Tissue metabolite composition driving metastatic organotropism in prostate cancer: the role of asparagine

SpT-27-1

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Prostate cancer (PC) is the second-leading cause of cancer death in men, mainly caused by metastatic disease. PC preferentially metastasizes to bone and lung. Emerging evidence underlines the crucial role of the distant organs' microenvironment in influencing metastatic cell distribution and tumour-reforming ability.
Here, we investigated the metabolic factors affecting metastatic organotropism of PC. The specific organ metabolite composition was analyzed by gas-mass spectrometry (GC-MS) on tissues collected from athymic healthy mice, identifying asparagine as one of the most common enriched metabolites in bone and lung. Asparagine is critical in tumour progression, supporting cell proliferation under metabolic stresses. The relevance of asparagine in metastatic colonization of PC cells was investigated in vitro by comparing normally adherent cells (2D cultures) and cells grown in non-adherent conditions (3D cultures) as a model mimicking loss of extracellular support occurring during early stages of metastasis.
We observed that asparagine exogenous supplementation increases 3D cell growth, while it does not enhance 2D cell proliferation nor increase cell migratory potential, indicating a specific role for asparagine in metastatic niche colonization. 3D cells display decreased mitochondrial oxidative metabolism and reactive oxygen species (ROS) accumulation. Mitochondrial ROS scavenging enhances 3D cell clustering, indicating the importance of limiting ROS during cell clustering. In addition, providing exogenous asparagine is sufficient to raise the oxygen consumption rate of 3D cells under metabolic stressful conditions. Asparagine supplementation in 3D cultures also increases the mammalian target of rapamycin complex 1 (mTORC1)-pathway activation and enhances protein synthesis. Together, these data advise that lowering asparagine availability in the bone and lung districts represents a promising strategy to target metastatic dissemination of PC cells.

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