OMICS International
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Metabolomics 2015, 4:3
http://dx.doi.org/10.4172/2153-0769.S1.029

4th International Conference and Exhibition on

Metabolomics & Systems Biology

April 27-29, 2015 Philadelphia, USA

Rare insights into cancer biology

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Cancer associated mutations have been identified in the metabolic genes Succinate dehydrogenase *(SDH),* Fumarate hydratase *(FH)* and Isocitrate dehydrogenase *(IDH)*, advancing and challenging our understanding of cellular function and disease mechanisms and providing direct links between dysregulated metabolism and cancer. Some striking parallels exist in the cellular consequences of the genetic mutations within this triad of cancer syndromes, including accumulation of oncometabolites and competitive inhibition of 2-oxoglutarate-(2OG)-dependent dioxygenases, particularly hypoxia-inducible factor prolyl hydroxylases (HIF-PHDs), JmjC domain-containing histone demethylases (part of the JMJD family) and the TET (ten-eleven translocation) family of 5methyl Cytosine (5mC) DNA hydroxylases. These lead to activation of HIF-dependent oncogenic pathways, inhibition of histone and DNA demethylation and hydroxylation of 5 mC. Mutations in FH, resulting in loss of enzyme activity, predispose affected individuals to a rare cancer, hereditary leiomyomatosis and renal cell cancer (HLRCC), characterized by benign smooth muscle cutaneous and uterine tumors (leiomyomata) and an aggressive form of collecting duct and Type 2 papillary renal cancer. Interestingly, loss of FH activity results in the accumulation of high levels of fumarate that can lead to the non-enzymatic modification of cysteine residues in multiple proteins (succination) and in some cases to their disrupted function; an example being succination of KEAP1 resulting in constitutive NRF2 expression. Here we consider that the study of rare diseases such as HLRCC, combining analyses of human tumours and cell lines with *in vitro* and *in vivo* murine models has provided novel insights into cancer biology, links associated with dysregulated metabolism, obesity and diabetes and represents a useful paradigm for cancer research.

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Metabolomic study of diurnal variation on pyrrolizidine alkaloid from *Jacobaea sp.* hybrids

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Recently, metabolomics have been applied to study the plant-host resistance. The cause of variation in results could be from biological variation rather than technical issues related to analytical platforms. Little attention has been paid to harvested time, although differences in the metabolomes may depend on day time. We investigated the effect of harvesting time on metobolomes of two hybrids of Jacobaea vulgaris and Jacobaea aquatica differing in their amount of the pyrrolizidine alkaloid jacobine N-oxide. Leaves of genotypes A and B (high and low levels of jacobine, respectively) were sampled daily at three harvest times: Morning (10:00 h), afternoon (15:00 h) and evening (19:00 h) during five consecutive days. Samples were subjected to 1H NMR. Qualitative and quantitative differences in metabolic profiles were analysed by multivariate analysis followed by a three-way ANOVA. The leaf metabolome was only affected by the harvesting time of the day, while the harvesting day had no influence. Independently from the genotype, senecionine N-oxide and succinic acid were accumulated in the morning while sugars and formic acid were accumulated towards the evening. For most compounds in the diurnal variation was similar, but jacobine N-oxide was found to have a significant interaction with both harvest time and genotype. Genotype A showed a much stronger accumulation in the morning. The results suggest that harvest time is an important factor in metabolomics results. Samples from the same genotypes collected at different times of the day may cause a metabolic variation, leading to equivocal conclusions.

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