# Development of metabolic priming strategies for precision redox strategies

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Aging and lifestyle-related diseases are linked to alterations in the cellular redox equilibrium, presenting opportunities for developing precision redox medicine strategies. Despite the promising benefits of antioxidants in in vitro studies, clinical trials often fail to produce the desired outcomes. To gain a deeper understanding of cellular redox responses and to mitigate the impact of artificial redox environments we evaluated NHDFs under various metabolic conditions (metabolic priming) that change the dependence on mitochondrial energy production.

To determine the impact of metabolic priming on the cellular effects of oxidants (H2O2 and t-BHP), NHDFs were grown under glucose deprivation in the presence of galactose (OXPHOS) and compared with cells grown in high-glucose (HG) and low-glucose (LG) conditions. We evaluated extracellular acidification rate (ECAR), oxygen consumption rate (OCR), mitochondrial network architecture, substrate oxidation, mitochondrial membrane polarization, and oxidative stress. Statistical analysis was performed using Dunn's multiple comparisons test and the Kruskal-Wallis post-hoc test. Differences with a p-value $\leq 0.05$ were considered significant.

The adaptation to OXPHOS increased both maximal and non-mitochondrial OCR ($p< 0.001$), as well as increased oxidation of Krebs cycle substrates, fatty acids, and lactate. This type of metabolic priming also led to an increase in basal oxidative stress ($p< 0.001$) and mitochondrial polarization ($p< 0.01$), and increased resistance to oxidants.

We conclude that metabolic priming of NHDFs by altering energy substrates in the cell culture medium results in both metabolic and redox reconfiguration, which can be valuable in pre-clinical studies involving redox agents.

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