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Editorial

Molecular and Cellular Advances in Gynecologic Cancer Research

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Gynecological cancers, including malignancies of the female reproductive system, present an enormous global burden affecting millions of women annually. Ovarian and endometrial cancers are predominantly associated with old age similar to vulvar and vaginal cancers; however, these later cancer types remain relatively rare in occurance. In contrast, cervical cancer, the most common gynecological cancer, can occur in women of any age. Although cervical cancer can be prevented by HPV (Human papillomavirus) vaccination and screening, it continues to be the most common among all gynecological cancers globally, and a staggering 565,540 new cases were detected in 2019. The highest incidence rates of cervical cancer are seen in China, India, Brazil, and the United States [1]. As estimated by the American Cancer Society, 114,810 new cases of gynecological cancers are predicted to be diagnosed in the United States in 2023, and are predicted to result in 34,020 deaths [2]. Diagnosing gynecological cancers prior to late stage disease when the tumor has already metastasized, remains the biggest hurdle to effective treatment and improved patient survival. Hence, non-invasive, blood-based liquid biopsies, as well as advanced imaging technologies such as nanoparticles coupled with photoacoustic (PA) imaging and surface-enhanced Raman spectroscopy (SERS) incorporated into gold nanorods are amongst those technologies being explored to enable early diagnosis of these cancers.

It is evident from the extensive research carried out in the last few decades, that cancer development is an extremely complex process, involving not only the aberrant proliferation of cells but also the recruitment of a wide range of other cell types in the tumor microenvironment (TME) such as immune cells, fibroblasts, platelets, and endothelial cells. Hence, the TME contains a heterogeneous mix of different cell types which the cancer cells utilize to meet their increased energy requirements and facilitate migration to form distant metastatic foci. The crosstalk between cancer cells and the cells within the TME results in changes in gene expression patterns and altered cell behavior. Such changes can ultimately aid cancer cell growth by providing a pre-metastatic niche with enhanced nutritional supply and a supporting framework for tumor development.

Recent advancements in high dimensional imaging and sequencing technologies, such as imaging mass cytometry (IMC) and NICHE-Sequencing, have enabled investigators to explore the TME in greater detail. These advances have allowed spatial tissue reconstruction, identification of gene expression programs, rare niche-specific immune subpopulations, as well as in-depth analyses of the spatial heterogeneity of marker expression and cellular interactions within the TME [3,4]. This has, in turn, facilitated the discovery of novel therapeutic targets and the development of new treatment strategies.

The past decade has witnessed the discovery of numerous important cellular markers associated with various cancers, many of which are being further explored as therapeutic targets. The PD-1/PD-L1 (programmed death 1) and CTLA-4 (cytotoxic T-lymphocyte-associated antigen 4) checkpoint blockade therapies are perhaps the most well-known of these, and have revolutionized the treatment of cancer. The development of chimeric antigen receptor (CAR) T-cells has also been proven a successful treatment strategy against hematological malignancies. (CAR) T-cells are, however, found to be largely ineffective against solid tumors, mostly due to the CAR T-cells not being able to penetrate into solid tumors. It was recently found that $CD163^+$ $Tim4^+$ tumor-associated macrophages (TAMs) present in the omentum promote ovarian cancer metastasis, and selective depletion of these cells attenuates tumor growth and metastasis [5]. Similarly, CD29 (integrin $\beta 1$), fibroblast activation protein (FAP), fibroblast-specific protein 1 (FSP1), and α-smooth muscle actin (α-SMA) are cancer-associated fibroblast (CAF) markers associated with the metastatic spread of high grade serous ovarian cancers (HGSOC). Moreover, the chemokine CXCL12β is specifically found to accumulate within the immunosuppressive CAF subset [6,7].

Another emerging concept is that of tumor-educated platelets (TEPs). When cancer cells interact with platelets in the TME, this interaction can promote changes in cancer cell gene expression and proliferation. An *in vitro* study has confirmed potent, dynamic, and bidirectional interactions between ovarian cancer cells and platelets. As a result of platelet interaction with ovarian cancer cells, tumor cells displayed altered gene expression patterns that lead to the activation of pro-angiogenic pathways [8]. Of note, platelets have also been found to alter the expression of PD-L1 on ovarian cancer cells [9].

There has also been extensive research investigating the role of non-coding RNAs such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) in regulat-

ing gene expression, mediating immunosuppression, and tumor proliferation in gynecological cancers. For example, the lncRNA nuclear paraspeckle assembly transcript 1 (NEAT1) enhances tumor growth, metastasis, and chemoresistance in gynecological malignancies by inhibiting various tumor suppressor miRNAs, thus acting as a competitive endogenous RNA (ceRNA) [10]. As a result, various downstream signaling pathways and metabolic pathways are affected by NEAT1, leading to pro-tumorigenic effects.

Therapeutic approaches currently being explored include nanoparticle-based drug delivery to enable precise targeting of tumor cells. Nanocarriers currently under study include liposomes, dendrimers, polymeric micelles, and polymeric nanoparticles. Nanotherapies are also being explored to modulate the epigenetics of ovarian cancer cells. For example, the activity of the histone methyltransferase enhancer of zeste homolog 2 (EZH2) was successfully attenuated by chitosan nanoparticle-based delivery vehicles loaded with small interfering RNA (siRNA) targeting EZH2, thereby preventing gene silencing induced by EZH2 [11]. However, carrying out large-scale clinical trials to test the safety and efficacy of new therapies continues to be a significant challenge prior to their widespread use in the clinic.

This collection on "Molecular and Cellular Advances in Gynecologic Cancer Research" includes research articles and reviews presenting cutting-edge advancements pertinent to novel cellular and molecular interactions, as well as devising efficacious therapeutic strategies. We hope readers will appreciate recent developments in this field and find this subject matter intriguing, and commit to delving deep into the intricacies of gynecological cancer.

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