine (C-X-C motif) ligand 1. Furthermore, NF-κB expression was enhanced by CAFs, which suggested that pro-tumorigenic signaling in the microenvironment of ovarian tumors via the NF-κB signaling pathway was mediated partly by CAFs (126). TGF-β is a fibrosis-associated cytokine that serves a significant function in cancer invasion and metastasis. Ovarian cancer cells exhibited increased motility when co-cultured with fibroblasts in the presence of exogenous of TGF-β1 and TGF-β2, suggesting that TGF-β modulated molecular crosstalk between ovarian cancer cells and CAFs in ovarian cancer microenvironment (127). In addition, CAFs may facilitate the invasiveness of originally non-invasive cancer cells, through protease-activated receptor-dependent Ca^{2+} signals and matrix metalloproteinase-1 upregulation (Fig. 1) (128,129).

4. Conclusions

Chronic inflammation serves an important function in stimulating tumorigenesis. A number of large case-control studies have identified an association between PID and ovarian cancer (4-6). Microorganisms including *C. trachomatis*, *M. genitalium*, HPV and CMV have been identified to induce ovarian cancer and other types of malignancy. In addition, angiogenesis, EMT, CSCs and CAFs are important factors that lead to ovarian cancer progression, viability and metastasis, and may be stimulated by microbial infection. Furthermore, the four processes are essential for the interaction between inflammation and the tumor microenvironment. The pathogenesis of inflammation-associated cancer remains unclear and a limited number of therapeutic methods are currently used to treat cancer. Therefore, the present review aimed at describing the function of microbial infection in inducing ovarian cancer and in the tumor microenvironment, and to assist the development of novel strategies to prevent and treat ovarian cancer.

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