The interplay between cellular redox state and metabolic flux.

Johan Nyberg*

Division of Molecular Cell Biology, Uppsala Science University, Sweden.

Introduction

The intricate relationship between the cellular redox state and metabolic flux is a central theme in cellular physiology, linking energy production, biosynthetic pathways, and signaling mechanisms to the maintenance of homeostasis. The redox state, which reflects the balance between oxidized and reduced species within the cell, influences and is influenced by the flow of metabolites through various metabolic networks. Redox couples such as NAD+/NADH, NADP+/NADPH, and GSH/GSSG are not only vital in maintaining cellular health but also act as metabolic sensors and modulators, integrating signals from the environment and cellular activity to orchestrate appropriate biochemical responses. The interplay between redox status and metabolic flux is thus critical for cell survival, adaptation, and function, and its dysregulation is a hallmark of many pathological conditions, including cancer, neurodegeneration, and metabolic disorders [1].

At the heart of cellular metabolism lies the need to generate ATP and biosynthetic precursors through pathways such as glycolysis, the tricarboxylic acid (TCA) cycle, and oxidative phosphorylation. These processes inevitably involve the transfer of electrons, making redox reactions intrinsic to metabolic activity. NAD+ and NADH form one of the most crucial redox pairs, shuttling electrons between catabolic and anabolic processes. In glycolysis, NAD+ is reduced to NADH during the conversion of glyceraldehyde-3-phosphate to 1,3-bisphosphoglycerate. The generated NADH must then be oxidized back to NAD+ to sustain glycolytic flux. Under aerobic conditions, this is achieved through the electron transport chain (ETC) in the mitochondria, where NADH donates electrons that ultimately reduce molecular oxygen to water, generating ATP in the process. Thus, the availability of NAD+ directly regulates the pace of glycolysis, and a highly reduced NADH/NAD+ ratio can lead to metabolic bottlenecks [2].

Similarly, the TCA cycle relies heavily on redox reactions. Several enzymes within the cycle reduce NAD+ and FAD to NADH and FADH2, respectively. These reduced cofactors are then oxidized by the ETC, enabling continued operation of the cycle. The flow of substrates through the TCA cycle is tightly linked to the redox capacity of the mitochondria, and imbalances in redox status can lead to accumulation of intermediates and impaired energy production. Mitochondrial redox homeostasis is therefore vital for sustaining oxidative metabolism, and disruptions in ETC function—such as in mitochondrial diseases or hypoxic conditions—can have profound effects on the entire metabolic network [3].

In addition to energy metabolism, redox status significantly influences anabolic pathways. NADPH, the reduced form of NADP+, is a critical cofactor in biosynthetic reactions, including fatty acid, nucleotide, and amino acid synthesis. It also plays a central role in maintaining the antioxidant defense system by regenerating reduced glutathione (GSH) and supporting the activity of thioredoxin. NADPH is primarily generated through the pentose phosphate pathway (PPP), the malic enzyme, and isocitrate dehydrogenase. These pathways not only provide reducing power but also link redox demands with metabolic flux. For instance, when oxidative stress increases, cells often divert glucose flux from glycolysis into the PPP to boost NADPH production and restore redox balance [4].

The cellular redox environment is also modulated by the glutathione system, comprising reduced (GSH) and oxidized (GSSG) glutathione. GSH serves as a major antioxidant, neutralizing reactive oxygen species (ROS) and maintaining protein thiols in a reduced state. The GSH/GSSG ratio is a sensitive indicator of oxidative stress and redox status. This redox buffer system is intimately connected to metabolism, as GSH synthesis requires ATP and amino acid precursors, and its regeneration from GSSG depends on NADPH. Thus, shifts in metabolic flux that alter NADPH availability can directly impact the cell's antioxidant capacity, influencing susceptibility to oxidative damage and redox-sensitive signalling [5].

Beyond serving as cofactors and antioxidants, redox couples also function as signaling molecules that influence gene expression and enzymatic activity. The redox-sensitive transcription factors such as Nrf2, HIF-1α, and FOXO respond to changes in redox state by regulating the expression of genes involved in metabolism, detoxification, and stress responses. For example, under oxidative stress, Nrf2 is stabilized and translocates to the nucleus, where it upregulates genes involved in NADPH generation, glutathione synthesis, and ROS scavenging. These transcriptional responses alter metabolic flux to reinforce redox homeostasis and enhance cellular resilience [6].

HIF-1α, another key transcription factor, is stabilized under hypoxic and redox-altered conditions. It promotes a metabolic shift from oxidative phosphorylation to glycolysis by upregulating glucose transporters and glycolytic enzymes

***Correspondence to:** Johan Nyberg, Division of Molecular Cell Biology, Uppsala Science University, Sweden, E-mail: j.nyberg@cellmetabol.se

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while suppressing mitochondrial respiration. This adaptation, often referred to as the Warburg effect in cancer cells, helps to minimize ROS production from dysfunctional mitochondria and maintain ATP production under stress. The redox regulation of HIF-1α thus exemplifies how redox state can reprogram metabolism in response to environmental cues [7].

Sirtuins, a family of NAD+-dependent deacetylases, further highlight the interface between redox and metabolism. These enzymes regulate mitochondrial biogenesis, fatty acid oxidation, and stress responses through deacetylation of metabolic and transcriptional regulators. Because sirtuin activity depends on NAD+ availability, the cellular NAD+/NADH ratio serves as a metabolic rheostat that tunes sirtuin-mediated signaling. During fasting or caloric restriction, NAD+ levels increase, activating sirtuins and promoting metabolic adaptations that enhance mitochondrial function and longevity [8].

The compartmentalization of redox states across cellular organelles adds another layer of complexity to this interplay. The cytosol, mitochondria, nucleus, and endoplasmic reticulum (ER) each maintain distinct redox environments, tailored to their specific functions. For instance, the ER operates under a relatively oxidizing environment to facilitate disulfide bond formation in protein folding, whereas the mitochondrial matrix maintains a highly reduced state to support oxidative metabolism. Metabolite transporters and redox shuttles, such as the malate-aspartate shuttle, play essential roles in redistributing redox equivalents between compartments, coordinating metabolic flux with organelle-specific functions [9].

Perturbations in redox-metabolic coupling are implicated in a wide range of diseases. In cancer, metabolic reprogramming often includes increased glycolysis and altered redox balance to support rapid proliferation and resist apoptosis. Cancer cells upregulate pathways that enhance NADPH production and glutathione metabolism to combat oxidative stress while sustaining anabolic growth. Targeting redox vulnerabilities, such as by disrupting NADPH synthesis or inhibiting antioxidant systems, is a promising strategy in cancer therapy [10].

Conclusion

In conclusion, the interplay between the cellular redox state and metabolic flux is fundamental to the regulation of energy homeostasis, biosynthesis, and signaling. Redox couples act as both effectors and regulators of metabolic pathways, shaping the cellular response to internal and external cues. This bidirectional relationship ensures adaptability and resilience, allowing cells to fine-tune their metabolism according to changing demands and stress conditions. Disruptions in this delicate balance underlie a spectrum of pathological states, underscoring the importance of redox-metabolic coupling in health and disease. Continued exploration of this dynamic interface holds promise for novel therapeutic interventions that target metabolism and redox regulation in an integrated manner.

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