Unraveling the Metabolic Transformation and Biomechanical Shifts Driving Cancer Progression

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Cancer metabolism constitutes a dynamic landscape where the tumor microenvironment (TME) and metabolic adaptations intricately interact, exerting influence on tumor progression and responses to therapies. In this study, we illustrate this intricate interplay in both head and neck squamous cell carcinomas (HNSCC) and prostate cancer, emphasizing the pivotal role of cell mechanics and metabolic reprogramming.
HNSCC presents considerable clinical heterogeneity, largely attributable to the complex TME. Distinct mRNA subtypes of patient-derived cancer-associated fibroblasts (CAFs) exert influence over cancer cell metabolism while concurrently altering cell stiffness, thereby facilitating cancer cell migration and invasiveness. Specifically, cancer cell stiffness correlates with mitochondrial ATP production and lactate exchange within the microenvironment, as evidenced by MCT transporter expression. Notably, our findings reveal a bidirectional relationship between CAFs and cancer cells, carrying significant clinical implications. Patients displaying the basal mRNA subtype (characterized by high TP63 and EGFR and low SOX2 expression) along with overexpression of lactate transport-associated genes face a less favorable prognosis.
Crucially, this association between metabolic adaptability and changes in the biomechanical properties of cancer cells extends beyond HNSCC. In the context of prostate cancer, manipulation of mitochondrial aconitase by zinc results in heightened mitochondrial ATP production, a shift in epithelial-mesenchymal characteristics, and an increase in cell stiffness.
In summary, our research brings together these findings, offering insight into how mitochondrial function influences cancer cell mechanics. It unifies the metabolic characteristics of HNSCC and prostate cancer through shared elements within the TME, alterations in cell mechanical properties, metabolic adaptations, and mitochondrial dynamics.
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