

Exploring the Role of Histopathology in Cancer Immunotherapy: Insights and Challenges

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Abstract

Cancer immunotherapy has emerged as a promising approach in cancer treatment, leveraging the body's immune system to target and destroy cancer cells. Histopathology, the examination of tissue changes at a microscopic level, plays a crucial role in understanding the complex interactions between tumors and the immune system. This research article provides insights into the role of histopathology in cancer immunotherapy, highlighting its significance in patient stratification, response prediction, and treatment monitoring. Furthermore, it discusses challenges associated with histopathological assessment in the context of immunotherapy and suggests potential solutions to overcome these hurdles.

Keywords: Cancer immunotherapy • Cytotoxic T lymphocytes • Immunotherapy

Introduction

Cancer immunotherapy has revolutionized cancer treatment by harnessing the power of the immune system to recognize and eliminate tumor cells. Unlike traditional treatments such as chemotherapy and radiation therapy, which directly target cancer cells, immunotherapy works by stimulating the body's immune response against cancer. While immunotherapy has shown remarkable success in some patients, its efficacy varies widely among individuals and cancer types. Understanding the underlying mechanisms of response and resistance is critical for optimizing treatment outcomes. Histopathology, with its ability to characterize tumor microenvironments and immune cell infiltration, plays a pivotal role in unraveling the complexities of cancer immunotherapy.

Histopathological analysis provides valuable insights into the composition and dynamics of the tumor microenvironment, including immune cell infiltration, presence of immune checkpoints, and expression of immunomodulatory molecules. This information helps in identifying tumors that are more likely to respond to immunotherapy. Histopathology enables the identification of predictive and prognostic biomarkers for immunotherapy response. Biomarkers such as programmed death-ligand 1 expression, tumor mutational burden, and immune cell subsets within the TME have been associated with response to immunotherapy agents [1-3].

Biomarker identification in the context of cancer immunotherapy involves the discovery and validation of specific molecular or cellular markers that can predict a patient's response to immunotherapy or their prognosis. These biomarkers help in identifying individuals who are most likely to benefit from immunotherapy treatments and can guide treatment decisions. PD-L1 is a protein expressed by cancer cells that interacts with the PD-1 receptor on T cells, suppressing the immune response. High levels of PD-L1 expression in tumors have been associated with increased response to PD-1/PD-L1 checkpoint inhibitors.

Literature Review

TMB refers to the total number of mutations present in a tumor's DNA.

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Tumors with higher TMB are more likely to produce neoantigens, which can trigger an immune response. Patients with high TMB have shown better responses to immune checkpoint inhibitors. TILs are immune cells that have infiltrated the tumor microenvironment. High levels of TILs, particularly cytotoxic T lymphocytes, indicate an active anti-tumor immune response and are associated with improved outcomes in immunotherapy. MSI is a condition characterized by the accumulation of genetic mutations due to defects in DNA mismatch repair. Tumors with high MSI are more likely to respond to immune checkpoint inhibitors, such as pembrolizumab. Tumor-associated Macrophages. The presence of specific immune cell subsets within the tumor microenvironment, such as M1-like macrophages or CD8+ T cells, can influence the response to immunotherapy.

Studies have demonstrated that tumors with high levels of infiltrating cytotoxic T lymphocytes and activated immune cells are more likely to respond to immunotherapy. Conversely, tumors with immunosuppressive microenvironments, characterized by regulatory T cells and myeloid-derived suppressor cells, tend to be resistant. Spatial heterogeneity within the tumor, characterized by variations in immune cell distribution and PD-L1 expression, poses challenges for accurate assessment of immunotherapy biomarkers. Advanced imaging techniques and multiplex immunohistochemistry are being developed to overcome these challenges.

Discussion

Biomarker identification involves various techniques, including immunohistochemistry, next-generation sequencing, and flow cytometry, to assess the expression levels or presence of these markers in tumor samples. By understanding the molecular and cellular characteristics of tumors, clinicians can better personalize treatment regimens and improve patient outcomes in cancer immunotherapy. Histopathological assessment of tumor specimens before, during, and after immunotherapy allows monitoring of treatment response and identification of potential resistance mechanisms. Changes in immune cell infiltration patterns and tumor morphology can provide early indications of treatment efficacy or failure.

There is a lack of standardized assays for assessing immune-related biomarkers, leading to variability in results across different laboratories and platforms. Tissue sampling bias and variability in tissue processing can impact the accuracy of histopathological assessment, particularly in heterogeneous tumors. Tissue sampling bias refers to the potential for errors or inaccuracies in the results of histopathological analysis due to the selection of tissue samples that may not fully represent the entire tumor or its heterogeneity. In cancer, tumors can exhibit spatial and temporal heterogeneity, meaning that different regions of the tumor may have distinct characteristics, including genetic mutations, levels of immune infiltration, and response to treatment.

When taking a biopsy or tissue sample for analysis, there's a risk that

the chosen sample may not adequately capture this heterogeneity, leading to misleading conclusions about the tumor's properties and potential response to therapy. Biopsies are often taken from accessible sites or regions that appear abnormal on imaging, but these areas may not be representative of the entire tumor. Subclonal populations with different molecular profiles or immune microenvironments may exist in other areas of the tumor. Tumors can have diverse cell populations within the same lesion, such as areas of necrosis, hypoxia, or regions with varying degrees of immune cell infiltration [4,5].

Biopsies may inadvertently sample only one part of this heterogeneity, leading to incomplete information about the tumor's biology. The size of the biopsy or tissue sample can influence the accuracy of histopathological analysis. Small or inadequate samples may miss important features of the tumor microenvironment or fail to capture enough cells for reliable analysis. Variability in tissue processing techniques, including fixation, sectioning, and staining, can introduce artifacts or distortions that affect the interpretation of histopathological findings.

To mitigate tissue sampling bias, clinicians and pathologists may use techniques such as multi-site biopsies, imaging-guided sampling, or serial biopsies taken at different time points during treatment. Additionally, advances in imaging technologies and molecular profiling methods allow for a more comprehensive understanding of tumor heterogeneity, helping to guide treatment decisions and improve patient outcomes. The TME is highly dynamic, and its composition can change over time and in response to treatment, necessitating serial biopsies for accurate monitoring.

Advancements in technology, including digital pathology, artificial intelligence, and single-cell analysis, hold promise for overcoming the challenges associated with histopathological assessment in cancer immunotherapy [6]. Integration of multi-omics data and development of novel biomarkers may further enhance our understanding of immunotherapy response and resistance mechanisms. Despite the challenges, histopathology remains indispensable in guiding personalized cancer immunotherapy strategies, ultimately improving patient outcomes.

Conclusion

Histopathology serves as a cornerstone in the era of cancer immunotherapy, providing crucial insights into the tumor-immune interactions and guiding treatment decisions. While challenges such as standardization and tissue heterogeneity persist, ongoing research efforts are poised to address these issues and further optimize the use of histopathological assessment in personalized cancer care.

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Conflict of Interest

There are no conflicts of interest by author.

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