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Opinion

Choline, Ketones and Purines: Cracking the Metabolic Enigmas of Soft Tissue Sarcoma

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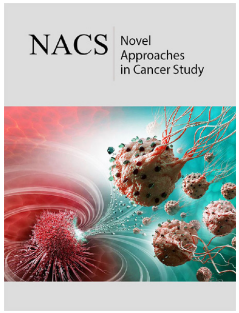

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Abstract

Soft tissue sarcomas (STS), a diverse group of mesenchymal malignancies, present a diagnostic mystery due to their heterogeneity and the restrictions of traditional methods. Invasive biopsies offer a stationary outline of a dynamic process, failing to capture the tumor's evolving metabolic landscape. This opinion conceives that untargeted metabolomics, specifically when applied to liquid biopsies, offers an exemplar shift in STS diagnostics. By cross-examining the circulating metabolome, we can gain real-time insights into tumor behavior, treatment response, and metastatic potential. This method moves beyond static genetic markers, revealing a metabolic illusion that replicates the tumor's adaptation to its microenvironment. Important metabolites, such as ketone bodies, choline derivatives, and purines, emerge as potential biomarkers, offering a preview into altered energy metabolism, membrane dynamics, and cell proliferation. Integrating metabolomic data with genetic profiling provides a universal understanding of STS biology, paving the way for earlier detection, personalized therapies, and improved patient outcomes. A call for collaborative action is essential to harness the full potential of untargeted metabolomics in the fight against STS.

Keywords: Cancer metabolomics; Soft-tissue sarcomas; Oncogenic-physiology; Personalized therapy; Liquid biopsies

Abbreviations: STS: Soft Tissue Sarcomas; GC-MS: Gas Chromatography-Mass Spectrometry; LC-MS: Liquid Chromatography-Mass Spectrometry; LC-MS/MS: Liquid Chromatography with Tandem Mass Spectrometry (also known as LC-MS2); MRI: Magnetic Resonance Imaging; FISH: Fluorescence In Situ Hybridization; RNA-seq: RNA Sequencing; 18F-FDG: 18-FluoroDeoxyGlucose; EWSR1-FLI1: Ewing Sarcoma; RNA Binding Protein 1-Friend Leukemia Integration; Transcriptional Activator; FUS-CHOP: Fusion-CCAAT/Enhancer Binding Protein Homologous Protein; SS18-SSX: Synovial Sarcoma Translocation; Chromosome 18-Synovial Sarcoma X breakpoint; COL1A1-PDGFB: Collagen Type I Alpha 1 Chain-Platelet-Derived Growth Factor Subunit B; MDM2: Mouse Double Minute 2; CDK4: Cyclin-Dependent Kinase 4; TP53: Tumor Protein P53; RB1: Retinoblastoma 1; PIK3CA: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha; AKT: Protein Kinase B; mTOR: Mammalian Target of Rapamycin; CT: Computed Tomography; US: Ultrasound; PET: Positron Emission Tomography; ATP: Adenosine Triphosphate; GTP: Guanosine Triphosphate; DNA: Deoxyribonucleic Acid; RNA: Ribonucleic Acid; ctDNA: Circulating tumor DNA; CTCs: Circulating tumor cells

Introduction

Soft tissue sarcomas (STS), the heterogenous, infrequent yet intensely aggressive group of malignancies originating from the body's structural framework of mesenchymal tissues, present a considerable snag in the field of oncology. With a composition of around 1% of all adult cancers and nearly 15% of solid pediatric tumors, this family brags more than 70 individual subtypes, each flaunting its own distinctive genetic blueprint and behavioral characteristics in a clinical setting. STSs are caused due to multiple reasons inclusive of which are mesenchymal tissue origin, genetic abnormalities like gene fusions, mutations, and chromosomal aberrations. As it stands, the complex nature of these tumors complicates the diagnosis, severely cutting short the effectiveness of available treatment strategies, and ultimately contributes to a 5-year survival rate that tenaciously lingers between 50-

70%. Traditional analytical methods, particularly invasive tissue biopsies, often fall short, providing nothing more than a transitory foretaste of the ever-changing metabolic processes driving cancer progression, while completely ignoring potential genetic interactions that could spur the process on. We're essentially trying to predict a hurricane with a single snapshot of a cloud – woefully inadequate. As treatment strategies for these types of cancer all too often fall short, the implementation of research that could have new pathways to target or focus is highly expedient for a successful treatment outcome for future patients. The current methods for treatment and diagnosis are flawed and incomplete, meaning it is absolutely necessary for there to be new ways to fight and target STS and similar cancer types. It is essential that the world begin to focus on these cancers as a world epidemic that must be targeted as soon as possible. With these diseases being an orphan for most countries when it comes to care, a call for research is an essential component of these new strategies [1].

The roots: causatives of STSs

Genetic aberrations are recognized as critical drivers in STS; however, gene fusions also play a crucial role in tumor formation. Specific examples illustrate this point: the EWSR1-FLI1 fusion in Ewing sarcoma, where the EWSR1 gene on chromosome 22 fuses with partner genes, resulting in aberrant transcriptional regulation; the FUS-CHOP fusion observed in myxoid liposarcoma; and the SS18-SSX fusion, pathognomonic for synovial sarcoma, involving the fusion of the SS18 gene on chromosome 18 with one of the SSX genes (SSX1, SSX2, or SSX4) on the X chromosome. Additionally, the COL1A1-PDGFB fusion in dermatofibrosarcoma protuberans leads to the overexpression of PDGFB and subsequent autocrine stimulation of PDGF receptors. Beyond fusions, copy number alterations and point mutations are also implicated in STS pathogenesis. These include amplifications of oncogenes, such as MDM2 and CDK4 in well-differentiated and dedifferentiated liposarcomas, and deletions of tumor suppressor genes, such as TP53 and RB1, as well as activating mutations in genes such as PIK3CA leading to activation of the PI3K/AKT/mTOR signalling pathway. However, relying solely on genetic snapshots is like navigating a ship by looking at the stars while ignoring the currents beneath the surface. STS tumors are not static entities defined by their genetic mutations; they are dynamic ecosystems constantly adapting to their environment. While genetic testing provides a valuable foundation, it's time to acknowledge its limitations and explore the more fluid metabolic landscape that dictates a tumor's behavior [1,2].

From subtle signs to solid diagnostics

Spotting a soft tissue sarcoma can be tricky at first. Often, the earliest sign is just a lump that you might not even notice because it doesn't hurt. It's usually deep under the skin and feels kind of firm. But this isn't your average bump-it tends to stick around and gradually get bigger, and that's when it might start to cause some discomfort. Where else it pops up can lead to different clues. If it's on an arm or leg, you might see swelling or feel a mass, and things might get stiff around a nearby joint. If it's in your belly, you could have ongoing pain, feel bloated, or notice changes in how your bladder or bowels are working. Sometimes, you might just feel full quickly when eating or even lose weight without trying. If it's near your lungs, you might develop a cough that won't quit or have chest pain and trouble breathing. By the time someone gets an ultrasound or MRI, delays can creep in, especially if the imaging isn't interpreted with sarcoma in mind. That's why getting to a specialist quickly matters: they know to order the right scans and avoid pitfalls like unplanned biopsies, which can complicate treatment later. A proper diagnosis hinges on a good biopsy, analyzed by experts who can spot subtle clues under the microscope. Nowadays, genetic testing adds another layer, pinpointing unique mutations or fusions that guide personalized care [2].

Limitations of traditional investigation and new advancements

The disadvantages associated with tissue biopsies in the widespread exploration of STS' convoluted dynamics have grown progressively ostensible. Tissue biopsies, priceless during the initial steps of both diagnosis and classification, deliver only a solitary, time-constrained evaluation of the tumor's defining features. However, tumors must not be viewed as fixed entities; they possess the capacity to evolve and transform with the passing of time, demonstrating remarkable spatial as well as temporal heterogeneity. Traditional investigations for this type of cancer have been difficult as scientists are only able to see one point in time of cancer, while not allowing for the dynamic changes that the cancer goes through. In simpler terms, a biopsy, when sampled from one specific region of the tumor at a discrete point in time, may fail to provide a comprehensive reflection of the tumor's collective conduct or its reaction to various treatment strategies. What is more is the very character of this, means it's a small preview of what is potentially going on [3,4].

Liquid biopsies, in sharp contrast, offer scientists a more approachable technique, one that provides a close-up view of a tumor's metabolic processes, and the ability to witness it firsthand, and in actual time. By examining circulating biomarkers inside the bloodstream, liquid biopsies manage to provide a more comprehensive and fluid understanding of exactly how tumors conduct themselves. The ability to collect liquid biopsies at multiple points throughout the span of a disease's existence allows researchers to monitor progress and see how the treatments are affecting the cells *in vivo* [2,4].

The assurance of untargeted metabolomics

The inherent variety within STS adds complexity to the already multidimensional challenge, and also makes the need for comprehensive and adaptive strategies all the more apparent. Possessing over seventy distinct forms, each brandishing unique physical traits and displaying distinct biological manners, STS is a symbol of the wide range of cancers that is hard to understand or categorize. A "one-size-fits-all" method for both diagnosis and subsequent treatment isn't just challenging, it's almost impossible.

With the variety of the cancer being a hindrance on progress, it is also very hard to create new strategies and treatments, all of which is a perfect reason for a push for more research and funding to combat STS [1-4].

Untargeted metabolomics, in conjunction with nuclear magnetic resonance, has potential as a new approach. By examining a broad spectrum of components, untargeted metabolomics dives deep into the world of biological functions and cellular processes, and may even shine a light on the manner in which metabolic pathways react and relate to different biological and chemical states. This approach is far more accessible and adaptable in the world of cellular and molecular biology [2,3].

"A case study: Untargeted metabolomics, employing GC-MS and LC-MS/MS, was utilized to profile plasma from 95 glioma patients, 68 meningioma patients, and 71 healthy controls, revealing distinct metabolic signatures associated with each tumor type. Comparative analysis identified 97 significant metabolites in gliomas versus controls, 56 in meningiomas versus controls, and 27 differentiating gliomas from meningiomas, implicating pathways such as arginine biosynthesis and metabolism, the Krebs cycle, and lysine degradation. Notably, 2-aminoadipic acid emerged as a potential discriminatory metabolite between gliomas and meningiomas, offering a deeper understanding of the metabolic changes underlying brain tumor development and progression" [2].

Unveiling metastatic processes: choline, ketones, and purines

Cancer cells exhibit an altered metabolism in order to sustain energy demands, support proliferation, and adapt to the environment surrounding the tumor, including increased energy consumption, rapid multiplying and expansion. Over time, this will lead to the body weakening in different key areas. Tumors must adapt and evolve. The constant monitoring of said tumors allows scientists to track how each tumor progresses and how treatments have affected the individual. A combination of genome and metabolism readings can ensure that a patient has the right treatment and is able to target cells [5] (Table 1 & 2).

Table 1: Advantages and Disadvantages of various Diagnostic methods employed in STSs Diagnosis.

Diagnostic Method	Advantages	Disadvantages	Specific Considerations/ Limitations	Reference
Tissue Biopsy	Confirms diagnosis; Subtype determination; Grading of tumor; Information on tumor architecture.	Invasive; Sampling error (may not represent entire tumor); Limited temporal resolution (snapshot in time); Doesn't capture tumor heterogeneity; Potential for complications (seeding).	Requires expert pathologist interpretation; Should be performed by experienced surgeon/radiologist to minimize complications; Site selection is crucial for accurate diagnosis; Doesn't always inform about metastatic risk or therapeutic response.	[3,4]
Liquid Biopsy	Non-invasive; Real-time monitoring of tumor dynamics; Can capture tumor heterogeneity (circulating biomarkers).	Lower sensitivity than tissue biopsy (especially for early-stage disease); Limited information on tumor architecture; May not detect all STS subtypes; Standardization challenges.	Requires robust biomarker validation; Data interpretation can be complex; Circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), exosomes, and metabolites can all be analyzed. Not used in the case study.	[1,2]
Imaging (MRI, CT, US)	Non-invasive; Tumor localization and staging; Monitoring response to therapy; Can guide biopsies.	Limited ability to differentiate between benign and malignant lesions; Cannot provide definitive diagnosis without biopsy; Subjective interpretation; Can miss microscopic disease.	MRI is preferred for local staging; CT for detecting lung metastases; Ultrasound can differentiate cystic from solid masses; Functional imaging (e.g., PET) can assess metabolic activity. Combining imaging modalities can improve diagnostic accuracy.	[2,6]
Untargeted Metabolomics	Captures global view of metabolic changes; Potential for identifying novel biomarkers; Can reveal dysregulated pathways.	High cost; Requires specialized equipment and expertise; Data analysis can be complex; Metabolite identification challenges; Limited translational validation in STS (needs more STS-specific studies).	Can be performed on tissue or biofluids (e.g., plasma); Requires robust experimental design and statistical analysis; Integration with other "omics" data (genomics, proteomics) can provide a more comprehensive view of STS biology. High cost and specialization required might not be a great decision when there's other options.	[1,2]

The Table elucidates the advantages and the disadvantages of various diagnostic methods used to diagnose soft tissue sarcomas along with specific considerations or limitations.

Table 2: This table informs the readers about various metabolites which can be used as biomarkers in diagnosis of soft tissue sarcomas.

Metabolite	Potential Role in STS	Supporting Evidence (If Available)	Analytical Method (Example)
Ketone Bodies	Altered energy source for tumor cells; may indicate metabolic stress or adaptation to nutrient deprivation; could influence metastasis.	General knowledge of ketone body metabolism in cancer cells adapting to low-glucose environment; no specific STS reference in the provided text. (Need to find ext. source)	LC-MS
Choline & Derivatives	Membrane biosynthesis (phospholipid synthesis); cell signaling; potential link to cell proliferation; membrane dynamics in liquid biopsies.	General knowledge of choline metabolism in rapidly dividing cells and its connection to phospholipid synthesis; No specific STS reference in the provided text. (Need to find ext. source)	LC-MS
Purines (ATP, GTP, etc.)	Energy metabolism; DNA/RNA synthesis; cell signaling; could indicate altered proliferation rates or immune responses within the tumor.	General knowledge of purine metabolism's role in cell growth, DNA synthesis, immune responses; No specific STS reference in the provided text. (Need to find ext. source)	LC-MS
Arginine	Involved in the synthesis of polyamines, which are essential for cell proliferation and growth. May play a role in immune suppression within the tumor microenvironment	Study finds Arginine is key to cancer proliferation	GC-MS
2-aminoadipic acid	Might be related to the altered lysine degradation process inside the cell, with more cancerous cell	Study finds 2-aminoadipic acid is key to cancer proliferation	GC-MS

Abbreviations used: ATP: Adenosine Triphosphate, GTP: Guanosine Triphosphate, Arg: Arginine (standard three-letter amino acid abbreviation), 2-AAA: 2-Aminoadipic Acid (non-standard abbreviation; derived contextually), STS: Soft Tissue Sarcoma, LC-MS: Liquid Chromatography-Mass Spectrometry, GC-MS: Gas Chromatography-Mass Spectrometry

Metabolic alterations may encompass changes in ketone body metabolism, choline metabolism, and purine metabolism, each potentially reflecting distinct aspects of the disease process. For instance, altered ketone metabolism could indicate shifts in energy utilization within endometriotic lesions, while changes in choline metabolism might reflect altered phospholipid synthesis or degradation. Purine metabolism, vital for DNA/RNA synthesis and energy transfer, could also be dysregulated, mirroring increased cellular proliferation or altered immune responses observed in endometriosis [6].

Conclusion: A Call for Collaborative Action

In conclusion, the future of STS diagnostics lies in a collaborative approach that synthesizes our growing understanding of both genetic and metabolic landscapes. By integrating genetic profiling-identifying key drivers like gene fusions (e.g., EWSR1-FLI1) and mutations in tumor suppressor genes with untargeted metabolomics, we can gain a more holistic view of STS biology. This integrated approach allows us to detect specific metabolic signatures, including alterations in ketone metabolism (reflecting energy utilization), choline metabolism (indicating membrane dynamics), and purine metabolism (tied to cell proliferation). These metabolites, when combined with genetic markers, hold the potential to improve diagnostic accuracy and risk stratification, leading to earlier detection, more personalized treatment strategies, and ultimately, improved outcomes for STS patients.

Acknowledgement

Yashi Mahendra solely wrote the opinion

References

1. Grasso D, Marzocchi B, Scoccianti G, Palchetti I, Campanacci DA, et al. (2025) Untargeted metabolomics and liquid biopsy investigation of circulating biomarkers in soft tissue sarcoma. Cancers 17(3): 553.
2. Chang L, Hou X, Li D, Wang X (2025) Metabolite changes in patients with endometriosis: New potential diagnostic and therapeutic targets. Reproductive and Developmental Medicine.
3. Godlewski A, Mojsak P, Pienkowski T, Lyson T, Mariak Z, et al. (2025) Metabolomic profiling of plasma from glioma and meningioma patients based on two complementary mass spectrometry techniques. Metabolomics 21(2).
4. Ghabrial J, Stinnett V, Ribeiro E, Klausner M, Morsberger L, et al. (2024) Diagnostic and Prognostic/Therapeutic significance of comprehensive analysis of bone and soft tissue tumors using optical genome mapping and next-generation sequencing. Modern Pathology 38(4): 100684.
5. Menyailo ME, Kopantseva EE, Khozyainova AA, Korobeynikova AA, Denisov EV (2024) Soft tissue sarcomas at the single-cell and spatial resolution: new markers and targets. Cancer Gene Therapy 32(1): 11-21.
6. Wu T, Xie J, Feng H, Zhang H, Tao J, et al. (2025) Correlation between METTL3 overexpression and 18F-FDG uptake in patients with soft tissue sarcoma. BMC Cancer 25(1): 27.