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Session 9) Metabolism & Medical Application of Isotopologue

Isotopologue biomarkers for cancer

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In the past decades, cancer cell metabolism has been extensively studied using metabolomics and/or proteomics, but very few metabolic biomarkers have been used in the clinic. Challenges include small variations in concentration, difficulty in capturing metabolic flux patterns and limitations in the use of ^{13}C-labelled tracers, which are expensive and raise ethical issues. By probing the (bio)chemical origin of metabolites at the atomistic level, the abundance of stable isotopes captures metabolic fluxes, thereby providing a comprehensive and dynamic view of metabolism that is key to define relevant biomarkers. A change in stable isotope abundance during enzyme or transporter activity, referred to as isotope effects, stems from uneven velocities of heavy and light isotopic molecules (also called isotopologues). Hence, metabolic perturbations in cancer cells are expected to result in drastic changes in the abundance of isotopologues which define a specific metabolic fingerprint [1-3].

We developed a workflow to measure the ^{15}N and/or ^{13}C isotopic composition of specific compounds and positions within defined metabolites from biological samples collected from breast cancer patients and cell cultures. In doing so, we explored different analytical strategies for Position Specific Isotope Analysis (PSIA) in arginine, which is likely to be at the origin of the ^{15}N depletion observed in breast cancer [2]. We also assessed several methods using an on-line pyrolysis system and Gas Chromatography-Combustion-IRMS (GC-C-IRMS). This enabled us to identify potential breast cancer biomarkers and to obtain valuable information on site-specific isotope fractionation in complex mixtures. The generation of new isotopic data will improve our understanding of the metabolic origins of isotopic signatures by reconstructing metabolic patterns.

References

[1] Tea, I., Martineau, E., Giraudeau, P., Akoka, S. & Barillé-Nion, S. (2012) Method to characterize the origin and/or the state of pathological or healthy cells, and its applications in biology. International patent, WO2012/123886(A1).

[2] Tea, I., Martineau, E., Antheaume, I., Lalande, J., Mauve, C., Gilard, F., Barillé-Nion, S., Blackburn, A.C. & Tcherkez, G. (2016) ^{13}C and ^{15}N natural isotope abundance reflects breast cancer cell metabolism. Scientific Reports, 6.

[3] Tea, I., De Luca, A., Schiphorst, A.M., Grand, M., Barillé-Nion, S., Mirallié, E., Drui, D., Krempf, M., Hankard, R. & Tcherkez, G. (2021) Stable Isotope Abundance and Fractionation in Human Diseases. A review. Metabolites 11, 370