

New Methods for Studying Cancer Metastases Using Metabolomics

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Abstract

90% of cancer patients' deaths are the result of metastasis. The lack of reliable and sensitive tools to record metabolic processes in metastatic cancer cells has hampered our understanding of the involvement of metabolism during this process. We go over the current research methodologies for investigating I cancer cell metabolism in primary and metastatic tumours, and metabolic interactions between cancer cells and the tumour microenvironment (TME) at various stages of the metastatic cascade. We list the benefits and drawbacks of each approach and talk about how these tools and technologies will deepen our understanding of metastasis[1-15]. Modern metabolomic research into the intricate metabolic rewiring of many cells has the potential to disclose novel biological mechanisms and therapeutic approaches for treating human malignancies.

All cellular processes revolve around metabolism since it is what ultimately produces and uses the ATP needed for cellular activity. Numerous diseases, including cancer, can develop as a result of metabolic changes. Different metabolic pathways can be activated and suppressed by cancer cells. In addition, metabolic alterations found in cancer cells as opposed to non-cancer cells suggest possible metabolic weaknesses that could be medically modified to slow the progression of cancer. Understanding the metabolic control of cancer cells has advanced significantly in recent years, particularly when it comes to the metabolism of primary tumours. However, there is still much work to be done in order to fully understand how cancer cells regulate their metabolism during metastasis. Each and every biological activity depends on metabolism.

Introduction

The complicated process of metastasis includes I unchecked growth of cancer cells at the primary site, local invasion into nearby tissue, intravasation into blood or lymphatics, movement through circulation, extravasation into distant tissues, and colonisation of secondary organs. The majority of cancer cells do not survive through this metastatic cascade, making metastatic spread extremely inefficient. However, certain cancer cells go through metabolic modifications to improve survival in these challenging conditions.

In order to maximise survival in particular microenvironments, cancer cells up- and down-regulate intrinsic metabolic pathways at various stages of the metastatic cascade. For instance, anaerobic glycolysis is used by cancer cells in primary tumours, which frequently have hypoxic. Because of the substantial intratumoral heterogeneity, cancer cells that potentially metastasise separate from the primary tumour, face significant oxidative stress, and must adapt their metabolism and transcription to survive in the harsh blood environment. Cancer cells must rewire their metabolism to survive and multiply by utilising the nutrients and oxygen present at secondary sites after extravasation and seeding in distant organs.

Despite the fact that metabolomic technologies have made it increasingly clear that cancer cells acquire some metabolic traits for their proliferation and maintenance through the metastatic cascade, it is challenging to characterise the heterogeneous metabolic states of not only cancer cells but also immune and stromal cells in order to develop metabolic inhibitors to prevent metastasis formation.

Subjective Heading

Sensitive and trustworthy metabolomic methods are crucial for the few cancer cells that may be examined at various stages of the metastatic cascade from various primary tumours, circulating tumour cells (CTCs), and distant metastatic organ locations. Instrumentation improvements have made it possible to investigate the metabolomic patterns of small numbers of cancer cells. With a focus on cancer cells that have migrated to patients' bodies and preclinical models of the

disease, we present an overview of the most modern metabolomic technologies available to analyse the metabolism of cancer cells in this review. We discuss the advantages, disadvantages, and challenges associated with each strategy. It is essential to comprehend the

Quantitative metabolomics has long been a powerful analytical technique for evaluating metabolites in biological materials. As metabolomic technologies advance, new advancements in modelling, software, computational methods, and analytical approaches are made to boost sensitivity and specificity. This resembles a lot of “-omics” disciplines. Decades-old techniques like NMR spectroscopy, gas chromatography-mass spectrometry (GC-MS), and liquid chromatography-MS (LC-MS) (Box 2) have made it possible to detect and quantify metabolites in cancer metastasis. These approaches can't detect metabolic heterogeneity in a single cell and require a large number of cancer cells (>10,000 cells). The effectiveness of metastasis and the potential outcome of Quantitative metabolomics has long been a powerful analytical technique for evaluating metabolites in biological materials. As metabolomic technologies advance, new advancements in modelling, software, computational methods, and analytical approaches are made to boost sensitivity and specificity. This resembles a lot of “-omics” disciplines. Decades-old techniques like NMR spectroscopy, gas chromatography-mass spectrometry (GC-MS), and liquid chromatography-MS (LC-MS) (Box 2) have made it

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Discussion

Using single-cell analysis, which has been used to determine the abundance of the transcriptome, proteome, and metabolome, one can get insight into the cellular heterogeneity and dynamics in individual cells. Single-cell metabolomics (SCM) can be utilised to identify metabolic variability within a population of cancer cells in primary and metastatic tumours. Furthermore, SCM has been used to find modifications necessary for metastasis or for medication resistance and is helpful for revealing unique metabolic profiles of individual cell types within a tumour (i.e., immune cells and stromal cells). SCM has been utilised to show that tumour and non-tumour cells within the TME have different metabolic activity that was not observed in original and metastatic tumours of head and neck malignancies, metastatic melanoma, and Due to its great relevance as a liquid biopsy biomarker for metastasis and strong inpatient heterogeneity, low-cell number metabolomics is particularly helpful in the investigation of CTCs in blood. For instance, purine production was found to be downregulated in circulating melanoma cells in comparison to original tumour cells. The metabolic study of CTCs is still difficult, nevertheless. In a flow cytometer, CTC isolation is frequently carried out (Figure 1). However, because of shear pressures and osmotic pressure, the isolation procedure might put individual cells under metabolic stress. To prevent metabolic abnormalities, straight sorting into appropriate quenching solutions (such as methanol) and brief time periods are advised. The Parsortix™ Cell Separation Cassette System, a microfluidic device that captures CTCs, provides an alternative for enrichment of CTCs. Compared to flow cytometry, the technique has a lesser flow-through, and there are restrictions on how many CTCs can be collected on a cassette. In conclusion, SCM is an area that is developing quickly, and recent substantial advancements in robust sampling, ionisation techniques, and metabolite detection have been made. SCM analysis will benefit from further development of sample preparation techniques to increase the metabolic integrity of examined cells.

After transit through the bloodstream, cancer cells adapt their metabolism to invade and outgrow at distant organs. Metabolic profiling of cancer cells in distant organs is of utmost importance to prevent metastasis formation and elucidate why some cancer cells metastasize to specific organs. Therefore, *in situ* MS technologies have appeared as valuable technologies to characterize the metabolism of cancer cells in the metastatic environment.

An innovative method called matrix-assisted laser desorption/ionization-MS imaging (MALDI-MSI) enables single-cell metabolic analysis of processed materials without labels and histological tissue samples (*in situ*). A matrix-based technique called MALDI-MSI can provide spatial resolution to metabolomics study data at a single-cell level (5–50 μm) by differentiating between metabolism from tumour, immunological, and stromal cells *in situ*. Sequential tissue sections are photographed and immunohistochemistry or immunofluorescence is used to classify the various cell subtypes and their metabolism. To identify the cell subtype and associated metabolites, they virtually merged. By demonstrating how distinct organ microenvironments and the various nutrients present in these microenvironments affect cancer metastasis, this approach offers the potential to identify new therapeutic targets.

MALDI-MSI has been used in cancer studies to measure metabolites, find biomarkers for diagnostics and prognostics, and comprehend therapeutic bioavailability within tumours thanks to advancements in matrix chemistry and sophisticated apparatus. Scupakova and coworkers recently MALDI-MSI was skillfully used to examine the glycosylation of breast cancer cells as they spread via tissue microarrays, showing that metastatic tumours contain larger amounts of N-glycans than initial tumours. In primary endometrial carcinomas, MALDI-MSI has also been used to predict whether lymph node metastases will occur or not. Furthermore, Andersen and colleagues have demonstrated using MALDI-MSI that stroma and non-cancer epithelium contain less phospholipids than prostate cancer cells in models of prostate cancer. These pioneering research, along with others, show that MALDI-MSI is a very promising technology for diagnosis, comparing primary tumours and metastases to guide treatment decisions, and quantifying metabolites in a sample.

Conclusion

With the advent of the new technologies and tools mentioned in this review, the area of cancer metabolomics research has significantly advanced. With the use of these technologies, metabolic changes in primary tumours and far-off metastatic sites have been found, and these changes have been used in the clinic for cancer diagnosis and treatment. However, new developments in these technologies have made it possible to analyse cancer cells that have spread to other organs. By using these methods, it may be possible to understand how cancer cells alter metabolically, why they metastasize to particular secondary organs, and why only some cancer cells survive in the circulation after metastasis. Improvements in the sensitivity of metabolite detection, characterization of “malignant” metabolic patterns of cancer cells that are metastasizing for patient classification, prognosis and treatment are yet unclear. Over the following ten years, novel therapeutic targets with the potential to lessen metastatic spread and enhance patient prognosis and survival will continue to be identified by identifying and targeting the metabolic pathways in metastatic cancer cells.

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Conflict of Interest

The authors declare that they are no conflict of interest.

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