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Molecular characterization and clinical relevance of Metabolic Signature Subtypes in Gastric cancer

Abstract: Recent studies highlighted the clinicopathologic importance of tumor metabolic reprogramming in delineating molecular attributes and therapeutic potentials. However, the comprehensive metabolic characteristics in gastric cancer (GC) have not been comprehensively recognized. Here, metabolic signature-based clustering analysis identifies three subtypes (termed as MSC1, MSC2, MSC3) with distinct molecular and clinical features: MSC1 showed better prognosis and upregulation of the tricarboxylic acid (TCA) cycle and lipid metabolism, combined with frequent TP53 and RHOA mutation; MSC2 had moderate prognosis and elevated nucleotide and amino acid metabolism, enriched by intestinal histology and mismatch repair deficient (dMMR); and MSC3 exhibited poor prognosis and enhanced glycan and energy metabolism, accompanied by diffuse histology and frequent CDH1 mutation. The Shandong Provincial Hospital (SDPH) in-house dataset with matched transcriptomic, metabolomic, and spatial-metabolomic analysis also validated these findings. We also constructed a metabolic subtype-related prognosis genes (MSPG) scoring model to quantify the metabolic risk activity of individual tumors, where a low score is associated with glycosaminoglycan biosynthesis, and worse prognosis. Intriguingly, the cuproptosis signaling is positively correlated with MSPG-score in GC. Immunotherapy analyses indicate that tumors with low MSPG-score and MSC3 subtype are responsible for worse clinical response to immune check-point inhibitors (ICI) therapy. In conclusion, comprehensive recognition of the metabolite signature can enhance the understanding of diversity and heterogeneity in GC.

Keywords: Gastric cancer, Metabolic signature, Prognostic, Metabolic subtype

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