Acute Oxygen Sensing: Molecular Mechanisms and Medical Impact

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Oxygen (O_2) is necessary for oxidative phosphorylation, the major source of energy for the cells. Adaptive responses, which can be acute or chronic, have evolved to minimize the detrimental effects of O_2-deficiency (hypoxia). Unraveling the mechanisms underlying O_2 sensing by cells is among the major advances in modern biomedical research. During sustained (chronic) hypoxia, transcription factors are activated to induce (in hours or days) the expression of "O_2-sensitive" genes, which decrease the cellular needs of O_2 and increase O_2 supply to the cells. In mammals, hypoxia also triggers fast (in seconds) life-saving cardiorespiratory reflexes (hyperventilation and sympathetic activation) to increase gas exchange in the lungs and delivery of O_2 to critical organs, such as the brain and heart. These acute responses to hypoxia are mediated by cells of the "homeostatic acute O_2 sensing system", which contain O_2-regulated ion channels. The main arterial chemoreceptors are glomus cells in the carotid body, which express K^+ channels that are inhibited by hypoxia. This leads to depolarization, Ca^{2+} influx and the release of transmitters that activate nerve fibers impinging upon the respiratory center. The mechanism whereby glomus cells "sense" changes in O_2 tension to signal membrane K^+ channels has remained elusive. We have shown that genetic disruption of the quinone binding site in mitochondria complex I selective abolishes acute O_2 sensing, and proposed a model in which accumulation of reduced quinone during hypoxia increases mitochondrial NADH and reactive O_2 species to signal membrane K^+ channels. Gene expression analyses suggest that O_2-sensitive cells have a signature profile, composed of specific metabolic enzymes and transporters, ion channels, and subunits of mitochondrial electron transport. Knowledge of the molecular mechanisms of acute O_2 sensing helps design more efficient therapies for severe and highly prevalent diseases in the human population.