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Spatial immune remodeling of the liver metastases: discovering the path to antimetastatic therapy

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ABSTRACT

The intrinsic characteristics of metastatic tumors are of great importance in terms of the development of antimetastatic treatment strategies. Elucidation from a spatial immune perspective has the potential to provide a more comprehensive understanding of the mechanisms underlying immune escape, effectively addressing the limitations of relying solely on the analysis of immune cell subpopulation transcriptional profiles. Advances in spatial omics technology enable researchers to precisely analyze precious liver metastasis samples in a high-throughput manner, revealing spatial alterations in immune cell distribution induced by metastasis and exploring the molecular basis of the remodeling process. The aggregation of specific cell subpopulations in distinct regions not only modifies local immune characteristics but also concurrently affects global biological behaviors of liver metastatic tumors. Identifying specific spatial immune characteristics in pretreatment or early-stage treatment tissue samples may achieve accurate clinical predictions. Moreover, developing strategies that target spatial immune remodeling is a promising avenue for future antimetastatic therapy.

BACKGROUND

The poor therapeutic outcomes of liver metastases remain a significant challenge to improving patient prognosis, particularly in gastrointestinal tumors. Current antimetastatic treatments are often designed based on the biological behavior and microenvironmental characteristics of primary tumors, ignoring the unique features of metastatic tumors. Accumulating evidence indicates that the liver metastatic niche (LMN) exhibits higher levels of immunosuppression compared with the primary tumor microenvironment (TME), and patients with liver metastases tend to have a worse response to immunotherapy. These phenomena suggest that exploring immune remodeling of LMN holds considerable potential for clinical applications. The pursuit of extreme depth in probing the heterogeneity and function of immune cells sometimes fails to elucidate the tumor immune escape. This paradox arises because tumor immunity is not solely governed by immune component functions. Spatial characteristics, such as the different regional infiltration of immune cells, the physical distance between homogeneous/heterogeneous cells, and the gradient distribution of soluble molecules also play pivotal roles and must not be overlooked. Recent advances in spatial sequencing techniques have enabled researchers to explore spatial information of TME with unprecedented throughput and detail.[1] Unfortunately, data depicting the spatial immune landscape of the LMN remains limited. From a spatial perspective, we seek to analyze the immune remodeling of the LMN and explore the mechanisms driving immune escape in metastatic tumors. Ultimately, we propose how spatial-related characteristics and technological advances may influence clinical decisions and therapeutic options in the future.

The liver is a functionally compartmentalized organ where the spatial distribution of immune cells varies physiologically; this feature is closely linked to the development of liver diseases. Generally, T cells and Kupffer cells are enriched in the portal zone, whereas macrophages and dendritic cells accumulate in the central zone. This immune spatial homeostasis is disrupted with the occurrence of metastasis. Despite differences in specific definitions, the view of the spatial composition of tumors according to compartmentalization as the core, border, and adjacent tissues is generally accepted.[1] This compartmentalization is typical of most liver metastatic tumors. Each region exhibits distinct immune characteristics, which also serve as one

of the key determinants for distinguishing between "cold" and "hot" tumors. Even within the same type of immune cells, the spatial distribution of different subpopulations is often heterogeneous; this spatial information holds predictive value for clinical prognosis.[2 3]

EXTENDED PROMETASTATIC IMMUNE SIGNATURE OF TUMOR BORDER

The general consensus is that the tumor border represents a continuous zone of gradual transition from tumor to adjacent tissue. The intricate crosstalk between tumor cells, adjacent tissue cells, and immune cells establishes a unique immunosuppressive ecosystem at the tumor border. Morphologically, immune cells tend to cluster, forming a "borderline" that demarcates adjacent tissue from tumor.[4] Immune cells, including myeloid cells, T/B lymphocytes, and dendritic cells, were enriched at the tumor border compared with the tumor core or adjacent tissue. These immune cells were more in an immunosuppressive state, characterized by high expressions of PD-L1, Foxp3 and VEGFR2. In addition, their antigen-presentation and tumoricidal capabilities were greatly impaired.[5] Cortese *et al* found that a high density of GPNMB+ macrophages in the LMN suggested a poorer patient prognosis. GPNMB+ macrophages were virtually absent from adjacent tissue but gradually increased within the tumor border, clustering more prominently at the edge. GPNMB+ macrophages release a variety of anti-inflammatory factors and suppress T cell responses, contributing to the maintenance of immunosuppressive features.[3] Neutrophils at the tumor border directly interact with tumor cells, exhibiting pro-invasive characteristics and decreased cytotoxicity. Xu *et al* identified S100A12+ neutrophils as the predominant borderline prometastatic subpopulation, characterized by high expressions of S100A12, S100A8/9, MMP9, and PADI4.[6] In addition, physical contact induces a reprogramming of lipid metabolism in neutrophils, leading to the release of various prometastatic factors and metabolic substrates for tumor cells.[4]

LOCALIZED IMMUNE CELL AGGREGATES FORM MULTIFUNCTIONAL COMMUNITIES

At smaller spatial scales, cell-to-cell contacts form diverse functional communities. This localized community not only reshapes the functional characteristics within a specific region but also influences global biological behavior. Reciprocal interactions between hematopoietic progenitor cells (HPCs) and fibroblasts determine the formation of dispersed premetastatic niches. Resident fibroblasts in metastatic organs express fibronectin, attracting VEGFR1+ HPCs to infiltrate and together form premetastatic clusters. VEGFR1+ HPCs release molecules such as MMP9 and SDF-1, which in turn attract tumor cells, promoting the aggregation and formation of overt metastatic lesions. The formation of this unit is predictive of future metastatic sites and represents a highly promising target for clinical intervention.[7] Rapid vascular construction of metastatic tumors exploits budding endothelial cells, enabling the swift extension of hepatic blood vessels into and around the metastases. Localized clusters of F4/80+ macrophages, derived from Kupffer cells, stimulate the expression of numerous critical angiogenic molecules in the contacting endothelial cells. This localized unit directs the growth of neovascularization within the tumor, ensuring adequate intratumoral blood perfusion.[8] Another important functional unit is the maturation of tertiary lymphoid structures (TLSs) mediated by the interaction of fibroblasts with B cells. CCL19+ fibroblasts were found to adhere around TLSs; these fibroblasts secrete CCL19, recruiting nearby CCR7+ B lymphocytes into the TLSs. Subsequently, IgG plasma cells expand abundantly, generate tumor-targeting antibodies and mediate antitumor immunity, inhibiting metastatic progression.[9]

Current strategies targeting spatial immune remodeling of the LMN, such as using VEGFR1 antibody, Class IIa Histone deacetylase inhibitor TMP195, or combined CCL19 and CXCL13 treatment, have shown promising antimetastatic effects in preclinical models. However, more high-quality evidence is still needed to substantiate their translational value.

BIOLOGICAL SIGNIFICANCE OF THE SPATIAL CHARACTERISTIC OF LYMPHOCYTES

Currently, the resolution is still limited in terms of the biological information suggested by lymphocyte differential spatial distribution. Recent studies have highlighted that the quality of cytotoxic lymphocyte infiltration within the tumor is more critical than the overall quantity. Without distinguishing spatially relevant locations, lymphocyte proportion may not be an effective prognostic indicator of clinical outcomes.[10] Histologically, smaller metastases often lack PD-L1 expression and are characterized by an accumulation of CD8+ T cells in the tumor core. In contrast, larger tumors exhibit a more immunosuppressive LMN with high PD-L1 expression, and CD8+ T cells were excluded from accessing the tumor interior.[11]

HOW CURRENT THERAPIES INFLUENCE SPATIAL IMMUNE REMODELING

Chemotherapy/immunotherapy not only induces changes in the quantity and function of immune cells, but also reshapes the spatial immune distribution patterns. Compared with non-responders, responders to immunotherapy are characterized by greater intratumoral infiltration of CD8+ GZMB+ T cells and CD8+ PD1+ TEx cells[12]. In addition, the presence of lymphoid aggregates is unrelated to the response to immunotherapy in tumors with innate resistance. However, in tumors exhibiting either an initial or complete response to immunotherapy, lymphoid

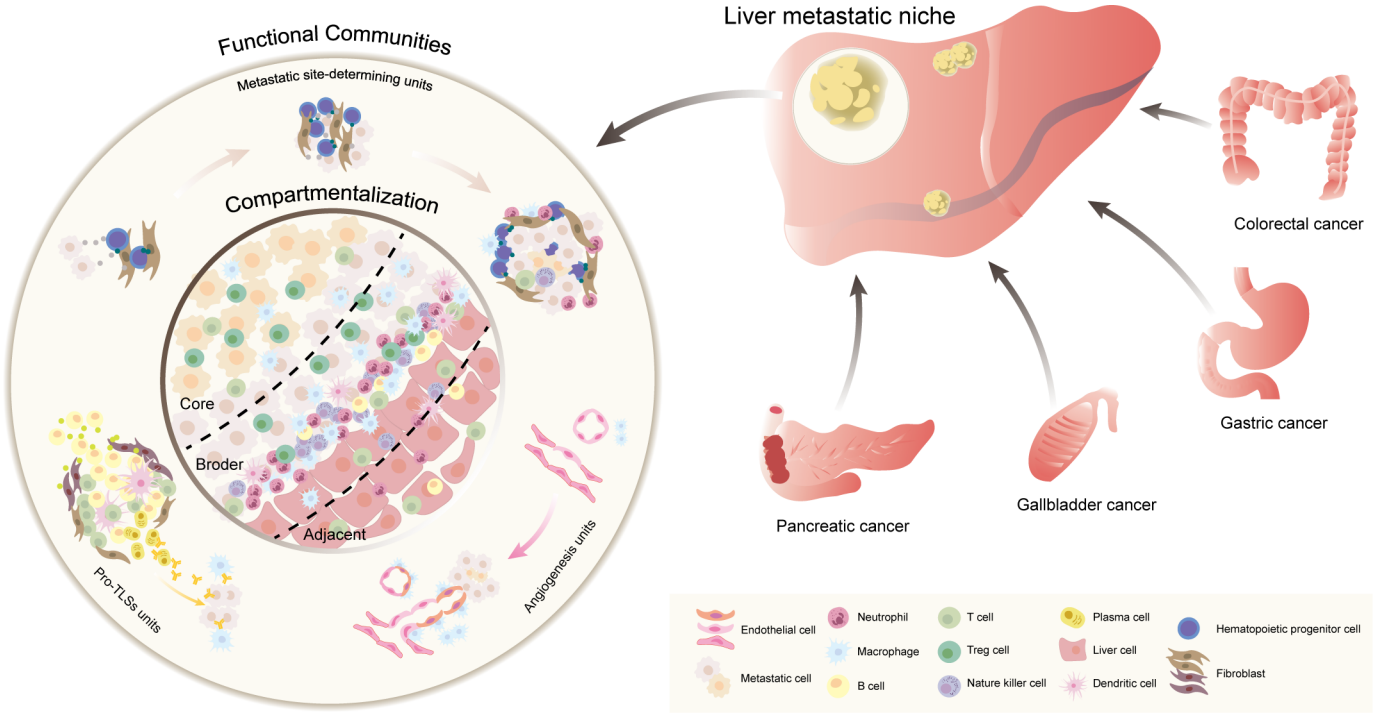

Figure 1 Focusing on spatial immune remodeling of the liver metastases. Liver metastatic tumors are primarily characterized by two major spatial immune characteristics: functional communities and compartmentalization. Exploring the characteristics and molecular mechanisms of spatial immune remodeling of the LMN holds promises to provide more valuable insights into clinical decisions and the development of antimetastatic therapy. LMN, liver metastatic niche; TLSs, tertiary lymphoid structures.

aggregates are predominantly localized within the tumors.[10] Wu *et al* found that neoadjuvant chemotherapy (NAC)-responsive patients with liver metastases exhibited a reduction in SPP1+ macrophages and an increase in cytotoxic cells, such as GZMK+ and XCL1+CD8+ T cells, within the tumor. In contrast, the number of cytotoxic FGFBP2+GZMB+ CD8+ T cells was significantly reduced in non-responsive metastatic patients. Additionally, the proportion of GZMB+CD8+ T cells in adjacent liver tissue and blood system was significantly higher in NAC-responsive patients, whereas this trend was opposite in non-responsive patients.[13] Targeted therapy also reshapes the spatial immune characteristic of the LMN. Studies have found that the combination of irreversible electroporation and CD40 agonistic antibody promotes the intratumoral infiltration of CD8+T cells and increases the population of activated dendritic cells throughout the liver metastases. These cells were restricted to the periphery in sham-treated tumors. The treatment group has fewer regulatory T cells and Ly6G+myeloid-derived cells, which are also restricted to the tumor periphery.[14]

CONCLUSIONS

Due to the spatial heterogeneity of the LMN, searching for biomarkers related to therapeutic efficacy based on spatial compartmentalization may be more accurate.[15] Some spatial immune characteristics, such as the enrichment of certain cell subpopulations in specific regions, the average physical distance between particular cell pairs, have been demonstrated to better predict clinical outcomes and immunotherapy responses. Conducting tissue biopsies before or in the early stages of treatment, combined with specific spatial detection techniques to assess the presence/quantity of immune characteristics may achieve precision immuno-oncology in future clinical trials and practice. Additionally, strategies targeting spatial immune remodeling, such as interfering with chemotactic signals, modulating angiogenesis and reshaping the physical isolation ability of stromal cells as well as the migratory capacity of immune cells, may be promising options for antimetastatic treatment. As an emerging field, the study of spatial immune remodeling of the LMN enhances our understanding of the relationship between immunity and metastasis (figure 1). However, some unsolved problems remain: the assumption that spatially proximate cells are more likely to interact has yet to be fully validated, and the existence and the extent of such interactions still need to be further verified; there is a lack of stable experimental models capable of simulating and replicating this process.

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