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Abstract

Ninety percent of cancer deaths are the result of metastasis. The development of robust and sensitive technologies that capture metabolic processes in metastasizing cancer cells has hampered understanding of the role of metabolism during metastasis. We discuss the current technologies for studying metabolism in primary and metastatic cancer cells, as well as metabolic interactions between cancer cells and the tumour microenvironment (TME) at various stages of the metastatic cascade. We discuss the benefits and drawbacks of each method, as well as how these tools and technologies will help us better understand metastasis [1-15]. Studies using cutting-edge metabolomic technologies to investigate the complex metabolic rewiring of different cells have the potential to reveal novel biological processes and therapeutic interventions for human cancers

Metabolism is essential to all cellular functions because it ultimately drives the generation and utilisation of ATP required for cellular activity. Changes in metabolism can lead to a variety of diseases, including cancer. Cancer cells have the ability to activate and suppress various metabolic pathways. Furthermore, metabolic differences found in cancer cells versus non-cancer cells suggest potential metabolic vulnerabilities that could be therapeutically modulated to slow cancer progression. There has been remarkable progress in understanding the metabolic regulation of cancer cells in recent years, particularly in the context of primary tumour metabolism. However, a thorough understanding of the metabolic regulation of cancer cells during metastasis remains an active area of investigation.

Metastasis is a multifaceted process that includes uncontrolled proliferation of cancer cells at the primary site, local invasion into surrounding tissue, intravasation into the bloodstream or lymphatics, transportation through circulation, extravasation into distant tissues, and colonisation of secondary organs. Because most cancer cells do not survive in these harsh environments, metastasis via this metastatic cascade is a highly inefficient process. However, some cancer cells undergo metabolic adaptations to maximise survival in these harsh environments.

Introduction

The ability of cancer cells to move from their primary site and disseminate through the bloodstream or lymph to form a tumour in distant organs is referred to as metastasis. Cancer cells must first invade the tumor-associated stroma and undergo an epithelial-to-mesenchymal transition (EMT), which causes epithelial cells to lose polarity and gain the ability to invade, resist stress, and disseminate with a mesenchymal-like phenotype. Several metabolites, including 2-hydroxyglutarate, have been shown to modulate EMT via transcription factor modulation. Cancer cells initiate the intravasation process after successful invasion. Cancer cells elongate, forming protrusions that allow cells to pass between endothelial cells in blood and lymphatic vessels and migrate into the circulation. Some metabolites appear to be proangiogenic and prolymphangiogenic, increasing vessel density in the primary tumour, supplying oxygen and nutrients, maintaining tumour metabolism, and promoting metastasis. Circulating tumour cells (CTCs) are exposed to environmental stress, such as oxidative stress and ferroptosis, and are forced to metabolically adapt in order to survive in such a harsh environment. CTCs that survive in the bloodstream extravasate through endothelial cells and colonise the metastatic niche. CTCs have a proclivity to metastasize in specific organs, a phenomenon known as organotropism. Finally, the cells of the metastatic tumour rewire.

Cancer cells do this by upregulating and downregulating intrinsic metabolic pathways at various stages of the metastatic cascade to maximise survival in specific microenvironments. Cancer cells in primary tumours, for example, are frequently found in hypoxic TMEs and use anaerobic glycolysis for cell growth and proliferation. Cancer cells that can metastasize detach from the primary tumour, experience high levels of oxidative stress, and must undergo metabolic

and transcriptional changes to survive in the harsh environment of the blood. Cancer cells that have been extravasated and seeded in distant

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examine the metabolomic profile of a small number of cancer cells. We summarise the most recent metabolomic technologies available for analysing cancer cell metabolism, with a focus on metastasizing cancer cells in preclinical models and patients. We discuss the benefits and drawbacks of each method, as well as the challenges that must be overcome. Understanding cancer's metabolic vulnerabilities during metastasis is critical for developing new therapies to prevent metastasis formation.

Discussion

For a long time, quantitative metabolomics has been a powerful analytical tool for evaluating metabolites in biological samples. Metabolomic technologies, like many '-omics' sciences, are constantly evolving, driving new developments in analytical techniques, models, software, and computational methods to improve sensitivity and specificity. NMR spectroscopy, gas chromatography-mass spectrometry (GC-MS), and liquid chromatography-MS (LC-MS) techniques developed decades ago have proven to be important tools for the detection and quantification of metabolites in cancer metastasis. However, these techniques necessitate a large number of cancer cells (>10,000 cells) and are incapable of distinguishing metabolic heterogeneity on a single-cell level. It is critical to characterise the metabolic heterogeneity within a tumour because differences in subsets of cancer cells within a tumour can influence the extent of efficient metastasis and potential response to therapies. The presence or absence of specific metabolic qualities in subsets of cancer cells may be useful in predicting which cancer cells are likely to efficiently metastasize, and thus may serve as diagnostic prognostic.

Analytical tools for studying metabolism, such as MS and NMR spectroscopy, became available in the 1940s. Mass spectrometers were coupled to gas chromatography (GC-MS) or liquid chromatography (LC-MS) in the 1950s, which increased analyte resolution by increasing specificity and sensitivity. GC and LC, as their names suggest, separate metabolites by injecting a sample into a column (stationary phase) or a gas or liquid mobile phase, respectively. The gas chromatography-mass spectrometry (GC-MS) technique has been used to analyse polar (e.g., amino acids) and nonpolar (e.g., lipids) metabolites in culture, primary tumours, and plasma, providing a comprehensive metabolomic profile. To reduce polarity, GC-MS frequently requires chemical. Metabolites' thermal stability and volatility are improved through derivatization. As a result, LC-MS is primarily used to analyse compounds that are difficult to volatilize, such as lipids and nucleotides. As evidenced by recent work revealing the importance of lipid adaptations in cancer cells for efficient metastasizing LC-MS has been demonstrated to be a valuable technology in the field of cancer metastasis and lipidomics analyses. NMR identifies metabolites in an intact sample, whereas MS requires sample isolation and processing. NMR analyses a sample's chemical properties by exciting specific nuclei in a molecule (typically ^{13}C or ^1H) with radiofrequency radiation in a magnetic field. NMR has a significant advantage over MS-based methods in that it is quantitative, highly reproducible, and provides structural details and the low sensitivity, because most metabolites are found in trace amounts in biological samples. Magnetic resonance spectroscopy (MRS) and positron emission tomography (PET) have been used in the clinic to expand quantitative metabolomic technologies (PET).

The most common application of these techniques is ^{18}F -FDG (fluorodeoxyglucose) PET imaging of glucose uptake. Because it can image glucose uptake in the human body, ^{18}F -FDG PET combined with computed tomography (PET/CT) is an outstanding technology in cancer diagnostics. Hyperpolarization is another molecular imaging

technique. This technique, which employs polarised substrates to assess metabolic changes in real time, has been applied to a variety of models, including prostate cancer metastasis. Hyperpolarization, a benefit in the field of cancer metastasis.

Single-cell analysis is an extremely promising technology that has been used to measure transcriptome, proteome, and metabolome abundance. Single-cell metabolomics (SCM) can be used to reveal metabolic heterogeneity within a cancer cell population in primary and metastatic tumours. Furthermore, SCM is useful for determining the metabolic profiles of individual cell types within a tumour (i.e., immune cells and stromal cells) and has been used to identify adaptations required for metastasis or therapy resistance. SCM has been used in metastatic melanoma as well as primary and metastatic head and neck cancers to show that tumour and non-tumour cells within the TME coexist. Different metabolic activity not found in bulk tumour tissues. Because of the high intratumour heterogeneity and applicability as a liquid biopsy biomarker for metastasis, SCM and low-cell number metabolomics are particularly useful in the analysis of CTCs in blood. For example, circulating melanoma cells have been shown to have lower purine biosynthesis than primary tumour cells. However, metabolic analysis of CTCs remains difficult. CTC isolation is frequently performed using a flow cytometer. However, due to shear forces and osmotic pressure, the isolation process can cause metabolic stress in individual cells. As a result, direct sorting into appropriate quenching solutions (e.g., methanol) and short time periods are advised. Avoid metabolic disruptions. The ParsortixTM Cell Separation Cassette System, a microfluid platform that captures single CTCs based on size, is a gentler method for CTC enrichment than flow cytometry. However, when compared to flow cytometry, this microfluid system has lower flow-through, and the number of CTCs that can be collected in a single cassette is limited. To summarise, SCM is a rapidly evolving field that has recently seen significant advances in robust sampling, ionisation methods, and metabolite detection. SCM analyses will benefit from further development of sample preparation protocols to improve the metabolic integrity of analysed cells.

Cancer cells adapt their metabolism after passing through the bloodstream in order to invade and outgrow in distant organs. Metabolic profiling of cancer cells in distant organs is critical for preventing metastasis and understanding why some cancer cells metastasize to specific organs. As a result, *in situ* MS technologies have emerged as valuable tools for characterising cancer cell metabolism in the metastatic environment.

MALDI-MSI has been used in cancer studies to quantify metabolites, discover biomarkers for diagnostics and prognostics, and understand drug bioavailability within tumours due to advancements in matrix chemistry and advanced instrumentation. Scupakova and colleagues recently used MALDI-MSI to study glycosylation of breast cancer cells in tissue microarrays during metastatic progression, demonstrating that metastatic breast cancers have higher levels of N-glycans than primary tumours. MALDI-MSI has also been used to predict the presence or absence of lymph node metastasis in primary endometrial carcinomas. Furthermore, Andersen and colleagues using MALDI-MSI in prostate cancer models discovered that stroma and non-cancer epithelium contain fewer phospholipids than prostate cancer cells. These and other foundational studies show that MALDI-MSI is a highly promising technology for the diagnosis, comparison of primary tumours and metastasis for therapy decision, and quantification of metabolites within a sample. However, MALDI-MSI has limitations such as low sensitivity; some matrices cannot ionise a

wide range of analytes, including low molecular weight ions. Second, metabolite delocalization caused by matrix tissue mounting reduces the specificity of metabolites detected at individual spatial points. These constraints can be overcome by improving matrix composition and sample preparation for the method of choice for matrix application. In addition, matrix-free in situ metabolomics technologies such as desorption electrospray ionization-mass spectrometry imaging (DESI-MSI) and secondary ion mass spectrometry (SIMS) are available. SIMS and MALDI-MSI both have a single-channel detector, DESI-MSI does not have cell/subcellular spatial resolution and has a spatial resolution of 200 μm . As a result, the method of choice for in situ SCM (i.e., MALDI-MSI and SIMS) is determined by the mass-to-charge ratio (m/z) detection range, sensitivity, sample preparation time, and data analysis time. Due to its high sensitivity and ease of spectra analysis, MALDI remains the most popular ionisation technique for MSI to this day. The combination of cell-intrinsic (such as cell origin) and cell-extrinsic (such as cell-cell interactions and local nutrient fuels) factors modulates and reprograms tumour cell metabolic pathways. As a result, detecting and analysing metabolic changes in tumour cells during metastasis in vivo is critical. In vivo models combined
