ONCOIMMUNOLOGY
2022, VOL. 11, NO. 1, e2019896 (4 pages)
https://doi.org/10.1080/2162402X.2021.2019896

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AUTHOR'S VIEW

Immune sunrise: from the immunome to the cancer immune landscape

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ABSTRACT

The complex dynamics of the tumor-immune interaction during tumor progression have been characterized by integrating genomic and proteomic experiments. The Immunome, a reference compendium of markers for the majority of immune cell subpopulations was used to describe the immune landscape in cancer. The immune contexture is at the cornerstone in the success of cancer immunotherapies. Markers with the highest clinical relevance were summarized as the consensus immunoscore. This immune evaluation refines the prognosis of the patients and the chemotherapy decision-making process and was introduced as essential and desirable diagnostic criteria into three major international guidelines.

ARTICLE HISTORY
Received 7 December 2021
Revised 14 December 2021
Accepted 14 December 2021

KEYWORDS
T-cells; tumor microenvironment; colorectal cancer; prognosis; survival; immunity; immunoscore; immune landscape; immunotherapy; chemotherapy

The last two decades have been marked by a major evolution in the understanding of how tumors develop and evolve. Cancer has been for a long time considered to be a multistep disease in which the malignant transformation of normal cells occurs progressively through dynamic alterations of the genome. Collaborative efforts have enhanced the knowledge of cancer mechanistics by highlighting the role of the local immune infiltrate in shaping tumors. First investigations have demonstrated that particular immune subpopulations infiltrating tumors, like cytotoxic T cells and memory T cells, were significantly associated with the survival of the patients.[1] The intra-tumoral immune contexture (i.e., type, functional orientation, density and location of immune cells) of solid tumors, defining the cancer immune contexture, could be a dominant determinant of clinical outcome.[2] An ample effort for the characterization of the complex dynamics of the tumor-immune interaction during tumor progression has followed. We have investigated in depth the microenvironment of large cohorts of colorectal cancer patients in the attempt of having the most complete view of the intratumoral players. For this, we have integrated and analyzed multiple, heterogeneous datasets obtained from genomic and proteomic experiments performed in our laboratory, as well as shared through data repositories.

From the immunome to the immune landscape

A very important first step was to define a standardized way of analyzing the immune infiltrate that provides a systematic view of all immune subtypes, it is reproducible and easy applicable to other tumor types or other diseases. Immune cells can be identified within tissues by specific genes preferentially expressed in certain experimental conditions. Although such specific immune markers were known already, a complete analysis and comparison of the transcriptome of most frequent immune cells was not yet done. We thus collected publicly available datasets derived from purified adaptive and innate immune cell subsets and integrated them into a data matrix. To improve the biomarker selection, we compared the transcriptome of immune subpopulations also with samples derived from normal distant colon, and colorectal cancer cells. Highly distinctive transcriptional profiles of all cell types were selected as well as markers for functionally relevant groups of immune subpopulations or meta cell types like "T cells" (all T cell subtypes), T helper cells (all T helper subtypes), and Cytotoxic cells (CD8 T cells, gamma-delta T-cells (Tgd) and NK cells). This compendium profiling the majority of immune cell types constituted the Immunome, a standard reference that can be used to identify immune cells in complex tissues, healthy or diseased.[3] We have used Immunome compendium to characterize the immune reaction in colorectal tumor microenvironments, and proposed the first immune landscape of tumors (Figure 1).[3] The heterogeneity observed among the Immunome of colon cancer patients could reflect their genetic diversity that influences the generation of immune responses. Another mechanism influencing the immune cell infiltration could involve the chromosomal instability of chemokines and chemokine receptor genes. Immune densities quantified within the center (CT) and at the invasive margin (IM) of the tumor and their changes with the tumor stage were then illustrated as the immune landscape. This broad analysis revealed the impact on patient survival of all immune cells infiltrating tumors.

The Immunome was the first comprehensive compendium of markers of immune cell subpopulations. Nowadays the Immunome and other immune selections are frequently used it to investigate the immune infiltrate of multiple types of cancer[4,5] and other diseases. Extensive pan-cancer immunogenomic

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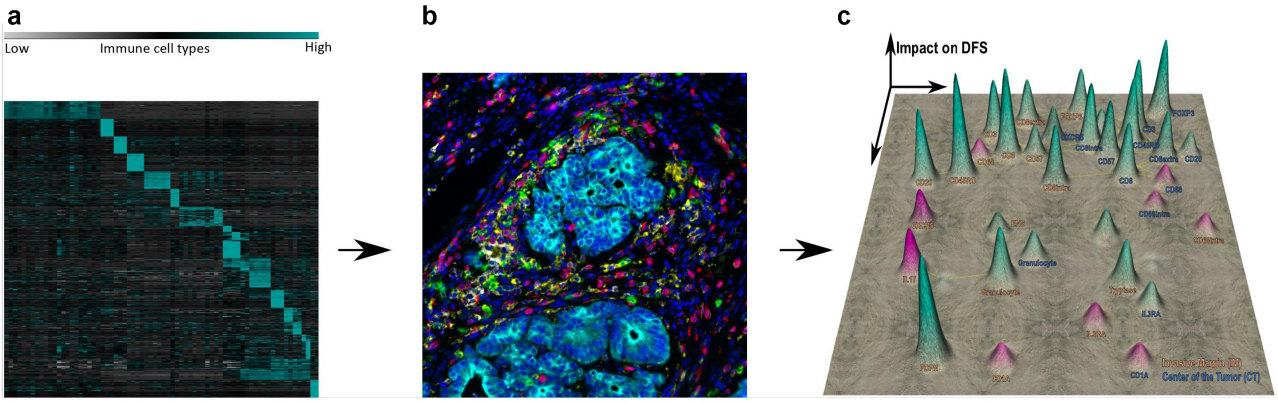

Figure 1. From the immunonome to the cancer immune landscape. (a).Transcriptome data for purified adaptive and innate immune cells (immunome). Five hundred seventy-seven cell-type-specific genes highly expressed by 28 purified immune cell populations (DCs, T cells, T helper cells, and NK cells) and by cells with common cytotoxic properties (cytotoxic cells: CD8 T cells, Tgd, and NK cells). (b) Spatial analysis and quantification of immune cell subpopulation by immunohistochemistry and digital pathology. (c) The immune landscape of cancer, illustrating the prognostic impact of immune cell subpopulations quantified by immunohistochemistry and digital pathology. The 3D visualization of the tumor immune landscape with the height of individual peaks (z axis) representing the clinical outcome visualized by log2-transformed HRs for DFS (disease-free survival). Blue (good outcome), Red (bad outcome)

analysis of The Cancer Genome Atlas (TCGA) data included the Immunome and revealed six stable, reproducible immune subtypes associated with prognosis, genetic, and immune modulatory alterations that may shape the immune environments.[5] Recent data provided evidence for the impact of germline genetics on the composition and functional orientation of the tumor immune microenvironment, and to the immune landscape of cancer.[6] Tumor immune environment plays an important role in prognosis as well as response to therapy, thus the definition of the immune subtype of a tumor is essential in predicting disease outcome as opposed to relying solely on cancer-related features.[5] To facilitate such analyses, Immunome and other gene sets and tools were benchmarked into the ConsensusTME method.[4]

The consensus immunoscore

Moreover, markers of T cells and cytotoxic T cells, immune cells with the highest clinical relevance, can be now quantified in the CT and IM and summarized as a novel scoring system, the consensus Immunoscore. This is the first worldwide recognized and standardized consensus assay to quantify the preexisting immunity, internationally validated with the help of the Society for Immunotherapy of Cancer (SITC). Patients with a high Immunoscore had the lowest risk of recurrence at 5 years compared to those with an intermediate or low Immunoscore.[2,7] The consensus Immunoscore was investigated in relation with known tumor-related parameters in clinical relevant groups of patients and it was proven to be a powerful predictor of the prognosis of the patients.[2,7] The clinical utility of Immunoscore has been further reinforced by the recent publications demonstrating the prognosis value of Immunoscore in Stage III CC patients, and its predictive value in response to chemotherapy.[8,9] Immunoscore outperforms the classical Tumor-Node-Metastasis (TNM) system in predicting the clinical outcome in early and advanced stage patients with CC.[7,10,11] The major role of the immune microenvironment in cancer development and survival of the patients was demonstrated from pre-cancer lesions[12] to late metachronous metastases.[13]

These efforts advance the knowledge of the intertwined evolution of tumors with the microenvironment[11] and demonstrated the impact of a strong immunity on the tumoral process.[1] Hallmarks of successful anticancer immunotherapy have been proposed.[14,15] The immune contexture, including the type, density, localization, and functional orientation of the immune infiltrate has a prominent impact on anticancer immunity.[11,14,16] Furthermore, clinical evidence showed that NK cells may also be a key immune constituent in the protective anti-tumor immune response.[17] In addition to immunosuppressive effects, conventional chemotherapeutics have immunostimulatory effects, which can be beneficial in the context of immunotherapy.[18–20] The effectiveness of chemotherapy was also shown to be dependent upon the preexisting intratumoral T-cells, and Immunoscore.[8,9,21]

Genomic alteration of malignant cells, favoring the emergence of immunogenic tumor neoantigens, has been associated with differential T-cell responses and to sensitivity to immunotherapy.[18,20,22] Tumor immunogenicity and immune cells involved in anti-tumor responses may also be affected by epigenomic alterations.[23] In addition, DNA damage response (DDR) deficiency has also emerged as an important determinant of tumor immunogenicity.[24] Indeed, DDR-targeted therapies can increase the antitumor immune response by promoting antigenicity, enhancing adjuvanticity and favoring reactogenicity by modulation of the tumor-immune cell synapse.

Most importantly, the effectiveness of immunomodulatory strategies depends on the presence and on the unleashing of preexisting immunity,[25] thus it is becoming critical to understand the mechanisms responsible for hot, altered, or cold immune tumors in order to boost a weak anti-tumor immunity.[15]

Conclusion and Implications

The immune component of the tumor microenvironment is now widely recognized as a hallmark of cancer. The immune response measured with the consensus Immunoscore was introduced as essential and desirable diagnostic criteria for

colorectal cancer, in the latest (5th) edition of the World Health Organization (WHO) Digestive System Tumors classification. In addition, Immunoscore was introduced into in the 2020 European and 2021 Pan-Asian European Organization for Medical Oncology (ESMO) Clinical Practice Guidelines for gastrointestinal cancer[21,26] to refine the prognosis and thus adjust the chemotherapy decision-making process.

Acknowledgments

The work was supported by INSERM, the LabEx Immuno-oncology, the Transcan ERAnet European project, the Society for Immunotherapy of Cancer (SITC), Association pour la Recherche contre le Cancer (ARC), Site de Recherche intégrée sur le Cancer (*SIRIC*) CAncer Research for PErsonalized Medicine (CARPEM), La Ligue contre le Cancer, The Qatar National Research Fund (QNRF) grant number NPRP11S-0121-180351, Assistance publique – Hôpitaux de Paris (AP-HP), HalioDx, Louis Jeantet Prize foundation, Agence Nationale de la Recherche (ANR Grant TERMM ANR-20-CE92-0001), and Institut National du Cancer, France (INCa).

Disclosure statement

JG and BM have patents associated with the immune prognostic biomarkers. JG is co-founder of HalioDx biotech, a Veracyte company. Immunoscore® a registered trademark from the National Institute of Health and Medical Research (INSERM) licensed to HalioDx.

Funding

This work was supported by the Agence Nationale de la Recherche (ANR) [TERMM ANR-20-CE92-0001]; The Qatar National Research Fund (QNRF) [NPRP11S-0121-180351].

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