CHAPTER 04

Investigating the Role of Immunotherapy in the Management of Ovarian Cancer

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SUMMARY

Cancer is a medical condition defined by the uncontrolled division and growth of abnormal cells in the body. The aberrant cells give rise to masses known as tumors, which can invade the nearby tissues and spread to other distant regions in the body. The impact of cancer is notable, as it halts normal cellular functions and can lead to severe health risks. Ovarian cancer (OC) is a complex and heterogeneous disorder with certain histological subtypes, indicating substantial challenges in the on-time detection and treatment. The asymptomatic nature of early-stage OC frequently results in late diagnosis, thereby contributing to its elevated mortality rate. OC subtypes exhibit variations in identifiable risk factors, cells of origin, molecular compositions, clinical features, and treatment approaches. Immunotherapy has emerged as a promising treatment for the amelioration of various kinds of cancers, operating the body's immune system to combat different lethal diseases. Certain immunetherapy approaches such as chimeric antigen receptors (CAR) T cell therapy and checkpoint inhibitors (CKI) possess the ability to activate as well as enhance the immune response facilitating improved identification and elimination of cancer cells (CCs). In contrast to conventional treatments, immune therapy holds the promise of enhanced effectiveness with potentially reduced side effects. Despite advancements in treatment approaches such as surgery and chemotherapy, managing advanced-stage OC remains a significant clinical challenge. Therefore, in this chapter, we will explore the possible role of immune therapy in the management of OC.

INTRODUCTION

Cancer is among the complex group of diseases that arise from the unregulated development and division of an aberrant group of cells throughout the body. These irregular cells, commonly recognized as cancer cells (CCs) which can infiltrate and disrupt the normal physiological function of tissues as well as organs. Carcinogenesis is the process of cancer development that encompasses the accumulation of genetic mutations over time, typically influenced by a combination of genetic predisposition and ecological factors (Woodruff, 2007). At the molecular level, cancer begins when normal cells undergo genetic changes that enable them to evade the body's regulatory mechanisms, leading to unchecked cell proliferation. This alteration can affect key genetic elements responsible for regulating the cell cycle, DNA repair, and apoptosis, the programmed cell death process (Akbar & Ijaz, 2024). The accumulation of genetic impairments gives CCs a survival advantage, allowing them to outpace normal cells in growth and survival (Declares & Harrington, 2020). Cancer is a heterogeneous disease, with numerous types distinguished by the tissue or organ of origin. Each type has its own unique set of characteristics, progression patterns, and treatments approaches. Early detection and diagnosis play a crucial role in improving outcomes, as cancer is often more manageable when identified at an earlier, localized stage (Schaaij-Visser et al., 2013).

Ovarian cancer (OC) is a form of malignancy that primarily initiates in the ovaries. During its initial stages, this disorder is frequently unnoticed, as symptoms may be vague or non-specific (Lengyel, 2010). However, as the disease progresses, particular signs i.e., pelvic discomfort, abdominal bloating, changes in bowel habits and a regular need to urinate may arise. OC can affect women of all ages, but the risk escalates with age, exhibiting a higher incidence in women over 50 (Curtin et al., 2013). The development of OC is intricate, involving wide range of factors i.e., family history, genetic mutations as well as hormonal influences, contributing to an increased risk. Certain subtypes of OC i.e., epithelial OC, are more prevalent and can be exceptionally challenging to diagnose in the artery (enclaves & Harrington, 2020). The diagnosis is indispensable for effective treatment as well as substantial outcomes (Lengyel, 2010).

Immunotherapy is a remarkable methodology in cancer management that boosts the body's immune system to destroy CCs. The immune system, which normally enables the body to fight against infection and foreign substances, can be operated to recognize as well as attack CCs. In contradiction to traditional cancer treatments i.e., chemotherapy and radiation, immunotherapy operates by accelerating the natural efficacy of the immune system to differentiate and eliminate CCs (Par

How to Cite: Nazir N, S Shamshad, A Muneer, A Ijaz, M Fatima, R Tahir, M Gulfam & M Awais, 2024. Investigating the role of immunotherapy in the management of ovarian cancer. In: Zoology: Advancements and Research Trends (Ijaz MU, N Ehsan, M Imran & S Yousaf, eds): FahumSci, Lahore, Pakistan, pp: 23-30. ISBN: 978-627-7745-02-8. https://doi.org/10.61748/Zool.2024/04

doll, 2003). One key aspect of immune therapy incorporates utilizing immune CKI. These are particular drugs that impede certain protein factors on the outer boundary of immune cells (ICs) and CCs, averting them from constraining the immune system's response. By controlling the different processes immunotherapy enables the immune system to analyze as well as attack the CCs. Immune CKI has demonstrated remarkable success in treating various cancers, including lung cancer, melanoma, and certain types of kidney as well as bladder cancers (Margolick et al., 2014).

Besides immunotherapy incorporates adaptive cells (ACTs) transfer, where ICs i.e., T cells (TCs) are derived from the patient, changed in the laboratory to improve their capability to target CCs, and then reintroduced into the body of affected individual. Furthermore, this approach has confirmed potential outcomes in the management of certain blood cancers i.e., lymphoma and leukemia (Rosenberg et al., 2008). While immunotherapy has demonstrated substantial success in the treatment of some cancers, its potential may vary among different individuals and cancer types. Therefore, in this chapter we will examine the role of the immune system in the management of OC.

MEDICAL HETEROGENEITY OF OC

OC exhibits substantial heterogeneity i.e., a characteristic that influences its response to the treatment as well as prognosis. Heterogeneity refers to the existence of certain cell populations in the tumor, each with particular genetic as well as molecular infrastructure. This variability induces a profound obstacle against developing potent treatment approaches, because different types of OC may respond in different ways to standard therapies (Kroeger & Drapkin, 2017). OC is broadly divided into various histologic types i.e., endometrioid, serious, clear cell as well as mucinous. Every subtype demonstrates particular genetic alterations and molecular characteristics, contributing to the observed heterogeneous profile. The response to conventional treatments i.e., surgery as well as chemotherapy, may vary substantially among aforementioned subtypes (So slow, 2008; Vaughan et al., 2011).

The efficiency of management approaches substantially influences the prognosis as well as survival rates of patients diagnosed with OC. Surgical interventions i.e., debulking surgeries that aim to remove as much tumor tissue as possible are essential in the primary phases of the disease. Additionally, the integration of chemotherapy, often in combination with surgery, has been a cornerstone in managing OC (Chandra et

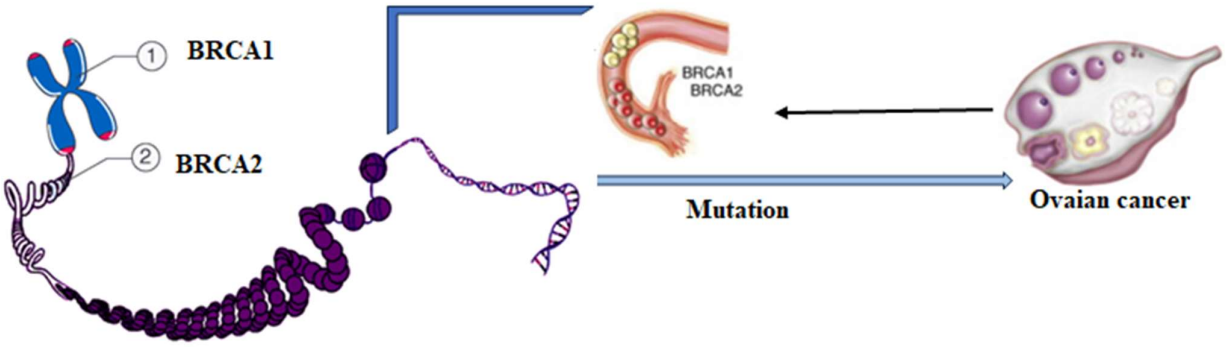

Fig 1. Genetic alterations and ovarian cancer

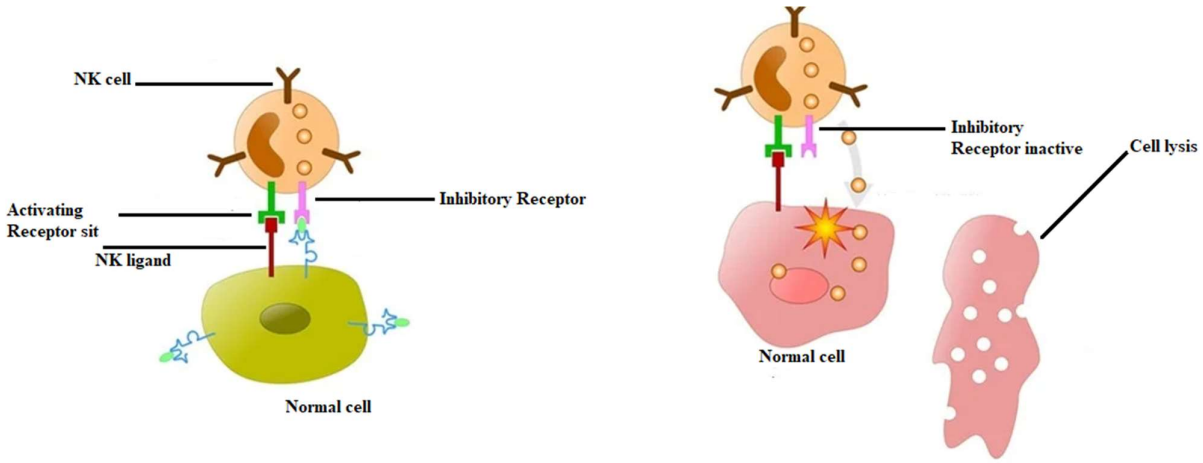

Fig 2. NK cell and removal of abnormal cells

al., 2019). One of the foremost challenges in managing OC is the frequent diagnosis at an advanced stage, often resulting in limited treatment options and diminished survival rates. Unlike some other cancers, OC lacks early symptoms that are easily recognizable, leading to delayed detection (Badgwell & Bast, 2007). OC is disreputable for its non-specific symptoms in the primary phases, which may incorporate abdominal pain, bloating and alterations in urinary habits. These symptoms are frequently unnoticed or attributed to more benign conditions, contributing to the late detection of the disorder.

By the time symptoms become noticeable, the cancer may have already progressed to an advanced stage, complicating treatment strategies (Jayde et al., 2010). Late-stage diagnosis significantly influences the success of treatment interventions. Advanced OC often necessitates more effective therapeutic approaches, such as extensive surgery and intensive chemotherapy, which may lead to increased treatment related complications. Early detection is crucial for implementing less invasive treatments and achieving more favorable outcomes (Jelovac & Armstrong, 2011).

OC is characterized by a multitude of genetic alterations that drive tumorigenesis. Mutations in genes such as BRCA1 and BRCA2 are frequently implicated in OC development (Welcsh & King, 2001) as shown in Fig 1. The molecular and genetic diversity observed in OC highlights the effectiveness of personalized medicine. Investigation of treatment regimens based on the specific genetic makeup of an individual's tumor holds the potential to enhance treatment efficacy and reduce unnecessary side effects (Modugno & Edwards, 2012). Furthermore, targeted therapies, including anti-angiogenic agents, have emerged as promising ways in OC treatments (Mirza et al., 2020). These therapies involve specific molecular vulnerabilities in CCs, providing a more precise and effective approach. Precision medicine, incorporating genomic profiling and biomarker analysis, enables the identification of patients who are likely to benefits from these targeted interventions enables the identification of patients who are likely to benefit from these targeted interventions (Faulkner et al., 2020).

FUNDAMENTALS OF IMMUNOTHERAPY

Immunotherapy has emerged as one of the innovative approaches in cancer treatment, accelerating the body's own IS to combat against cancer. The immune system operates as a vigilant defender to counteract abnormal cells, incorporating those that may participate in the development of cancer (Raghani et al., 2023). The immune system exhibits certain specialized cells i.e., TCs and natural killer (NK) cells, that possess the capability of recognizing and eradicating abnormal cells as illustrated in Fig 2. These cells are continually involved in the maintenance of the body's defensive action against cellular abnormalities, including mutations that may lead to cancer. The immune system's ability to distinguish between healthy and aberrant cells is a crucial aspect of cancer surveillance (Wu et al., 2020).

It is revealed that the key to cancer investigation is the mechanism of antigen appearance, wherein ICs present fragments of abnormal proteins, known as antigens, on their surface. This presentation of antigen acts as a signal to other ICs, stimulating an immune response to counteract the recognized aberrant cells. The association among numerous ICs accelerates a targeted attack that causes amelioration of potential risks to the body's homeostasis (Garg et al., 2010). The immune system's substantial memory capacity ensures a quick as well as specific response upon encountering familiar antigens (Timmis et al., 2004). This memory function is indispensable in averting the recurrence of cancer as well as contributes to the accomplishment of immunotherapeutic interventions, which aim to stimulate and augment the immune system's potential to recognize and target CCs (Kalinski et al., 2013).

Immune checkpoint (CP) regulation

Immune CP regulation acts as the indispensable mechanism for the maintenance equilibrium of IS, ensuring its potential to defend the body against various threats while preventing unwarranted attacks on normal tissue. This mechanism incorporates a series of CP or regulatory pathways that regulate the activation as well as inhibition of IR (Loftus et al., 2022) as shown in fig 3. The immune system is a remarkable network of cells, tissue, and molecules that is employed together to protect the body from infections, foreign invaders as well as aberrant cells. To prevent extensive immune response that could halt normal tissue, the immune system has evolved CP molecules that act as brakes to control TCs activity (Modjtahedi & Clarke, 2007). Two prominent immune CP are CTLA-4 and PD-1 along with ligand PD-L1. CTLA-4 acts initially in the immune response by mitigating the activation of TCs in the lymph nodes. PD-1, on the other hand, serves as an indispensable element in peripheral tissue, suppressing TCs activity as well as preventing ICs from attacking normal cells (Quezada & Peggs, 2013).

CCs often employ these natural CP to evade detection as well as destruction by the immune response. By upregulating CP molecules and their ligands CCs can halt the immune response, allowing them to proliferate unchecked. This ability to evade IS is a hallmark of cancer and highlights the significance of understanding immune CP regulation in developing effective cancer therapies (Man et al., 2013). The field of cancer has garnered a significant shift with the arrival of immune CKI (ICKIs).

These drugs target and block the CP, releasing the brakes on the immune system and releasing a potent anti-tumor immune response. Among these are antibodies that inhibit CTLA-4 (e.g., ipilimumab) or PD-1/PD-L1 (e.g., nivolumab) have shown extraordinary effect in treating different cancers (Jiang et al., 2021).

Immune CP inhibition works by disrupting the communication between CCs and TCs, thereby reactivating the IS against the tumors. CTLA-4 inhibitors enhance the activation of TCs, in the lymph nodes, while PD-1/PD-L1 inhibitors discharge TCs in the tumor microenvironment. These dual approaches ensure a comprehensive immune

Table 1. IT Strategies in Cancer Treatment

Checkpoint and therapies	Principal	Examples	References
Immune CP Inhibition	This approach targets immune CPs to release the brakes on the immune system	PD-1/PD-L1 inhibitors	Wilky, 2019
ACTs Therapies	Involves the extraction and genetic modification of a patient's ICs	CAR T-cell therapy	Chruściel et al., 2020
Cytokine-Based immune system	Utilizes cytokines to stimulate the immune system to counteract cancer	IL-2	Samadi et al., 2023
TVCs	Designed to stimulate the immune system to recognize and attack CCs by using tumor-specific antigens	Sipuleucel-T	Candeias & Gaipl, 2016
Oncolytic Viruses	Engineered to selectively infect and destroy CCs	T-VEC	Howells et al., 2017

response against CCs at different stages of the immune cycle (Wei et al., 2018).

IT in targeting various components of the IS

The versatile property of immunotherapy extends beyond immune CP inhibition, encompassing a broad spectrum of approaches that target different components of the immune system. This diversity allows for a regulated and complicated approach to cancer treatment highlighting the unique characteristics of each patient's immune response and tumor profile (Wilky, 2019). ACTs therapies involve the extraction and modification of a patient's own ICs i.e., TCs, to improve their anti-tumor activity. Chimeric antigen receptors (CAR)-T-cell therapy is a notable example that involves genetically modifying TCs to express receptors that specifically recognize CCs surface antigens. The modified TCs are then infused back into the patient, where they seek out and destroy CCs (Chruściel et al., 2020). Cytokinesis is signaling proteins that regulate immune response. Immunotherapies using cytokinesis such as IL-2 and interferon-alpha, aim to stimulate the immune system and enhance its anti-tumor activity. While these therapies have shown efficacy in certain cancers, their use is often accompanied by side effects, prompting ongoing efforts to refine and optimize their application (Samadi et al., 2023).

Furthermore, therapeutic vaccines (TVCs) aim to stimulate the immune system to recognize and attack CCs. Unlike preventive vaccines that prevent infections, TVCs are designed to target existing CCs. These vaccines typically contain tumor-specific antigens, encouraging the immune system to accelerate a targeted and sustained response against the cancer (Candeias & Gaipl, 2016). Oncolytic viruses are engineered to selectively infect and destroy CCs, triggering an immune response against the tumor. This dual mechanism of action makes oncolytic viruses a promising agent in cancer immunotherapy. These viruses not only directly target CCs but also induce are immune-mediated anti-tumor response, enhancing the effectiveness of the treatment Table 1.

IMMUNOTHERAPY IN OVARIAN CANCER

A significant challenge in the successful deployment of cancer immune therapy for OC patients lies in the immunosuppressive (IMSP) tumor microenvironment. Even when immune therapy generates substantial numbers of neoplasm-specific TCs in patients, these cells can face difficulties in effectively eradicating tumor targets in vivo (Morand et al.,2021). Previous investigations have identified key immune resistance pathways in OC. These mechanisms comprise extrinsic suppression of CD8þ effector cells by modulatory TCs, metabolic deregulation via tryptophan catabolism by the immunoregulatory enzyme, engagement of the inhibitory receptors PD-1 by the ligand PD-L1/B7-H1, and the emergence of antigen loss variants. Additionally, myeloid-derived suppressor cells (SCs) and inhibitory cytokines such as TGF-b contribute to this IMSP network (Pawłowska et al., 2023).

In various cancer systems, evidence has shown that the expression of ICKIs receptors by TCs is one of the most significant mechanisms through which tumor evades or dampen host immunity (Tsai & Hsu, 2017; Hayat et al., 2024). These receptors, including PD-1 negatively regulate TCs function. Interfering with PD-1 has demonstrated clinical benefit in several human cancers. CTLA-4 modulates TCs priming and activation, leading to the expansion of auto-reactive TCs, including tumor-specific TCs (Beenen et al., 2022). Anti-CTLA-4 therapies are associated with more significant immune-related toxicities compared to PD-1 blockade. PD-1 is a cell surface receptor interacting with known ligands i.e., PD-L1., resulting in the inhibition of TCs signaling and cytokine production (De Velasco et al., 2017).

Blocking these inhibitory receptors (IRCs) with specific antibodies aims to reinstate existing antitumor responses through strategies such as inhibiting IMSP receptors expressed by activated T lymphocytes and inhibiting the principal ligand of these receptors. While these CP blocking antibodies have shown promise in mediating tumor regression in melanoma and other solid tumors, their response rates in OC have been modest (Turnis et al., 2015). Despite the promising initial results of CKI in OC, they are relatively uncertain compared to the remarkable outcomes reported for melanoma and bladder cancer. Potential reasons for the limited antitumor efficacy in OC include low intrinsic tumor immunogenicity. It is demonstrated that multiple IRCs are often co-expressed on tumor-antigen specific TCs (Mancini et al., 2021) Table 2.

In OC, cells specific to tumor antigens exhibit co-expression of PD-1 and demonstrated impaired production of IFN-c in comparison to cells that express PD-1 alone. Blockade of PD-1ex-vivo restored effector function to a greater extent than single CP blockade, suggesting that monotherapy may not be sufficient for eliciting a robust

antitumor response (Lalami & Awada, 2016). It is reported that the blockade of PD-1 alone conferred a compensatory upregulation of the other checkpoint, enhancing their capacity for local TCs suppression. This could be overcome through combination blockade strategies. During antitumor immunity was most strongly associated with the increased number of CD8Þ TCs, the frequency of cytokine-effector TCs, reduced frequency of arginine-expressing SCs in the peritoneal tumor microenvironment (Huang et al., 2017).

To generate effector TCs with the tremendous ability to recognize tumors in vivo, cancer vaccines (CVCs) have emerged as an immunotherapeutic approach aiming to mediate the working of the immune system, extend reduction rates, and prevent further malignant growth. The biological principle underlying CVCs is to stimulate an immune response specifically directed against malignant cells, allowing for prophylactic and therapeutic application (Aly, 2012). Prophylactic vaccination seeks to boost an immune response that recognizes and eradicates CCs early to prevent malignant progression. Additionally, CVCs can serve therapeutically as a 'booster' for pre-existing antitumor immune response or activate antitumor immunotherapies administrated to the patient (Finn, 2018). The adaptability of CVCs is influenced by the nature of the tumor antigen, playing a crucial role in eliciting anticancer immune responses in various cancer immune system applications. However, identifying effective and safe vaccine targets in OC remains a major question (Wang et al., 2020).

Human tumor antigen is categorized into differentiation antigens, mutational antigens, amplification antigens, splice variant antigens, glycolipid antigens, viral antigens, and cancer testis (CT) antigens, provide potential targets for CVCs (Marth et al., 2019). CT antigens is a subclass encoded by 140 genes, are particularly promising due to their limited expression in normal tissue but high frequencies in tumor immunogenicity, and a potential role in tumor progression. Despite their poorly characterized biological function, CT antigens have become targets for CVCs in many solid tumors, including OC (Westdorp et al., 2014).

Table 2. The most significant inhibitory immune CPs in OC

CP	Function	Reference
PD-1	Negative regulation of TCs functions	Beenen et al., 2022
CLA-4	Regulate TCs priming and activation ultimately results in proliferation of auto-reactive TCs	De Velasco et al., 2017
CKI	Reinstate antitumor responses by blocking IRCs and inhibiting ligands	Turnis et al., 2015

NY-ESO-1 is one of the most spontaneous immunogenic tumor antigens, exhibits testis-restricted expression in normal tissue and immunogenicity. Studies have indicated its aberrant expression in a significant percentage of OC patients. NY-ESO-1 elicits both cellular and humoral immune response and humoral evidence suggests its potential expression in cancer 'stem cells'. Clinical trials targeting NY-ESO-1 in OC patients showed signal of clinical benefits, with a retrospective analysis indicating a 2-year survival advantage for vaccinated patients (Bodey, 2002). Advances in next generation sequencing and epitope prediction allow for the rapid identification of mutant tumor neoantigens. Efforts are ongoing to utilize these neoantigens for personalized cancer immunotherapies (Desrichard et al., 2016).

MECHANISM OF ACTION OF IT AGENTS ON OC CELLS

One of the key classes of IT agents in OC treatment is immune CKI. These agents target specific proteins on ICs and CCs, modulating the immune response to enhance the body's ability to recognize and eliminate CCs (Jiang et al., 2021). A prominent CP targeted in OC in the PD-1 and its ligand PD-l. PD-1 is expressed on the surface of TCs, while PD_L1 is often overexpressed on the surface of OC cells. The interaction between PD-1 on TCs and PD-L1 on CCs functions as a molecular brake, inhibiting TCs activity and allowing CCs to evade immune detection (Abiko et al., 2013) as shown in Fig 4.

Immune CKI including nivolumab interferes with this interaction. By blocking PD-1 these factors release the brakes on TCs, reinvigorating their capability to identify and attack OC cells. This process accelerates the anti-tumor immune response, potentially resulting in tumor regression (Babayakalı & Erbaş, 2021). Another immune CP pathway targeted in immunotherapy is CTLA-4. CTLA-4 is present on the surface of TCs as well as modulates the early stages of immune activation. OC cells can utilize CTLA-4 to decrease TCs concentration (Huang et al., 2017). Moreover, mediators including ipilimumab act by suppressing CTLA-4, averting its repressive signals. This inhibition upsurges the initiation of TCs, endorsing a robust immune response to counteract OC cells. Integrating immune CKI targeting various pathways, including PD-1 and CTLA-4, is an approach aimed at synergistically accelerating anti-tumor immunity (Huang et al., 2017). CAR T-cell therapy is one of the most prominent ACTs therapies. In this method, TCs are extracted from the patient and genetically modified to express CARs. CARs are synthetic receptors intended to recognize specific antigens present on the cell surface of OC (Zhu et al., 2017). For OC, CAR T-cell therapy targets antigens incorporating FRα, which is often overexpressed on OC cells. Once reintroduced into the affected patient, these CAR TCs appear out and attach to CCs expressing the targeted antigen, ultimately leading to their destruction (Zhu et al., 2017).

Besides, tumor-infiltrating lymphocytes (TILs) are ICs that are naturally found in tumors. ACTs therapies incorporating the isolation and expansion of TILs aim to support the patient's own immune response to counteract OC (Fanale et al., 2022). TILs are harvested from cancer tissues, selected for their specificity to antagonize CCs, and then extended outside the body. Once the TILs reach adequate numbers, they are infused back into the affected patient. The extended TILs can differentiate and attack OC cells, endorsing an upsurged and targeted anti-tumor immune response (Fanale et al., 2022).

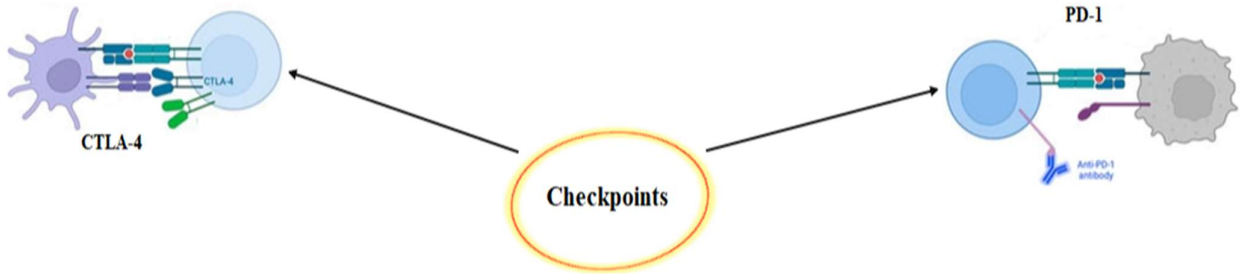

Fig 3. CPs that control the activation and inhibition of immune response

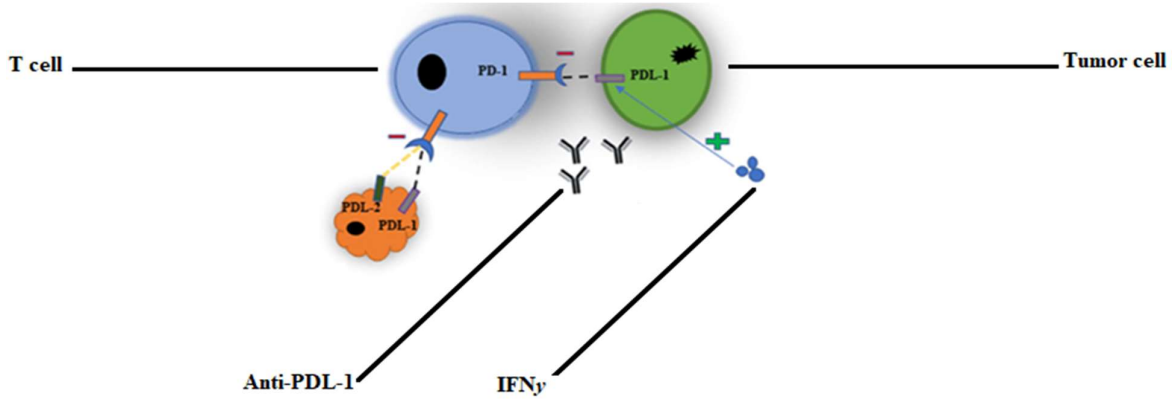

Fig 4. Interaction between PD-1 on TCs and PD-L1

TVCs represent a practical approach to stimulate the IS that enables it to recognize and boost an immune response to counteract OC cells. These vaccines typically incorporate specialized tumor antigens, encouraging the immune system to distinguish these antigens as foreign and activate an immune response against particular cells expressing them (Odunsi & Sabbatini, 2008). Besides, TVCs operate by presenting tumor-specific antigens to ICs, predominantly dendritic cells. Dendritic cells play an indispensable role in presenting antigens to TCs, originating an immune response. For OC, vaccines may contain antigens including NY-ESO-1 which are overexpressed in certain OC subtypes to alleviate their proliferation (Odunsi, 2017). The presentation of these antigens primes the immune system to distinguish and attack OC cells expressing the targeted antigens. This procedure augments the specificity of the immune response, directing it toward CCs while sparing healthy tissues (Macpherson et al., 2020).

TVCs aim not only to induce an instant immune response but also to establish immune memory. Immune memory ensures that the immune system remembers the specific antigens linked with OC. In the event of cancer recurrence, the immune system can accelerate a quicker and more potentially targeted response, contributing to long-term protection for the mitigation of the disease (Wang et al., 2020). Oncolytic viruses (OVCs) represent a novel class of immune therapy mediators that directly target and destroy CCs while concurrently triggering an immune response against the cancer (Lawler et al., 2017). OVCs are engineered to precisely replicate in CCs, ultimately leading to their deterioration. OC cells, just like many cancer conditions, often exhibit specific vulnerabilities that make them susceptible to OVCs (Russell & Barber, 2018).

The mechanism of oncolytic virus provoked cell death is immunogenic, meaning it stimulates the IS. As infected OC cells undergo cell death, they discharge signals and antigens that stimulate ICs. This stimulus enables the IS to diagnose and attack not only the infected CCs but also other CCs expressing similar antigens (Garg et al., 2015). To enhance the efficacy of OVCs, integrated strategies with immune CKI are being explored (Chiu et al., 2020). OVCs create a pro-inflammatory tumor microenvironment, and coupling this with immune CKI augments the anti-tumor IR. The combination strategy aims to overwhelm the IMSP nature of the tumor microenvironment, promoting sustained anti-cancer activity (Shi et al., 2020).

CONCLUSION

In conclusion, this chapter provides the challenges posed by OC, emphasizing its heterogenicity and late-stage diagnosis issues. The exploration of immune therapy as a potential solution provides hope for ameliorating these challenges. From immune CKI to ACTs therapies and TVCs, the diverse strategies discussed demonstrate the evolving approach to the OC treatment. Despite hurdles in the immunosuppressive tumor microenvironment, current explorations outcomes in the management of this complex disease.

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