Domande di biologia

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frontiers in Oncology

REVIEW
published: 12 March 2020
doi: 10.3389/fonc.2020.00156

Endometrial Cancer Immune Escape Mechanisms: Let Us Learn From the Fetal–Maternal Interface

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OPEN ACCESS

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Specialty section:
This article was submitted to Pharmacology of Anti-Cancer Drugs, a section of the journal Frontiers in Oncology

Received: *08 November 2019*
Accepted: *29 January 2020*
Published: *12 March 2020*

Citation:
Bruno V, Corrado G, Baci D, Chiofalo B, Carosi MA, Ronchetti L, Piccione E, Albini A, Noonan DM, Piaggio G and Vizza E (2020) Endometrial Cancer Immune Escape Mechanisms: Let Us Learn From the Fetal–Maternal Interface. Front. Oncol. 10:156. doi: 10.3389/fonc.2020.00156

The immune escape mechanisms at the base of tumor progression in endometrial cancer mimic immune tolerance mechanisms occurring at the maternal–fetal interface. The biological and immunological processes behind the maternal–fetal interface are finely tuned in time and space during embryo implantation and subsequent pregnancy stages; conversely, those behind cancer progression are often aberrant. The environment composition at the maternal–fetal interface parallels the pro-tumor microenvironment identified in many cancers, pointing to the possibility for the use of the maternal–fetal interface as a model to depict immune therapeutic targets in cancer. The framework of cancer environment signatures involved in immune adaptations, precisely timed in cancer progression, could reveal a specific "immune clock" in endometrial cancer, which might guide clinicians in patient risk class assessment, diagnostic workup, management, surgical and therapeutic approach, and surveillance strategies. Here, we review studies approaching this hypothesis, focusing on what is known so far about oncofetal similarities in immunity with the idea to individualize personalized immunotherapy targets, through the downregulation of the immune escape stage or the reactivation of the pro-inflammatory processes suppressed by the tumor.

Keywords: cancer immune escape, fetal–maternal immune tolerance, immunotherapy potential targets, immunological parallelism in cancer and pregnancy, personalized medicine

INTRODUCTION

Innate and adaptive immune response affects development and progression of cancer through a process named immunoediting (1). Similar immune-mediated processes occur at the maternal–fetal interface (2–8). There is a parallelism between biological processes behind cancer progression and those behind the maternal–fetal interface such as proliferation, invasion, and angiogenesis (2). While these processes are finely tuned during embryo implantation stages, they are conversely often aberrant in carcinogenesis. Interestingly, a recent study based on single-cell analysis

highlights that environment composition at the maternal–fetal interface parallels the pro-tumor microenvironment (TME) identified in many cancers (9), pointing to the possibility for the use of the maternal–fetal interface as a model to depict immune therapeutic targets in cancer.

Inflammation and immune tolerance are key mechanisms which ensure the proper establishment of pregnancy. The early stage of pregnancy is characterized by an inflammatory process responsible for proper implantation. This inflammatory stage should switch, in a second step, to a down-modulation of the immune response, ensuring the "non-rejection" of the semi-allogenic fetus. In pregnancy, the decidualized stromal cells, involved in the implantation process, are the gatekeepers of this key immune switching mechanism at the fetal–maternal interface, involving different immune cells, such as regulatory macrophages, natural killer (NK) cells, and T cells. In the last stage of pregnancy, and especially in activating labor, an inflammation process is required again; therefore, a new switching process is needed (10–18) (**Figure 1A**, left panel).

Several groups in the last years have shown that immunological properties acquired by both maternal–fetal interface and TME share the same molecular patterns related to the modulation of the inflammatory response involving innate and adaptive immune response (19). Tumor progression exploiting immune tuning mimics the immune maternal–fetal interface processes. In the early stage of carcinogenesis, the immune system recognizes cancer cells as non-self, inducing the proper pro-inflammatory environment to lead them to apoptosis. In a second step, the cancer cells are able to induce the switching of the immune system to an anti-inflammatory response, through different immune-editing mechanisms (20), thus leading to cancer immune escape. The fetal–maternal immune properties required to evade the immune system are limited in time and space; when labor starts, the immune system goes back to the initial steps. Conversely, the immune escape process in cancer goes on uncontrolled, and it does not revert to a pro-inflammatory feature (20) (**Figure 1A**, right panel). Therefore, the switching from immune suppression to immune activation occurring during pregnancy is lacking in carcinogenesis.

The existence of parallel situations between pregnancy and cancer gave rise to the term "oncofetal" and is common to many events. To take advantage of the knowledge of the similarities among immune regulation in pregnancy and tumor growth could lead to identification of new potential targets for cancer immunotherapy (2). Aberrations in placentation process, particularly in the modulation and tuning of the immune system, can lead to pregnancy complications; research has helped to develop the proper models to investigate immune tolerance in aberrant processes in pregnancy and to translate them to cancer investigations. Here, we summarize what is known so far about oncofetal similarities in immunity and which are the most recent and promising developments in this research area. A focus will be devoted to endometrial cancer (EC).

Therefore, this review is intended to focus on what is already known about the immune parallelisms between fetal–maternal interface immune tolerance and immune escape mechanisms during EC progression (**Figure 1B**).

FOCUS ON EC

EC is a relevant gynecological malignancy which occurs in fertile and postmenopausal women. The mean age of women affected by this tumor is decreasing; thus, the incidence in worldwide women under 40 years of age is on the rise (21). EC is linked to obesity (21), and the pandemic of obesity is a global threat. Patients with EC have a good prognosis at early-stage incidence, while the prognosis for recurrent or metastatic EC remains poor (22). It is therefore mandatory to understand the mechanisms fueling EC progression and ways to inhibiting them, to improve therapeutic chances (23). A deep knowledge of the interplay between positive and negative immunological molecular players and its timing in EC development and progression is still missing; several findings so far indicate that the immune escape mechanisms are at the base of EC progression and could be due to similar immune tolerance modulations occurring at the maternal–fetal interface (24). The EC is an ideal tumor model to study these mechanisms; EC tissue remains similar to the endometrial tissue of origin, and its related tumor progression develops in different steps, from endometrial hyperplasia to endometrioid carcinoma type 1 (grading: G1, G2, and G3), depending on its histological similarity to the physiological endometrial tissue (23). The immune escape pathways underlying the progression from physiological endometrium to carcinoma could represent new targets for personalized immunotherapy by the reactivation of the pro-inflammatory response processes suppressed by the tumor. A contribution to the immune escape in EC is also provided by the immunosuppressive interplay between regulatory T and regulatory B lymphocytes, regulatory NK, and tolerant dendritic cells, also traceable at the decidualized endometrial tissue in the fetal–maternal interface during implantation processes (24, 25).

The maternal–fetal interface and EC represent a "new" complex network where many immune cells of innate (dendritic cells, macrophages, and NK cells) and adaptive immune system cells (regulatory T and regulatory B lymphocytes) play a synergistic role in immune tolerance and immune escape mechanisms. The following part summarizes the similarities observed to date in the different cell lineages involved in the immunological processes underlying pregnancy and EC.

EC Traditional Classification and Biomolecular Classification

EC was historically classified into two different clinicopathological and molecular types: type I is the much more common endometrioid adenocarcinoma (80–90%), and type II comprises non-endometrioid subtypes such as serous, clear-cell, and undifferentiated carcinomas, as well as carcinosarcoma/malignant-mixed Müllerian tumor (10–20%) (26). Molecular data are now considered as an important part of pathologic evaluation, since type I carcinomas are associated with PTEN, KRAS, CTNNB1, and PIK3CA genetic

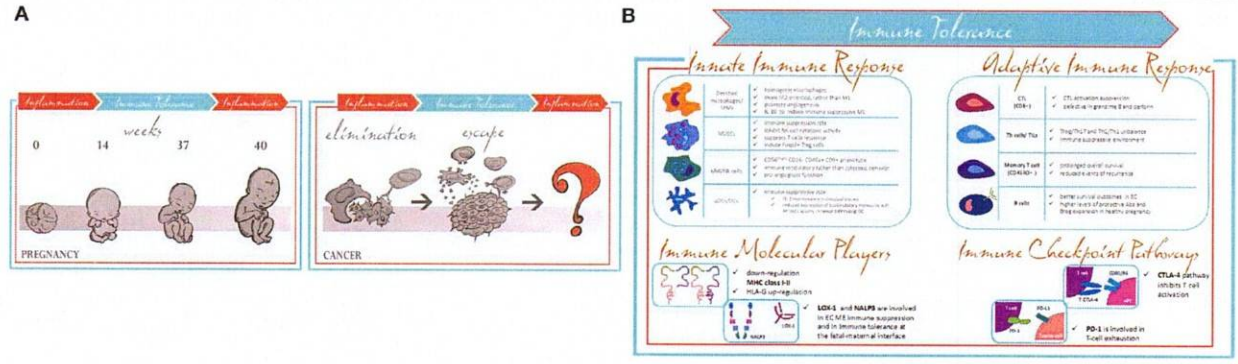

FIGURE 1 | (A) Pregnancy and cancer parallelism in switching from activation to modulation of the immune responses. **(B)** Common shared immune tolerance patterns in pregnancy and EC.

mutations and MLH1 promoter hypermethylation, whereas serous carcinomas show mostly TP53 mutations (27). Because of the limitations of this classification due to the wide molecular heterogeneity and, in turn, due to the discrepancy between the detected molecular pattern and tumor behavior, The Cancer Genome Atlas (TCGA) Research Network has gone further in the EC molecular landscape, providing more detailed molecular subclassifications, characterized, respectively by POLE mutation, mismatch repair deficiency, TP53 mutation, and a copy number low group without a specific driver mutation, each with a distinct prognosis (28): (i) POLE (ultra-mutated) tumors, (ii) microsatellite unstable (MSI) tumors, (iii) copy number high tumors with mostly TP53 mutations, and (iv) a remaining group without these alterations (29).

Histopathologic Grades (G)

GX: Grade cannot be assessed.
G1: Well-differentiated.
G2: Moderately differentiated.
G3: Poorly or undifferentiated (28).

FIGO Staging Classification

According to FIGO staging, EC is classified as below:

I Tumor confined to the corpus uteri

- IA No or less than half myometrial invasion
- IB Invasion equal to or more than half of the myometrium

II Tumor invades cervical stroma but does not extend beyond the uterus

III Local and/or regional spread of the tumor

- IIIA Tumor invades the serosa of the corpus uteri and/or adnexae
- IIIB Vaginal involvement and/or parametrial involvement
- IIIC Metastases to pelvic and/or para-aortic lymph nodes
  - IIIC1 Positive pelvic nodes
  - IIIC2 Positive para-aortic nodes with or without positive pelvic lymph nodes

IV Tumor invades bladder and/or bowel mucosa and/or distant metastases

- IVA Tumor invasion of bladder and/or bowel mucosa
- IVB Distant metastasis, including intra-abdominal metastases and/or inguinal nodes (28).

ESMO–ESGO–ESTRO Classification: Classes of Risk

The classification of risk groups defined in ESMO–ESGO–ESTRO consensus guidelines, comprehending a subdivision in low, intermediate, high-intermediate, and high risk, has been reached by a revision of the scientific literature within a consensus conference attended by a multidisciplinary panel of 40 experts. To sum up, these risk groups have been created by considering the clinicopathological prognostic factors which have an impact in identifying those patients who are at a higher risk of recurrence to properly address them to potential adjuvant therapies:

- ✓ Low-risk EC [stage I endometrioid, grades 1–2, <50% myometrial invasion, lymphovascular space involvement (LVSI) negative].
- ✓ Intermediate-risk EC (stage I endometrioid, grades 1–2, ≥50% myometrial invasion, LVSI negative).
- ✓ High-intermediate-risk EC (stage I endometrioid, grade 3, <50% myometrial invasion, regardless of LVSI status; or stage I endometrioid, grades 1–2, LVSI unequivocally positive, regardless of depth of invasion).
- ✓ High-risk EC (stage I endometrioid, grade 3, ≥50% myometrial invasion, regardless of LVSI status) (30).

MOLECULAR PLAYERS OF THE IMMUNE RESPONSE

Major Histocompatibility Complex: The Role of Human Leukocyte Antigens

Endometrial epithelial cells are potent antigen-presenting cells (APCs), while endometrial tumor cells show poor antigen-presenting capacity, leading to immune escape mechanisms.