



## Editorial: Metabolic Flexibility

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**Editorial on the Research Topic: Metabolic Flexibility**

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Metabolic flexibility is essentially defined as the capacity to switch among energy substrates to generate ATP. Because ATP turnover is high and ATP reserve small, such capacity to generate ATP from different sources allows eukaryotic cells to survive in conditions of fluctuating fuel supply. At the whole-body level, the transition from fasting to feeding states determines cyclic changes in circulating and tissue fuel availability. Metabolic flexibility becomes crucial in adapting fuel oxidation to such transient oscillations in fuel supply. On the one hand, increased glucose supply will boost glucose oxidation while suppressing fatty acid oxidation upon ingesting carbohydrates. On the other hand, the absence of exogenous glucose (e.g. overnight fast) increases fat mobilization. As a result, a higher fatty acid supply to tissues will replace glucose as an energy source. The coordinated switch among energy fuels according to fuel availability is the core concept defining metabolic flexibility.

Classically, metabolic flexibility has been determined by the extent to which the respiratory quotient (an index of the proportion of carbohydrate and fat being oxidized for energy) increases from fasting to glucose/insulin-stimulated conditions (e.g. clamp, meal test challenge). Pioneer work by Kelley et al.<sup>1</sup> measured metabolic flexibility by using euglycemic-hyperinsulinemic clamps. They noted that individuals with obesity or type-2 diabetes manifested impaired metabolic flexibility compared with their lean, healthy counterparts. Such results prompted the notion that impaired metabolic flexibility could lead to insulin resistance and metabolic alterations. Contemporary studies also highlighted a strong inverse association between insulin sensitivity and ectopic lipid content<sup>2</sup>. This latter finding reinforced the idea that a mismatch between fuel oxidation and fuel availability (i.e. impaired metabolic flexibility) underlies insulin resistance.

This Research Topic in Metabolic Flexibility aimed to attract studies providing insights about determinant factors of metabolic flexibility and the health consequences of being metabolically inflexible. In this regard, Graves et al. elaborated a systematic review on the association between adipose tissue features (e.g. total amount, distribution) with metabolic flexibility. Such research work faced the challenge of comparing studies that conceived different settings and markers of metabolic flexibility. This heterogeneity in assessing metabolic flexibility has dampened the possibility of conducting comprehensive inter-study data analysis, for instance, through meta-analyses, a crucial tool to ponder the overall relevance of individual studies. From this systematic review, Graves et al. noted that adipose tissue total amount, waist circumference, and visceral fat were associated with metabolic flexibility, mainly when assessed by using the classic euglycemic clamp method. Which functional aspects of adipose tissue can directly influence and explain such association remains

elusive. One may speculate that adipose tissue amount, distribution, or both could influence circulating adipokines and metabolites, affecting oxidative tissue capacity and tissue fuel availability (i.e. metabolic flexibility). Kalafati et al. conducted additional work about adipose tissue by taking advantage of publicly available datasets. They assessed the contribution of relative macrophage frequencies on overall subcutaneous adipose tissue gene expression. Their analysis showed that subcutaneous adipose tissue from donors with high macrophage frequencies displayed increased inflammatory gene expression profile and decreased gene expression of lipid- and mitochondrial respiration-related pathways. From these studies, one may speculate that impaired metabolic flexibility could be one of the systemic consequences of such differential enrichment in adipose tissue macrophages.

Another study on this Research Topic (Fernández-Verdejo et al.) assessed volunteers of similar excess body weight and composition, age, and sex but contrasted metabolic flexibility to an oral glucose load. In general, such contrasting metabolic flexibility did not associate with differences in metabolic health. However, metabolically flexible vs. inflexible individuals showed elevated abdominal subcutaneous fat depot and faster blood triglyceride clearance. This study may support the notion that adipose tissue fat storage capacity determines metabolic flexibility and health, as demonstrated in mice<sup>3</sup>.

Lactate captured attention in two publications included in this Research Topic, where lactate may serve as a potential circulating biomarker of metabolic flexibility. Still, more elaborated studies are required to understand lactate dynamics and its link to metabolic flexibility. The review by Zeng et al. reports on pyruvate dehydrogenase as a metabolic hub controlling lactate production. They proposed that pyruvate dehydrogenase could be a potential therapeutic target that can render benefit in extreme metabolic conditions such as sepsis. Lessons from that model may eventually translate to less extreme metabolic conditions. Lactate was also a matter of study in the original publication by San-Millan et al. The authors speculated that high lactate concentration might impair metabolic flexibility. They based that idea on the observation that chronic lactate exposure decreased mitochondrial fatty acid oxidation in a rat cardiomyocyte model.

These studies of diverse nature and focus somehow reflect our current knowledge regarding the role of metabolic flexibility on health outcomes. There is a need to define a setting and a validated set of metabolic flexibility biomarkers that ensues comparability among studies. Such biomarkers and appropriate analysis should isolate inter-individual differences in metabolic flexibility from known

confounders (e.g. fuel availability, baseline fuel oxidation, energy balance)<sup>4</sup>. Such knowledge should translate into reliable and feasible biomarkers applicable to cohort studies to assess the relationship between metabolic flexibility and disease risk. We hope this Research Topic may encourage the scientific community to bring insightful studies on those areas.

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