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Quantifying and mapping ATP distribution within tissues to inform targeted therapeutic strategies in drug development.

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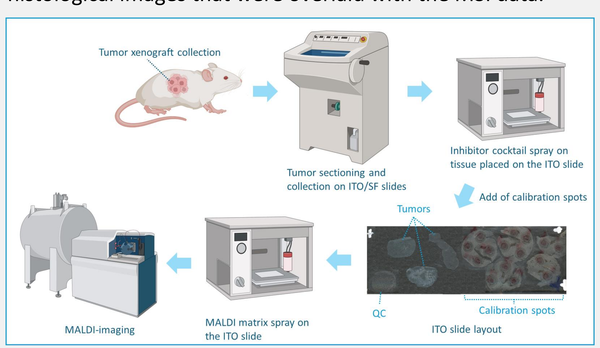
PURPOSE

ATP levels, as indicators of cellular metabolic activity, offer critical insights into the viability and growth dynamics of tumor cells, presenting potential targets for therapeutic strategies. The aim of this study is to explore how ATP distribution and quantification across various mouse tumor models can optimize drug development approaches. For this purpose, we utilized Quantitative Mass Spectrometry Imaging (QMSI) to measure ATP levels in different mouse models, determining the most suitable model for targeted drug development.

METHOD

Fifteen tumor biopsies from three distinct cancer models were sectioned using a cryostat and mounted on Indium-Tin-Oxide (ITO) glass slides or SuperFrost slides for mass spectrometry imaging (MSI) and Hematoxylin-Eosin (H&E) staining, respectively. Tissue sections on ITO slides were treated with a STOP solution to inhibit metabolization or conversion of ATP to ADO in the tissue sections. ATP-$^{13}C_{10}$,$^{15}N_5$ dilutions were applied to control tissues, and slides were coated with MALDI matrix containing ATP-$^{13}C_{10}$ for normalization purposes. The slides were analyzed using a Solarix 2XR 7T-MALDI FTICR. Data analysis was performed using Multimaging 1.3 software. Adjacent sections on SuperFrost slides were stained with H&E, producing histological images that were overlaid with the MSI data.



Workflow for ATP study by MALDI-imaging.

RESULTS

ATP concentration in Tumors

- In the three xenograft models studied, the highest ATP concentration is consistently found in tumor tissues compared to stromal and necrotic areas. This suggests that tumor cells have higher metabolic activity, requiring greater ATP production to support their rapid growth and proliferation.

Variation in ATP Concentration Between Models

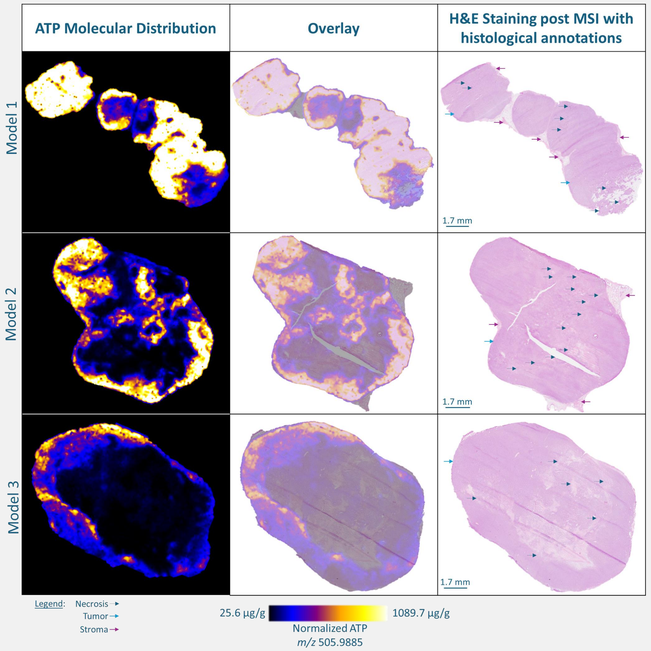
- The models show differences in ATP levels in tumor and necrotic areas. Model 1 has the highest ATP concentration in both areas (550.68 µg/g and 215.20 µg/g of tissue respectively) while Model 2 has the lowest (312.29 µg/g and 129.23 µg/g of tissue respectively). This may indicate that Model 1 represents a more aggressive or metabolically active type of tumor, whereas Model 2 could represent a less aggressive or metabolically less active tumor.

Implications on Tumor Metabolism

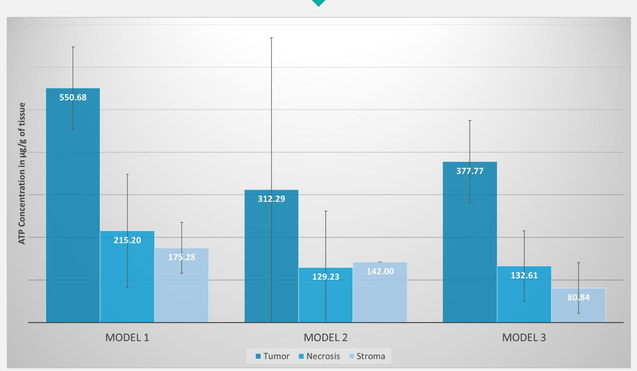
- The results suggest that energy metabolism, as represented by ATP concentration, varies not only between different tissue types (tumor, stroma, necrosis) but also between different xenograft models. This variation can be used to better understand the specific metabolic characteristics of tumors and to develop targeted therapeutic strategies based on the energy metabolism of tumor cells.

Importance of Model Selection

- The observed differences between models highlight the importance of selecting the appropriate model for preclinical cancer studies. Models with higher ATP levels in tumors might be more representative of aggressive human cancers and could be used to test the efficacy of new targeted energy therapies.



Example of endogenous ATP distribution in xenografts from each of the three studied models.



ATP Absolute quantification in xenografts from each of the three studied models (n=5)

CONCLUSIONS

Our research showcases the technical feasibility and potential applicability of utilizing ATP distribution and quantification as a dependable tool for steering therapeutic targeting in drug development. The successful utilization of Quantitative Mass Spectrometry Imaging (QMSI) methodologies to gauge ATP levels within tumor tissues underscores the accuracy and reliability of this approach. Through the integration of QMSI with advanced software-generated calibration curves, we achieved precise and quantitative evaluations of ATP concentrations across diverse tumor models. Ultimately, our findings underscore the importance of ATP distribution and quantification in facilitating targeted therapeutic approaches in drug development. By mapping the spatial distribution of ATP within tumor tissues derived from various models, we can pinpoint regions characterized by heightened metabolic activity, thus aiding in model selection and the optimization of targeted therapies.

REFERENCE

Accurate measurement of endogenous adenosine in human blood. Lars Löfgren, Susanne Pehrsson, Gunnar Hägglund, Henrik Tjellstroï, Sven Nylander. *PLoS One*. 2018; 13(10): e0205707.