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MICROSATELLITE INSTABILITY IN TRIPLE-NEGATIVE BREAST CANCER: PROGNOSTIC AND PREDICTIVE SIGNIFICANCE

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Abstract
Microsatellite instability (MSI) and mismatch repair deficiency (dMMR) are important molecular biomarkers associated with genomic instability and tumor immunogenicity. In triple-negative breast cancer (TNBC), their clinical significance remains under investigation because of the relatively low prevalence of these molecular alterations. This article reviews the biological mechanisms of MSI, its potential prognostic value, and its predictive role in identifying patients who may benefit from immunotherapy. Although MSI-high status is uncommon in TNBC, its identification may contribute to personalized treatment strategies and improved therapeutic outcomes.

Keywords: Microsatellite instability, triple-negative breast cancer, mismatch repair deficiency, prognosis, predictive biomarkers, immunotherapy, precision medicine.

Introduction

Triple-negative breast cancer (TNBC) is a biologically aggressive subtype of breast cancer characterized by the absence of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 expression. Due to the lack of these conventional therapeutic targets, treatment options are relatively limited compared with other breast cancer subtypes. TNBC is associated with considerable molecular heterogeneity, an increased risk of recurrence, and variable responses to systemic treatment. Therefore, identifying reliable molecular biomarkers is essential for improving prognostic assessment and selecting more effective therapeutic approaches [1]. Microsatellite instability is a molecular phenomenon resulting from defects in the DNA mismatch repair system. Microsatellites are short repetitive DNA sequences that are particularly susceptible to replication errors. Under normal conditions, mismatch repair proteins, including MLH1, MSH2, MSH6, and PMS2, correct these errors. When the repair system becomes dysfunctional, mutations accumulate within microsatellite regions, leading to genomic instability. This process may increase tumor mutational burden and promote the formation of neoantigens capable of stimulating antitumor immune responses [2].

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The scientific literature indicates that MSI and mismatch repair deficiency are clinically important biomarkers in several malignancies, particularly colorectal, endometrial, and gastric cancers. Their relevance in breast cancer, especially the triple-negative subtype, is less clearly established because MSI-high tumors occur relatively infrequently. Nevertheless, the presence of deficient mismatch repair may identify a biologically distinct group of patients with potential sensitivity to immune checkpoint inhibitors. A literature-based analytical approach was used to examine publications addressing MSI, mismatch repair deficiency, triple-negative breast cancer, prognosis, and immunotherapy. Particular attention was given to molecular mechanisms, diagnostic methods, clinical outcomes, and the predictive significance of MSI status. Immunohistochemistry and molecular testing are among the principal approaches used to evaluate mismatch repair status and microsatellite instability.

The prognostic significance of microsatellite instability in TNBC remains controversial. Several studies have reported that mismatch repair deficiency is uncommon in this subtype, and its association with survival outcomes has not been consistently demonstrated. Some investigations have identified patients with dMMR who experienced comparatively favorable survival, whereas other studies found no statistically significant differences in overall survival, disease-free survival, or clinicopathological characteristics between MMR-deficient and MMR-proficient groups [3].

The variability of reported findings may be explained by differences in patient populations, tumor stage, laboratory methods, sample size, and follow-up duration. Furthermore, mismatch repair protein expression may demonstrate intratumoral heterogeneity, potentially complicating the interpretation of biomarker results. Consequently, MSI status should not currently be considered an independent prognostic factor for all patients with TNBC without additional clinical and molecular evidence.

The predictive significance of MSI is particularly relevant in the context of immunotherapy. Defective mismatch repair may lead to the accumulation of mutations and the generation of tumor-specific neoantigens. These neoantigens can increase immune recognition of malignant cells and potentially enhance sensitivity to immune checkpoint blockade. Thus, MSI-high or dMMR status may identify a small subgroup of patients with advanced TNBC who could benefit from immunotherapeutic approaches. The clinical application of MSI testing requires appropriate laboratory assessment and careful interpretation. Immunohistochemical evaluation of MLH1, MSH2, MSH6, and PMS2 can identify loss of mismatch repair protein expression. Molecular assays may additionally confirm microsatellite instability. Combining these methods with other biomarkers, including PD-L1 expression, tumor mutational burden, and tumor-infiltrating lymphocytes, may provide a more comprehensive assessment of tumor biology and potential treatment response. Despite its potential value, MSI testing in TNBC faces several limitations. The rarity of MSI-high cases reduces the statistical power of clinical studies, while differences in testing methodologies may contribute to inconsistent results. Further prospective studies with larger patient populations are necessary to establish standardized testing protocols and determine the clinical utility of MSI assessment in different stages of TNBC.

The analysis of current scientific literature demonstrates that microsatellite instability and mismatch repair deficiency represent potentially important molecular characteristics of triple-negative breast cancer. Although MSI-high status is relatively rare in TNBC, its presence may reflect specific biological features associated with increased genomic instability, tumor mutational burden, and

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immune activation. The prognostic significance of MSI remains controversial, as clinical studies have reported inconsistent associations with overall survival, disease-free survival, and tumor progression. These differences may be related to variations in diagnostic methods, patient characteristics, tumor stages, and the limited number of MSI-positive cases included in clinical studies.

From a clinical perspective, the predictive significance of microsatellite instability is particularly important for the development of personalized treatment strategies. Mismatch repair deficiency may increase the immunogenicity of tumor cells and potentially enhance their sensitivity to immune checkpoint inhibitors. Therefore, MSI testing, together with the assessment of PD-L1 expression, tumor mutational burden, and other molecular biomarkers, may improve the identification of patients who are more likely to benefit from immunotherapy. Further large-scale clinical studies are required to clarify the prognostic value of MSI and establish its role in optimizing therapeutic approaches for patients with triple-negative breast cancer [5].

Conclusion

Microsatellite instability represents a biologically important molecular alteration in triple-negative breast cancer, although its prognostic significance remains insufficiently established. The rarity of MSI-high and mismatch repair-deficient tumors limits its routine application as a prognostic biomarker. However, its predictive value may be clinically meaningful because defective mismatch repair can increase tumor immunogenicity and potential sensitivity to immune checkpoint inhibitors. Further research integrating MSI status with other molecular and immunological biomarkers may contribute to the development of personalized treatment strategies and improved clinical outcomes in patients with TNBC.

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