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Commentary

Cancer prognosis: Considering tumor and its microenvironment as a whole

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In the past, the primary focus of cancer research has been on aspects of the tumor itself, such as oncogenes, signaling pathways, DNA mutations and methylations, and more that is within tumor cells. Although tumor microenvironment (TME) has been recognized as a pivotal influence for tumor cell proliferation and invasion [1,2], the interaction of tumor cells with the TME is regarded similar to the relationship between the "seed" and the "soil". In fact, along with our enriched knowledge and insights on cancer, the importance of TME is currently thought to be more important than we previously realized.

TME has been found to be involved in the epithelial-mesenchymal transition (EMT) of cancer cells, angiogenesis, cancer metastasis, regulation of immune infiltration and response, and the generation of therapy resistance, thereby affecting cancer treatment and prognosis [1,2]. TME consists of protean components, including malignantly transformed cells, cells of the immune system, blood or lymphatic vessels, fibroblasts, endothelial cells, pericytes, and the extracellular matrix (ECM) [1,3,4]. Studies have uncovered that dysregulated immune responses and reciprocal interactions between various cells in the microenvironment play important roles in tumor progression. For instance, tumor cells can release immune inhibitory cytokines resulting in the anergy of immune cells and the tolerance of tumor cells [2]. Stromal cells including fibroblasts and pericytes are reported to promote tumor progression through the secretion of growth factors, cytokines/chemokines, and restructuring of the ECM [1–3]. These secreted factors are involved in multiple regulatory effects of cells in TME and tumor mass. Reprogramming of tumor associated macrophages in order to enhance tumor infiltration and overcome immune suppression is also now a hot topic in preclinical research [2]. We have summarized earlier that based on our findings and those of other researchers, it could be an effective treatment approach for pancreatic cancer to target cancer-stroma interaction [4]. Recent research suggests that TME could be a critical "partner" to tumor cells. On top of that, the importance of TME has broadened its way from therapy to diagnosis and prognosis, as evidence for the communication between TME components and tumor cells influencing the prognosis of cancer treatment emerges.

Current management for colorectal cancer (CRC), a severe contributor to cancer mortality and morbidity, follows a protocol that is typical for many solid tumors: surgical resection of the tumor mass combined with adjuvant chemotherapy, including conventional chemotherapy, anti-EGFR or immune checkpoint-targeted therapies [5,6]. CRC prognosis and drug efficacy prediction relies on limited biomarkers, such as carcinoembryonic antigen–related cell adhesion molecule 5 (CEACAM5, so called CEA), cancer antigen 19-9 (CA 19-9), chromosome 18q loss of heterozygosity (18qLOH), and microsatellite instability (MSI). CEA is released from tumor cells into patient's serum, which is most often detected in CRC. Elevated CEA level is a sign of recurrence or metastasis [7]. CA 19-9 is a blood marker that may be elevated in colon cancer, but not exclusive to colon cancer [8]. 18qLOH detection is often applied in patients with CRC stage II or III and may have influence on prognosis [5]. The US National Comprehensive Cancer Network (NCCN) announced risk factors included in clinical management for CRC are BRAF/KRAS mutations and DNA mismatch repair (MMR) related to MSI, etc. [6]. Two commercial gene panels that have the potential for clinical utility are ColoPrint (an 18-gene panel, Agendia) and Oncotype DX colon assay (a 12-gene RT-PCR assay, Genomic Health) [7]. ColoPrint showed more accurate predictive power for the recurrence prediction of stage II colon cancer [9]. However, despite of the advances made in preclinical research, the importance of TME as a partner of the tumor has not yet been widely considered in clinical practice and prognosis prediction.

Liao and colleagues developed a prognostic panel utilizing R language and the machine learning method based on TME-relevant genes for stage I–III colon cancer patients, designated as the "tumor microenvironment risk score (TMRS)", which is published in EBioMedicine [10]. This is a breakthrough which includes TME genetic properties in the prediction of cancer prognosis. Zhou et al. proposed a 100-gene panel and demonstrated improved accuracy over the TNM staging system on the prediction of relapse-free survival and overall survival among colon cancer patients, which fills the clinical research gap. Moreover,

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they analyzed the gene panel prediction power on chemotherapy response and raised the possibility of using it for accurately identifying patients that could potentially benefit from adjuvant chemotherapy. In addition to colon cancer, they also extended the analysis of the TMRS panel and revealed it to be a reliable tool for prognostic prediction and chemotherapeutic decision-making in gastric cancer. Furthermore, immune checkpoint related analyses indicated that the TMRS panel enabled prediction of anti-PD-L1 and anti-PD-1 immunotherapy outcomes in both urothelial carcinoma patients and melanoma patients [10]. Zhou et al.'s work has made a paradigm shift in prognosis prediction for cancer patients.

One limitation of Zhou el al.'s work is that there is less emphasis on the tumor itself. The authors mentioned that during the analysis on the mutations of well-known suppressor genes and oncogenes such as p53, and Kras, no significant distribution was noted. Future studies that consider elements of the tumor itself and its surrounding TME components would be warranted. Moreover, clinical validation in prospective patients would also be necessary for the ultimate widespread acceptance of the TMRS gene panel.

In the era of precision medicine, prediction of patient outcomes is becoming increasingly crucial for clinical trials of adjuvant and neoadjuvant therapies, including conventional chemotherapy, targeted therapy, and immune checkpoint blockade therapy. Therefore, tumor communication with TME is an appealing topic that could add clarity to precision medicine and improve the appropriate application of new therapies to patients that would have the greatest benefit.

Conflict of interest

The authors declare no conflicts of interest.

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