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Genomic Analysis of Cellular Responses to Reactive Oxygen Species

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Cells maintain a suitable intracellular redox potential to ensure proper function of proteins and other redox-sensitive systems. In an aerobic organism, exposure to reactive oxygen species (ROS) can lead to cellular damage that has been implicated in many diseases, ageing and apoptosis. Many cellular defense mechanisms have evolved including systems that maintain resistance; antioxidant defenses including those that enable cells to adapt to oxidants; and cell cycle delay following exposure of cells to ROS. Under more severe stress, yeast cells also undergo a form of apoptosis and ROS have been implicated in the process of cell ageing.

We have used the genomic technologies available in yeast (genome-wide deletion mutants, DNA microarray and gene overexpression) to determine the role of genes in the cellular responses to different forms of oxidative stress and in maintaining redox homeostasis. Analysis of the sensitivity of the set of deletions in non-essential genes has shown that a surprisingly large number of genes are involved in the maintaining resistance to ROS stress. Yeast cells have different responses for different ROS species - there is no one ROS that is representative of oxidants in general. Mutants affected in the mitochondrial respiration are particularly sensitive to H_2O_2 relative to other oxidants. A secondary screen of hydrogen peroxide-sensitive mutants has identified functions that are important for adaptation to ROS, and similar screening has identified genes that affect cell cycle delay induced by exposure of cells to linoleate hydroperoxide. This has led to the identification of a molecular switch regulating a transcription factor that is important for cell cycle progression in to S phase.