Metabolomic profiling of Gastrointestinal Stromal Tumor (GIST) in Human Tissue Samples and Xenografts

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Background

There is a growing need for novel agents to treat resistant GIST. The goal of this study was to characterize and identify potential therapeutic targets in the metabolic profile of GIST.

Methods

Human GIST T1 cells were incubated with imatinib 0.5 μM with harvesting at time 0, 24 hrs and 48 hrs. Tumor, extracted for analysis. 1H-NMR adjacent control tissue samples from with imatinib 0.5 10 patients (Seven exposed to imatinib or sunitinib) and three tumor samples from xenografts in nude processed. Energy state, glucose cryoprobe head, were acquired and processed. Human GIST T1 cells were incubated with imatinib or sunitinib and identified with metabolic profile of targets in the metabolic profile of GIST.

The sample from patients and xenografts were identified and correlated with clinical and histopathologic findings.

Results

Findings in cell lines, tissues and xenografts suggest shift from cytosolic glycolysis (glucose decrease and increased lactate with minimal changes in pyruvate) towards the mitochondrial Krebs cycle (elevated glutamine and glutamate synthesis) in all tumor samples. Aspartate, myo-inositol, and cell membrane phospholipids such as phosphocholine/ gycerophosphocholine were greater in untreated GIST xenografts compared to treated tumors. Alanine, taurine, proline, ADP and phosphocholine were significantly higher in tumor tissue extracts compared to control (imatinib treated) (p<0.05). Tumor stage, mitotic index or mutation type did not correlate with metabolomics profile. Differences were accentuated among untreated patients. Partial Least Squares-Discriminant Analysis (PLS-DA) model successfully separated tumor tissues from controls (R²Y=0.56).

Conclusion

Metabolomic profiling of GIST cell lines, patient and xenograft GIST samples exposed to KIT inhibitors suggest that cytosolic glycolysis and phospholipid biology may be important not only in the GIST phenotype but may be ameliorated with KIT inhibition by imatinib. Further understanding of GIST metabolomics may lead to the identification of new therapeutic targets.