Cell cycle control by Reactive Oxygen Species: Defining Redox Switches within the Cell Cycle Machinery

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The cell cycle is tightly regulated by an internal control system that utilizes post translational modifications (PTMs) such as phosphorylation to regulate cell cycle progression. Besides this known control mechanism, the intracellular concentration of Reactive Oxygen Species (ROS) increases gradually during the cell cycle and this increase is necessary for cell cycle progression. Specific intracellular redox levels have been linked to different cell cycle phases, and we revealed that one of the key cell cycle kinases (CDK2), is directly targeted by ROS to promote S-phase progression. However, so far additional ROS targets within the cell cycle are largely unknown. To uncover whether further core cell cycle proteins are oxidized and protein oxidation could function as a cell cycle regulatory PTM, we performed a cell cycle-dependent redox proteomics analysis. We developed a protocol to label sulfenic acid-modified proteins in living human cells at different stages of the cell cycle, followed by identification via quantitative mass spectrometry. We identified cysteines that are dynamically oxidized to sulfenic acids throughout the cell cycle. Contrary to the gradual increase of ROS throughout the cell cycle, we observed that protein sulfenylation does not change uniformly. Furthermore, we have identified ~400 proteins whose sulfenylation states oscillate, and for each phase of the cell cycle we have distinct sets of sulfenylated proteins that are related to different biological processes such as replication, cell cycle control, and intracellular redox balance. Currently we are investigating whether the sulfenylation of selected candidate proteins involved in these processes influences protein function and ultimately cell cycle progression. Altogether, this work aims to provide a general understanding of how the redox state and cell cycle are connected. A connection that we know is often hijacked by cancer cells, where altered redox levels can promote tumorigenesis.