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Gut microbiota and its influence on ovarian cancer carcinogenesis, anticancer therapy and surgical treatment: A literature review

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ABSTRACT

Ovarian cancer (OC) is the most lethal gynecological malignancy and very little is known about the underlying tumorigenesis mechanisms. For other tumors, like colorectal cancer, a relationship between several opportunistic pathogens and cancer development and progression has been proven. Recent researches also underline a possible correlation between gut microbiota dysbiosis and cancer treatment efficacy and adverse effects. Several studies have also demonstrated a link between abdominal surgery and gut microbiota modifications. In this paper, we aim to review the available evidences of this issue in OC to understand if there is a relationship between gut microbiota modifications and efficacy and adverse effects of cancer therapies, either surgical and medical treatments. Well-designed clinical studies, with a robust translational component, are required to better understand the modulation of gut microbiota during OC treatment. The microbiota/microbiome composition analysis, in the near future, could represent a novel instrument to personalize anticancer therapies.

1. Introduction

Ovarian cancer (OC) represents the third cause of cancer-related death worldwide. Despite recent significant progress in its treatment, OC continues to be the most lethal gynecological malignancy, accounting for about 150,000 estimated deaths per year (Siegel et al., 2021).

In recent years, the presence of a possible link between microbiota and carcinogenesis has represented an emerging and debated issue. Gut microbiota comprises about 3×1013 bacterial cells and plays the leading role in the human microbiota. Its most represented bacteria belong to four different phyla: Firmicutes, Bacteroides, Actinobacteria, and Proteobacteria (Cho and Blaser, 2012). Gut microbiota seems to contribute to carcinogenesis through dysbiosis, which is related to a disruption of the physiological homeostasis of intestinal epithelial cells. In this scenario, several opportunistic pathogens, such as Helicobacter pylori and Salmonella enterica, have been recognized to promote gastrointestinal cancer development. Besides, bacteria, like Streptococcus gallolyticus, have been associated with disease progression by inducing cyclooxygenase-2 expression, and Fusobacterium nucleatum is associated with advanced tumor stage and worse prognosis in colon cancer patients (von Frieling et al., 2018).

A unique microbiota has been identified in OC patients and it could have a relevant role in modulating antitumoral therapy's activity, efficacy, and toxicity and could be modified by radical surgery.

This review aims to investigate the possible link between gut microbiota and OC carcinogenesis, anticancer therapy, and surgical treatment.

2. Material and methods

Medline was searched from inception to 28th March 2021 for relevant references according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines Moher et al., 2009). All

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the results derived from the search process were uploaded to a reference management software (Zotero), and duplicates were removed later. Two reviewers conducted the literature search independently, and a third reviewer was required to resolve disagreements on study selection by consensus.

The results of the literature search and the identification process of papers included in the present review are displayed using a flow diagram schematically in Fig. 1. In detail, we conducted four searches to analyze different issues: a possible link between gut microbiota and ovarian cancer carcinogenesis, the effect of gut microbiota on anti-cancer therapy, the relationship between gut microbiota modifications and radical surgery, and the link between gut microbiota modifications and immunotherapy.

Firstly, we used the keywords "ovarian cancer" AND "gut microbiota" and "ovarian cancer" AND "intestinal microbiota". A total of twenty-eight studies resulted from the search "ovarian cancer" AND "gut microbiota", whereas a total of nineteen studies from "ovarian cancer" AND "intestinal microbiota". Six out of twenty-eight studies were selected for the first search strategy, while six out of nineteen were considered in the second search. Six studies matched in the two searches and, thus, each study

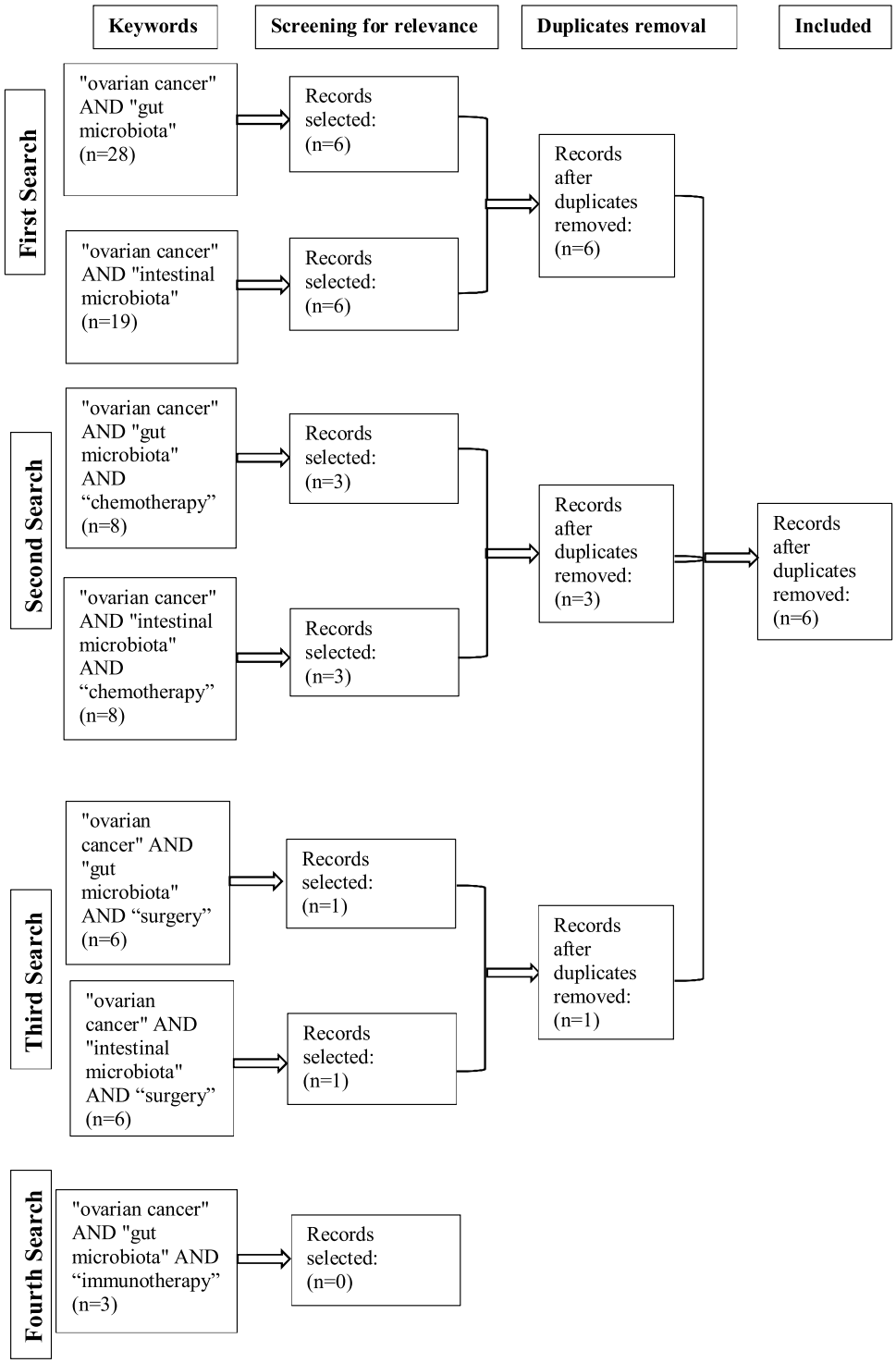

Fig. 1. Flow diagram of study selection process.

was included only once in the review.

Secondly, we used the search terms "ovarian cancer" AND "gut microbiota" AND "chemotherapy" to analyze the possible effect of gut microbiota on anti-cancer therapy. A total of eight studies were found, and only three were included in the review. Besides, we also searched using the terms "ovarian cancer" AND "intestinal microbiota" AND "chemotherapy". A total of eight studies were obtained, and only three of these were selected. The three studies matched in the two searches, and therefore, each study was included only once in the review.

Moreover, we used the keywords "ovarian cancer" AND "gut microbiota" AND "surgery" to analyze the possible link between gut microbiota modifications and radical surgery. A total of six studies were found and only one of these was included in the review. The research was also done with the terms "ovarian cancer" AND "intestinal microbiota" AND "surgery". A total of six studies were obtained, and only one was selected. The only study selected matched in the two searches and, thus, the study was included only once in the review.

Lastly, we used the search terms "ovarian cancer" AND "gut microbiota" AND "immunotherapy" to analyze the possible link between gut microbiota modifications and immunotherapy. A total of three studies were found, although none of these were included in the review. They were considered not consistent with the aim of the study because they do not evaluate a possible implication of gut microbiota in ovarian cancer patients treated with immunotherapy (Table 1).

3. Results

3.1. Gut microbiota and ovarian cancer carcinogenesis

A representative microbiota has been identified in women with ovarian cancer: a distinct group of viruses, bacteria, fungi, and also parasites has been found with a pan-pathogen array. In particular, specific Bacterial Firmicutes were identified in cancer samples such as Abiotrophia, Bacillus, Enterococcus, Erysipelothrix, Geobacillus, Lactobacillus, Lactococcus, Listeria, Pediococcus, Peptoniphilus, and Staphylococcus (Alizadehmohajer et al., 2020). Considerable efforts have been made to understand the pathophysiological mechanisms underlying microbially driven carcinogenesis. The tumor-permissive microenvironment, the epithelial barrier failure, and the immune dysregulation are well-documented factors related to specific bacteria which belong to dysbiotic bacterial communities. Schematically, bacteria can influence carcinogenesis in four different ways: by promoting cell proliferation or cellular death, through a mechanism of perturbation of immune system function, and by changing the metabolism within a host cell. In fact, the available evidence shows that some bacteria associated with colon cancer, such as F. nucleatum and enterotoxigenic B. fragilis, produce proteins involved in cell proliferation, migration, and angiogenesis through their influence on host Wnt–β-catenin signaling. Furthermore, B. fragilis can damage DNA by introducing high levels of reactive oxygen species (Łaniewski et al., 2020). Concerning the perturbation of immune system function, microbial lipopolysaccharide engages with Toll-like receptors promoting angiogenesis. This effect is enhanced by damage-associated molecular patterns that may also be present within the tumor microenvironment (Chase et al., 2015). In addition, the proximity of the microbiota and mucosal immune system also provides the potential for endogenous bacteria to impact the tumor microenvironment by stimulating a variety of pro-tumorigenic immune responses (e.g., B. fragilis polysaccharides has been reported to enhance antitumor immunity) (Alizadehmohajer et al., 2020).

Considering that the clinical presentation of OC patients at the diagnosis is characterized by gastrointestinal symptoms such as abdominal pain, bloating, indigestion, constipation, and early satiety, it is interesting to investigate a possible link between gut microbiota changes and OC carcinogenesis (Chase et al., 2015).

It has been proven that intestinal dysbiosis (IDB) can significantly stimulate the activity of macrophages and consequently the production

Table 1
Study results in PubMed database to investigate ovarian cancer carcinogenesis, anticancer therapy and surgical treatment.

Leterature Search	References	Clinical setting	Type of study
"ovarian cancer" AND "gut microbiota"/ "ovarian cancer" AND "intestinal microbiota"			
	Alizadehmohajer et al. (2020)	Association between microbiota and women's cancers: breast/uterine/ ovarian.	Review
	Łaniewski et al. (2020)	Microbiome (female reproductive tract and interactions with other microbiome) and gynaecological cancer carcinogenesis, prevention and therapy.	Review
	Chase et al. (2015)	vaginal and gastrointestinal microbiomes in gynecologic cancers: carcinogenesis, therapy related adverse-effect and treatment outcomes.	Review
	Xu et al. (2019)	Intestinal dysbiosis and consequent epithelial mesenchymal transition as a potential ovarian cancer carcinogenesis mechanism.	Pre-clinical study: in vitro and mouse models
	Perales-Puchalt et al. (2018)	Effect of cisplatin administration on the composition of intestinal and fecal transplant for the treatment of chemotherapy-associated intestinal damage.	Pre-clinical study: in vitro and mouse models
	Tong et al. (2020)	Changes of intestinal microbiota in ovarian cancer during treatment with surgery and chemotherapy	Pilot study
ovarian cancer" AND "gut microbiota" AND "chemotherapy"/ "ovarian cancer" AND "intestinal microbiota" AND "chemotherapy"			
	Chase et al. (2015)	vaginal and gastrointestinal microbiomes in gynecologic cancers: carcinogenesis, therapy related adverse-effect and treatment outcomes	Review
	Perales-Puchalt et al. (2018)	Effect of cisplatin administration on the composition of intestinal and fecal	Pre-clinical study: in vitro and

(continued on next page)

Table 1 (*continued*)

Leterature Search	References	Clinical setting	Type of study
		transplant for the treatment of chemotherapy-associated intestinal damage.	mouse models
	Tong et al. (2020)	Changes of intestinal microbiota in ovarian cancer during treatment with surgery and chemotherapy.	Pilot study
ovarian cancer" AND "gut microbiota" AND "surgery"/ "ovarian cancer" AND "intestinal microbiota" AND "surgery"			
	Tong et al. (2020)	Changes of intestinal microbiota in ovarian cancer during treatment with surgery and chemotherapy	Pilot study

of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) in the peripheral blood. The increased production of cytokines can promote the epithelial-mesenchymal transition (EMT), resulting in the development of advanced OC (Xu et al., 2019). Furthermore, the association between gut microbiota diversity and immunity suggests the exciting potential to develop microbiome-based therapy regimens for various malignancies, including gynecological cancers (Łaniewski et al., 2020). A study in mice models demonstrated the efficacy of administering a healthy gut microbiota to improve patient well-being and completion of chemotherapy (Perales-Puchalt et al., 2018). Indeed, emerging scientific evidence indicates either the existence of a correlation between changes in the gut microbiota and the adverse effects/response of chemotherapy or a possible correlation between surgical radicality and the microbiota (Tong et al., 2020).

3.2. Gut microbiota and ovarian cancer treatment: systemic therapy

3.2.1. Gut microbiota and chemotherapy

It has been demonstrated that the microbiome affects the efficacy of cancer therapies, with a challenging relationship between gut microbiota and cancer treatments, including chemotherapy, immunotherapy and radiotherapy (Tong et al., 2020; Routy et al., 2018a; Uribe-Herranz et al., 2020). Several mechanisms which can potentially influence the chemotherapy efficacy have been identified, such as translocation, immunomodulation, metabolism, and enzymatic degradation, depending on the type of therapy (Alexander et al., 2017). In particular, translocation describes the process through which commensal or pathogenic bacteria pass across the gut barrier into the systemic milieu, where they can contribute to the morbidity of chemotherapy. Cyclophosphamide and doxorubicin cause shortening of intestinal villi, focal accumulation of inflammatory cells and discontinuity of the intestinal barrier, with accompanying translocation of commensal bacteria into secondary lymphoid organs in mice models (Alexander et al., 2017). Furthermore, an intestinal mucosal inflammation status has been found in patients treated with anti-cancer therapies, possibly due to the development of intestinal micro-ecological disorders caused by chemotherapy (Perales-Puchalt et al., 2018).

However, only a few studies explored the changes in the gut microbiota of patients receiving systemic therapies for OC. Our literature search for "ovarian cancer" AND "gut microbiota" (or "intestinal microbiota") AND "chemotherapy" yield only few relevant results (Chase et al., 2015; Perales-Puchalt et al., 2018; Tong et al., 2020). In this section, we also reported the most pertinent evidence regarding the impact of microbiota on the most frequently used drugs in OC treatment (Table 2).

Nowadays, platinum-based chemotherapy following primary debulking surgery plays a primary role in the management of OC. Platinum-based regimens could significantly affect the intestinal microbiota, leading to increased adverse effects and a reduced efficacy (Perales-Puchalt et al., 2018; Alexander et al., 2017). The studies reported that platinum-based drugs have antibiotic effects on Gram-negative and Gram-positive bacterial strains, including some Bacillus and E. coli (Joyce et al., 2010). Zhao et al. demonstrated that altered intestinal microbiota, particularly the reduction of Firmicutes coloniae, would play a role in causing cisplatin-associated adverse effects, such as body weight loss and cardiac dysfunction (Zhao et al., 2018). Moreover, it has also been demonstrated that cisplatin may damage the intestinal mucosa through DNA binding and crosslinks formation that impairs DNA replication (Gori et al., 2019).

Besides, a decrease in Bifidobacterium and Lactobacillus with a concomitant increase in E. coli and Staphylococcus in patients treated with cisplatin or carboplatin was associated with diarrhea and increased levels of nuclear factor-kappa light chain enhancer of activated B cells (NF-κB), interleukin-1 beta (IL-1β), and TNF (Stringer et al., 2013). In this context, the use of lactobacillus supplementation can be evaluated. It seems to prevent cisplatin-induced side effects such as diarrhea and cardiotoxicity by inhibiting inflammation pathways (Zhao et al., 2018). Furthermore, a pre-clinical study reported that the dysregulation of the intestinal flora due to platinum-based chemotherapy favors adverse effects. This event is due to the pro-inflammatory state and induces a lower response to chemotherapy (Iida et al., 2013).

In the platinum-resistant setting, a correlation was found between chemotherapy and gut microbiota changes. In this context, recent studies support the hypothesis that paclitaxel could interfere with the intestinal barrier, decreasing the number and function of beneficial gut bacteria. Moreover, the reduction in A. muciniphila coloniae seems to be associated with the peculiar taxanes-induced neuropathic pain (Ramakrishna et al., 2019).

Concerning gemcitabine, it was found that Gammaproteobacteria can be involved in drug resistance by metabolizing the drug in its inactivate form through the expression of an isoform of the bacterial enzyme cytidine deaminase, the cytidine deaminase long-form (CDDL) (Geller et al., 2017; Panebianco et al., 2018).

Finally, cyclophosphamide is associated with a decrease in the relative abundance of Lactobacilli and Enterococci, and it can disrupt the mucosa integrity. This event results in the translocation of gram-positive bacteria across the epithelial barrier with a relative abundance of these germs in the mesenteric lymph nodes and in the spleen. In these sites, they stimulate the production of interleukin-17 (IL-17), interferon gamma (IFN-gamma) and IL-17 producing T-helper cells (Th17). The pro-inflammatory status generated by gram-positive bacteria reduces Th17 responses and resistance to cyclophosphamide (Viaud et al., 2013).

3.2.2. Gut microbiota and poly (ADP-ribose) polymerase (PARP) inhibitors

A correlation was found between changes in the intestinal microbiota and PARP-inhibitors that have represented a recent breakthrough innovation in OC management. The most common adverse events of PARPis, such as nausea, vomiting, diarrhea and constipation, seem to be related to changes in gut microbiota (Vida et al., 2018). Particularly, PARP1 deficiency was associated with a modulation of the colonic microbiota of the host that may cause an expansion of protective microbiota Clostridia clusters IV and XIVa and a concomitant increase in the frequency of mucosal CD4(+) CD25(+) Foxp3(+) regulatory T cells (Larmonier et al., 2016). Further studies are necessary to better understand the microbiome-related toxicities and how to overcome them to develop safe and effective therapies.

Table 2
Impact of microbiota on drugs frequently used in the ovarian cancer treatment.

Reference	Drug	Clinical setting	Impact of/on microbiota
Perales-Puchalt et al. (2018)	Cisplatin	Platinum-sensitive	healing of the intestinal mucosa and increasing bacterial translocation and neutrophilia, consequent low mucus production.
Joyce et al. (2010)	Cisplatin	Platinum-sensitive	antibiotic effects on both Gram-negative and Gram-positive bacterial strains, including some Bacillus and E. coli.
Zhao et al. (2018)	Cisplatin	Platinum-sensitive	decreased Firmicutes: cause of cisplatin-associated adverse effects, such as body weight loss and cardiac dysfunction.
Gori et al. (2019)	Cisplatin	Platinum-sensitive	Cisplatin: crosslinks that impair DNA replications of intestinal mucosa.
Stringer et al. (2013)	Cisplatin/ Carboplatin	Platinum-sensitive	Decrease in Bifidobacterium and Lactobacillus/concomitant increase in E. coli and Staphylococcus: increased levels of NF-κB, IL-1β and TNF and diarrhea.
Iida et al. (2013)	Platinum-based agents	Platinum-sensitive	dysregulation of the intestinal flora: pro-inflammatory state, lower response to chemotherapy.
Vida et al. (2018)	Parp-inhibitors	Platinum-sensitive	Changes in gut microbiota composition in Parp-knockout mice associated with inflammation and diarrhoea.
Larmonier et al. (2016)	Parp-inhibitors	Platinum-sensitive	PARP1 deficiency: expansion of SCFAs producing bacteria and increase in the mucosal regulatory T cells.
Ramakrishna et al. (2019)	Paclitaxel	Platinum-resistant	interference with the intestinal barrier and could decrease the number of beneficial gut bacteria, and their function; asspcoation between the decrease of A. muciniphila and taxanes-induced neuropathic pain.
Geller et al. (2017)	Gemcitabine	Platinum-resistant	Gammaproteobacteria: expression of CDDL → metabolization of gemcitabine in its inactive form.
Panebianco et al. (2018)	Gemcitabine	Platinum-resistant	Gammaproteobacteria: expression of CDDL → metabolization of gemcitabine in its inactive form.
Viaud et al. (2013)	Cyclophosphamide	Platinum-resistant	pro-inflammatory status generated by gram-positive bacteria is responsible of the reduction of Th17 responses and resistance to cyclophosphamide.

Abbreviations: nuclear factor kappa light chain enhancer of activated B cells (NF-κB); interleukin-1 beta (IL-1β); tumor necrosis factor (TNF); poly(ADP-ribose) polymerase (PARP); short-chain fatty acids (SCFAs); cytidine deaminase long form (CDDL); T-helper cells (Th17).

3.2.3. Gut microbiota and immunotherapy

Several clinical trials are examining the role of checkpoint inhibitors in different OC treatment settings. No studies about the correlation between OC, immunotherapy, and gut microbiota have been published so far. Therefore, we conducted a comprehensive literature search for articles published in English through search terms "gut microbiota" AND "immunotherapy" to analyze this issue.

The gut microbiome has been shown to influence immunotherapy by mediating T cell activation, increasing T cell priming and accumulation in the tumor site. Interactions between bacteria and the host immune system are critical factors in patient responsiveness to checkpoint inhibitors (Routy et al., 2018a). Early studies on microbiota demonstrated that the crosstalks are bidirectional and microbiota can also regulate the immune response to cancer cells. In fact, it has been reported that intestinal flora is required for the efficacy of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blockade. Furthermore, the use of antibiotics during immunotherapy could compromise the antitumor effects of CTLA-4–specific antibodies (Vétizou et al., 2015). The interaction between microorganism-associated molecular patterns and the pattern recognition receptors of the innate immune system has been shown to be the mechanism that can modulate therapy responses (Kamada et al., 2013). For example, B. fragilis polysaccharides can enhance antitumor immunity (Vétizou et al., 2015), and Bifidobacterium could improve dendritic cell function and tumor-killing skills of cytotoxic T cells (Sivan et al., 2015). In addition, the microbiome can be an important target for managing therapeutic toxic effects or immune-related adverse events (irAEs) (Alexander et al., 2017). A significant proportion of patients treated with immune checkpoint inhibitors had experienced treatment-limiting toxicities with anti-programmed death protein-1 (PD-1) (16 %) and anti-CTLA-4 (27 %), also when administered in combination therapy (65 %) (Larkin et al., 2015). Several pre-clinical and clinical studies have been conducted to explore the influence of the gut microbiota on immune checkpoint blockade toxicity (Vétizou et al., 2015; Chaput et al., 2017; Dubin et al., 2016; Frankel et al., 2017; Gopalakrishnan et al., 2018a). However, although several taxa are phylogenetically related, no perfect overlap between specific bacteria and immunotherapy-related toxicity was found among these published studies. The impact of the gut microbiota on immune-therapeutic response is well documented, probably influenced by dietary and lifestyle factors that could explain some of the differences in bacterial taxa observed across the studies (Gopalakrishnan et al., 2018b). Recently, some studies reported a negative impact of common concomitant medications (steroid, PPIs, antibiotics) on gut microbiota in immunotherapy-treated patients with solid tumors (Rossi et al., 2019; Cortellini et al., 2020).

3.3. Gut microbiota and ovarian cancer treatment: surgery

While several studies have demonstrated a correlation between abdominal surgery and gut microbiota modification in colon cancer, only one pilot study has shown a correlation between OC surgery and changes in the gut microbiota. In particular, the composition and diversity of intestinal microbiota in post-operative OC patients significantly differ from that of pre-operative patients. A higher prevalence of Proteobacteria in post-operative fecal samples than in the pre-operative ones (Tong et al., 2020). This study confirms the findings of Chen et al. in patients diagnosed with colon cancer undergoing surgery (Kong et al., 2019). A drastic increase of Enterobacter and Klebsiella and a decrease in short-chain fatty acids (SCFAs) producing bacteria were reported in these patients, such as Bacteroidetes, Faecalibacterium, Blautia, Roseburia, and Prevotella (Deng et al., 2018). Similarly, Tong et al. demonstrated a significant reduction of Bacteroides and Firmicutes in OC patients receiving radical surgery (Tong et al., 2020).

This bacteria imbalance leads to a dysbiosis responsible for a pro-inflammatory state of the gastrointestinal tract. The increase in Proteobacteria is a potential biomarker of intestinal inflammation (Tong

et al., 2020), also worsened by the reduction of SCFAs producing bacteria which have an anti-inflammatory, antitumor, and immunoregulatory role in the gastrointestinal tract (Routy et al., 2018b). Furthermore, an increase in Proteobacteria, particularly Acinetobacter spp, has been associated with inflammation-linked genetic profiles and the antibacterial-response genes seem to be involved in OC tumor progression. Moreover, the microbial composition changes may also impact on the local tumor immune-microenvironment. However, the mechanisms involved in tumorigenesis or progression of OC require further research (Zhou et al., 2019).

4. Conclusion

In the era of precision medicine, working knowledge of the microbiome may play a role in understanding if the modulation of gut microbiota may impact clinical practice treatment paradigms and represent a novel and important adjunct to current anticancer strategies. In recent years, several pharmaco-microbiomics studies have underlined the potential role of gut microbiota analysis to predict patients' response to treatments, allowing a more personalized approach based on the microbiota host environment (Alpuim Costa et al., 2021). Recent studies investigate the potential role of gut microbiota on OC pathogenesis and its relationship with efficacy and adverse effects of cancer therapies, either surgical and medical treatments (Chen et al., 2021). In this context, a recent pilot study suggests a possible relationship between gut microbiota and therapeutic response, with distinct dynamics of alpha and beta diversity and differences in the relative abundance trends of certain taxa in platinum-sensitive and platinum-resistant OC patients (D'Amico et al., 2021).

In conclusion, well-designed clinical studies with a robust translational component, are required to better address these issues and, even more interesting, to evaluate the potential preventive implications of microbiota in OC. According to recent literature, the relationship between gut microbiota and OC has to be considered not only a further element of knowledge about this tumor. In our opinion, it may help physicians in clinical practice predicting efficacy and therapeutic response for OC treatment in the near future.

Author contributions

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