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Anatomical dissection of metabolic systems of cancer by in vivo high-resolution imaging mass spectrometry

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Metastatic progression of cancer does not only upregulate their glucose metabolism but might utilize metabolic properties of host organs that benefit cancer metabolism, although such a hypothesis remains elusive. Newly developed microscopic imaging mass spectrometry combined with MS^2 analyses allowed us to collect micrographs of many different metabolites in a single frozen section, and combination with CE-MS data collected from the serial section provided semiquantitative information of individual signals. The current method revealed that human colon cancer xenografts metastasized in livers of super-immunodeficient NOD/scid/γnull (NOG) mice deprives L-alanine to support their metabolic demands for synthesizing glutathione and nucleotides. In this model, hepatic metastasis triggered regenerative responses of the host liver concurrently with hypoglycemia and accumulation of glutathione and nucleotides in the tumor-bearing liver. MS^2 analyses under loading $^{13}C_3$-L-alanine provided evidence for earlier filling of glutathione with $^{13}C_2$-γ-glutamylcysteine structure in metastases than surrounding liver parenchyma. The $^{13}C_3$-L-alanine loading also caused an increase in $^{13}C_2$-UDP in metastatic foci and in the host liver. MS^2 analyses to assess the pathways for ^{13}C incorporation revealed that L-alanine not only undergoes gluconeogenesis in the host to synthesize ribose but serves as a substrate to supply glutamate and pyrimidine carbons for nucleotide synthesis occurring in the metastases. Our results suggest that human colon cancer metastases utilize gluconeogenic substrates of the host not only through pentose phosphate pathway but through glutaminolysis, supporting their metabolic demand of glutathione and nucleotides to cause hypoglycemia.

Biography

Makoto Suematsu, MD, PhD is the leader of JST, ERATO Suematsu Gas Biology Project. The authors developed semi-quantitative imaging MS to examine spatio-temporal profiling of metabolites in mouse brain ischemia model (Antioxid Redox Signal 2010), and applied CE-MS-based metabolomics (Cancer Cell 2011) or high-resolution imaging MS to analyze metabolites of human cancer xenografts in superimmunodeficient mice (Anal Bioanal Chem 2011). Development of imaging MS was supported by Shimadzu and JST SENTAN, Japan.