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HYPOXIC AND REDOX SIGNALING PATHWAYS INTERACT TO MAINTAIN OXYGEN HOMEOSTASIS

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The dynamic relationship between oxygen levels within a cell leads to the activation of various signaling pathways to maintain homeostasis. If levels are low then hypoxic stress occurs and the classical hypoxia-signaling pathway via HIF-1 is activated. If oxidative stress occurs then high levels of reactive oxygen species (ROS) cause the induction of many antioxidant defense systems including the thioredoxin system. However recent evidence demonstrates that these two pathways interact and that both ROS and the thioredoxin system are essential components of the hypoxic signaling pathway. We have investigated thioredoxin expression in response to the complex oxygenation events that can occur within tissues and cells, such as during tissue development, organ transplantation and tumour formation. We grew breast cancer cells in either prolonged hypoxia or hypoxia followed by various lengths of reoxygenation and in each case we cultured cells with or without a hypoxic cycling pre-conditioning phase preceding the hypoxic growth. Since thioredoxin regulates Ref-1 activity, which in turn stimulates HIF-1 transcriptional activity, we assessed intracellular thioredoxin and Ref-1 protein levels in cells grown under these conditions. Thioredoxin levels were highest during the reoxygenation phase, however cells subjected to cycles of hypoxic-preconditioning displayed even higher thioredoxin levels, which also correlated with the highest levels of intracellular ROS. Reporter assays showed that activity of the thioredoxin and thioredoxin reductase gene promoters was also highest in the reoxygenation phase. These results together with those of other researchers contribute to the understanding that redox control systems play an integral role in the hypoxic response and also in other cell signaling pathways.