

Trialkylphosphines in Chemical Biology: Modulation of Intracellular Redox Homeostasis

Jade Nguyen, Alina Tirla and Pablo Rivera-Fuentes,

ETH Zurich and EPF Lausanne, Zurich and Lausanne/Switzerland

Redox homeostasis is essential for organelle function in eukaryotes and its disruption is associated with cancer, metabolic and neurodegenerative diseases. To control these processes with single-cell and intra-organelle precision, we developed targeted reducing agents based on tributylphosphine. These reagents shift the equilibrium of reduced to oxidized glutathione, inducing reductive stress in live cells. We first used a photoactivatable phosphine probe to demonstrate that these reducing agents are capable of cleaving disulfide bonds in the intracellular medium. Furthermore, we developed a novel class of enzyme-activatable, mitochondria-targeted probes. These chemical tools allowed us to focus the redox imbalance to a specific organelle. Using this probe, we recently discovered that mitochondrial reductive stress is resolved by activation of transcription factor ATF4, which influences mitochondrial redox homeostasis through modulation of genes involved in glutathione metabolism.