Metabolomics assisted with stable-isotope labeling: exploring neuronal metabolism related to Parkinson's disease

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Stellingen (Propositions)

Behorende bij het proefschrift

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Exploring neuronal metabolism related to Parkinson's disease

1. With the ongoing development of robust and mixed-mode stationary phases for hydrophilic interaction chromatography columns, a systematic evaluation aided by computational data analytics can facilitate the rapid determination of the optimal column type or chromatographic conditions for the analysis of the polar metabolome in a specific biological matrix. (*this thesis*)
2. From a metabolic perspective, genetic deficiency of PINK1 mutation involved in mitochondrial stress pathways could increase the susceptibility to neurodegeneration in response to the environmental toxin rotenone. Our results provide new insights into progressive neurodegeneration and hint at potential treatment strategies or possible early-intervention therapies. (*this thesis*)
3. The dynamic labeling changes conveyed by intact metabolite and moiety isotopologues obtained via our developed method can aid in the identification of altered enzyme activities along metabolic pathways of interest. (*this thesis*)
4. Integrating in vivo, in vitro, and in silico approaches with cellular metabolomics in attempts to understand the early-onset parkinsonism pathogenesis could ultimately accelerate the development of disease prevention and treatment in its early stages. (*this thesis*)
5. The effective and fair comparison of chromatographic performance in the analysis of a large number of molecules of diverse physicochemical properties is not trivial and necessitates innovative approaches, especially for the generation of descriptive illustrations. (*Lioupi et al. TrAC Trends in Analytical Chemistry. 2023*) Machine learning should be considered a future approach for predicting chromatographic performance targeting the global metabolome, next to experimental approaches.
6. Metabolic transformations through the network require numerous enzyme-catalyzed reactions that transfer the structural moiety among metabolites. Thus, the ability to track individual metabolic moieties will greatly reduce the ambiguities in metabolic network analysis. (*Fan et al. Journal of Biological Chemistry. 2022*) However, the sensitivity of the suggested approaches (NMR and DIA-MS/MS) is low; more extensive coverage of metabolites and capturing mass isotopologue distributions at both intact and moiety levels is possible with targeted MS/MS using high-resolution MS and Zeno trap pulsing.
7. Metabolomics, assisted with stable-isotope labeling shows power in addressing hypothesis-driven biological questions to unravel metabolic activity, but is largely restricted by the metabolite coverage. (*Wang et al. Nat Commun. 2022*) Tracing stable-isotope labeled metabolites with a global LC-MS method coupled with SWATH MS/MS analysis and automated extraction of metabolite isotopologues will be able to extend the required metabolite coverage.
8. Each cell type in the human nervous system displays a unique metabolic signature. Neurons and astrocytes are metabolically adapted cells that cooperate in fuel handling to meet the brain energy requirements of neurotransmission. (*Bonvento et al. Cell Metabolism. 2021*) Understanding the disruption of this complex neuron-astrocyte metabolic cooperation will benefit from stable-isotope labeling, tracer-based metabolomic analyses, and interactive metabolism model reconstruction.

9. A delicious dish generally encompasses diverse ingredients, each of which renders a unique contribution to the ultimate flavor. Likewise, it is the spirit of modern science to work across boundaries and beyond typical pigeonholing.
10. Above all, do not fear difficult moments. The best comes from them. (Rita Levi-Montalcini)

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