

New tactics for Evaluating Cancer Dissemination via Mass Spectroscopy

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Abstract

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 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 [1-15]. We list the benefits and drawbacks of each approach and talk about how these tools and technologies will deepen our understanding of metastasis. 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.

The complicated process of metastasis includes 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.

Introduction

It is difficult 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, 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.

For the few cancer cells that are available for investigation at different stages of the metastatic cascade from diverse original tumours, circulating tumour cells (CTCs), and distant metastatic organ locations, sensitive and reliable metabolomic tools are essential. It is now possible to examine the metabolomic profile of tiny numbers of cancer cells because of advancements in apparatus cancer cells that have spread to patients' bodies and experimental models. We go over each method's benefits, drawbacks, and obstacles to be overcome. Understanding the metabolic weaknesses of cancer during metastasis is essential for the creation of novel medicines to prevent the growth of metastases.

For assessing metabolites in biological samples, quantitative metabolomics has long been a potent analytical method. Metabolomic technologies are continually developing, leading to new improvements in analytical techniques, models, software, and computational approaches to increase sensitivity and specificity. This is similar to many '-omics' disciplines. NMR spectroscopy, gas chromatography-mass spectrometry (GC-MS), and liquid chromatography-MS (LC-MS) are just a few of the decades-old methods that have proven to be useful for detecting and quantifying metabolites in cancer metastasis. These methods can only distinguish the metabolic heterogeneity on a single-cell level and need a sizable number of cancer cells (>10,000 cells). Defining the metabolic Process heterogeneity within a tumour is crucial because variations in cancer cell subgroups within a tumour might affect the degree of effective metastasis and a patient's potential

response to treatments. It may be possible to forecast which cancer cells are likely to metastasis effectively using the presence or absence of key metabolic characteristics in subsets of cancer cells. These characteristics might then be used as biomarkers for diagnostic prognosis.

Subjective Heading

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 inside the TME have different functions in metastatic melanoma and primary and metastatic tumours of head and neck malignancies. In bulk tumour tissues, altered metabolic activity was not seen. Due to the significant inpatient heterogeneity and potential application as a liquid biopsy

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metastasis biomarker, SCM and low-cell number metabolomics are 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 analysis of CTCs is still difficult, though. Several studies have examined how cancer cells change their metabolism when they spread to distant organs and used isotope tracing to compare their metabolic patterns in primary tumours and metastasis. This method has been used on patient-derived xenografts (PDXs), where it was found that melanoma cells are dependent on lactate for effective metastatic seeding and become more sensitive to oxidative stress during metastasis. It has been demonstrated that the ability of detached cancer cells to metastasize affects the formation of clusters in lung cancer. When in By changing their metabolism to mitigate oxidative stress, cancer cells are shielded from reactive oxygen species that are prevalent in the bloodstream. Cancer cells from disseminated lung metastases have different metabolic requirements on pyruvate carboxylase activity than cancer cells from main tumours, as demonstrated by the infusion of (U-13C) glucose into mice with primary breast cancer. These findings show how the complicated interactions between *in vivo* metabolism and metastasis can be understood using isotope tracking.

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 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 inside the TME have different functions in metastatic melanoma and primary and metastatic tumours of head and neck malignancies. In bulk tumour tissues, altered metabolic activity was not seen. Due to the significant intrapatient heterogeneity and potential application as a liquid biopsy metastasis biomarker, SCM and low-cell number metabolomics are 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 initial 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 is an alternative for CTC enrichment that uses a gentler approach than flow cytometry. It catches individual CTCs depending on size. However, compared to flow cytometry, this microfluid system has a lower flow-through, and there are restrictions on the number of CTCs that may be collected in a single 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 advancements in sample preparation techniques that boost the metabolic integrity of the cells being studied. 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 colleagues recently demonstrated that metastatic breast cancers had larger levels of N-glycans compared with basic tumours by skillfully using MALDI-MSI to analyse glycosylation of breast cancer cells throughout metastatic progression in tissue microarrays [38]. 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 MALDI-MSI is a highly promising technology for the diagnosis, comparison of primary tumours and metastases for therapy decision-making, as well as for the measurement of metabolites inside a sample, according to foundational research and others.

MALDI-MSI is not without its drawbacks, however, including low sensitivity and the inability of particular matrices to ionise a range of analytes, including low molecular weight ions. Second, matrix tissue mounting by MALDI-MSI can result in metabolite delocalization, which lowers the specificity of the metabolites identified at individual spatial sites. With regards to the method of choice for matrix application, these restrictions can be removed by advancements in matrix composition and sample preparation. Desorption electrospray ionization-mass spectrometry imaging (DESI-MSI) and secondary ion mass spectrometry (SIMS) are two more matrix-free *in situ* metabolomics methods that are accessible. SIMS, MALDI-MSI, and DESI-MSI all have single-cell/subcellular spatial resolution. has a spatial resolution of 200 m and does not. The mass-to-charge ratio (m/z) detection range, sensitivity, sample preparation time, and data analysis time are thus factors that influence the approach for *in situ* SCM (i.e., MALDI-MSI and SIMS). Due to its great sensitivity and practical spectrum analysis, MALDI is still the most often used ionisation technology for MSI today.

The metabolic pathways of tumour cells are modulated and reprogrammed by the interaction of cell-intrinsic factors (such as cell origin) and cell-extrinsic factors (such as cell-cell contacts and local food sources). Therefore, it is crucial to spot and assess metabolic changes occurring in tumour cells during *in vivo* metastasis. The assessment of active metabolic pathways in tissues can be done directly using *in vivo* models and cutting-edge technologies, such as isotope tracking, and similar techniques can also be used with patient samples.

The tracking of nutrients marked with stable (such as ^{13}C , ^2H , and ^{15}N) or radioactive (such as ^{18}F , ^3H , and ^{14}C) isotopes that are then further studied by MS and/or NMR is known as “isotope tracing”. This technique pinpoints the locations where atoms from the injected substrate (tracer) are converted to (tracee). Therefore, isotope tracing offers thorough information on contributions to certain pathways, such as a substrate being metabolised through the tricarboxylic acid (TCA) cycle, pentose phosphate route, etc. There are a few prerequisites needed to quantify and understand isotope tracing studies: I the system must be at metabolic steady state the infusion of isotope tracer must occur at isotopic steady state ($ddt=0$), where the incorporation of the isotopically labelled atoms is consistent over time. equal to the blood level to guarantee route tracking and avoid isotope concentration-dependent activity. Because stable isotope tracers are naturally occurring and have a non-zero abundance, they have a lesser sensitivity than radioactive tracers. Particularly, the naturally occurring isotope abundances of ^{13}C , ^{15}N , and ^2H are 1.16%, 0.337%, and 0.0156%, respectively. Although ^{18}F -FDG (fluorodeoxyglucose), a radioactive glucose analogue, is frequently used in the diagnosis of cancer patients because it allows for the direct measurement of glucose uptake, radioactive tracers have a

number of drawbacks, including the possibility of radioactivity's toxic effects, the need for chemical separations, shorter half-times (^{18}F $t_{1/2} = 108$ min), and the requirement that radioactive and nonradioactive species for each metabolite be measured separately

In both adult and paediatric malignancies, the metabolism of the malignancy has also been studied using isotope tracers (Figure 1B). Johnston and colleagues showed that primary paediatric cancers use the TCA cycle and glycolysis to consume glucose *in vivo* using this method. Clear cell renal cell carcinomas (ccRCCs) have more glycolytic activity than primary and metastatic brain tumour lesions in adult patients, whereas TCA cycle activity is still inhibited, according to isotope tracing. In order to comprehend tumour metabolism and identify prospective treatment targets, isotope tracing is a useful tool.

However, there are drawbacks to isotope tracing, the main one being the cost since significant amounts of isotope reagent are needed for adequate enrichment. As tracer doses are given through infusions with bolus or injections and eventually spread across all bioavailable compartments in the animal model, another drawback is the unavoidable saturation of the injected isotope with time. As a result, non-invasive tracer delivery techniques such liquid meals may be a good choice for long-term administration. However, the liquid diet approach needs to be carefully considered. Depending on the proposed scientific hypothesis, differences in feeding behaviour will also encourage an unbalanced uptake of tracer. It is significant to highlight that while isotope tracing can offer details on active metabolic pathways, it only offers enrichment and does not, by itself, offer measurements of flow.

Metabolic flux analysis (MFA) is a technique for measuring intracellular metabolite production and consumption (fluxes) in a user-defined system that offers thorough insights into metabolic control and change. Flux balance analysis (FBA) and stoichiometric flux analysis are two examples of the many models of flux analysis that can be used to get a numerical solution and quantitative value. Isotopic tracing must be linked with external fluxes like as growth rates (biomass production), metabolite uptake/secretion rates, and others in formal isotope-based flux analysis. rates of isotope injection. MFA is typically carried out in tissue culture or microbe models, where it is simple to regulate the elements that cause variance. MFA, however, has recently undergone *in vivo* evaluation. It has been employed in tissue culture to show that glutamine is reductively carboxylated to produce citrate and to demonstrate that cell lines derived from Kras^{LSL-G12D/+}; Trp53^{loxP/loxP} lung cancers secrete more lactate.

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. The characterization of "malignant" metabolic patterns of cancer cells that are metastasizing and advancements in the sensitivity of metabolite identification are still needed for patient classification., The prognosis and treatment are still unclear (see Outstanding questions). 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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