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Active involvement of compartmental, inter- and intramolecular deuterium disequilibrium in adaptive biology

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The biosynthetic natural depletion of deuterium (^{2}H) in palmitic acid of tumor cells, when compared to water of fresh growth medium, readily distinguishes respiration from fermentation, as elegantly reported by Maloney et al. (1). Accelerated cellular growth remarkably decreased deuterium to protium (^{2}H/^{1}H) ratios, particularly in glycerol-respiring cells, by about 200‰ (~125 ppm). The authors conclude that metabolite ^{2}H/^{1}H ratios may be used "as passive natural trackers of eukaryotic metabolism" that complement complex isotope-tracer methods. The importance of water and product isotope chemistry is evident, which allows a systematic and, more importantly, a mechanistic interpretation, shifting the emphasis from passive to active role of deuterium in the regulation of metabolism in adaptive biology.

While fatty acids show a deuterium depleted ("deupleted") profile over extracellular water in rapidly dividing cells, another natural ^{2}H tracer study showed abnormally high deuterium content in collagen, just to redefine hydrogen chemical mass in biology (2). Notably, δ^2H values in (hydroxy)proline of collagen extracted from grey seals show about twice as much deuterium as its ceiling (~157 ppm) in seawater. This corresponds to at least four times higher δ^2H than in any previously reported biogenic sample. As diet was ruled out as a plausible mechanism for such anomalous enrichment, evolution seems to depend on deuterium-related regulatory processes via submolecular proton tunneling event (reaction) architectures, with coinciding significant isotope fractionation properties.

There are apparent adaptive mechanisms: Some derive from traditional biochemistry, whereas others are yet to be clarified behind the overwhelming disequilibrium patterns in compartmental, inter- and intramolecular deuterium levels reported in recent studies. The deupleted fatty acid profile in comparison with water, as reported by Maloney et al. (1) in rapidly dividing eukaryotic cells, also tracks ribonucleoside diphosphate reductase activity, for example, during the formation of deuterium rich deoxyribonucleotides, along with significant deuterium-trapping metabolic water production from ^{2}H-labeled glucose as the single tracer (3, 4). The natural depletion of deuterium in fatty acids occurs essentially the same way and involves identical enzymatic channels (routes). This is because compartmentalized water-related deuteron and proton tunneling reactions toward nonoxidative pentose-phosphate-dependent nucleotide synthesis (5, 6) readily limit mitochondrial fatty acid precursor (citrate) synthesis in rapidly dividing cells.

The mechanism of accumulation of deuterons in specific imino acids of bone collagen high above natural mean oceanic water abundance (2) is another example, yet more challenging to answer. This phenomenon, seen in predators with phenotypic adaptation to rapid dives in water, likely involves instant, reversible isomerase reactions with selective proton tunneling (7), nuclear quantum destabilization of metabolic water protons (8), and thus significant deuterium discriminating properties in hydrophobic cellular and mitochondrial nanoconfinements (9).

We suggest that deutenomics, the study of inherent autonomic hydrogen isotope discrimination processes in nature, should be introduced into translational research. It is important to determine the magnitude of intrinsic kinetic isotope effects, as they are critical in deuterium fractionation, yet often misinterpreted. The Human Deutenome should also not be ignored as an active player (as opposed to passive tracker) in forming the biological reaction coordinate (10).

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