PRC and c-MYC Act in Concert through Akt-GSK-3 Signaling to Mediate a Stress Response to Respiratory Chain Uncoupler

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PRC (PGC-1-related coactivator), a divergent member of the PGC-1 family of regulated coactivators, has a dual role in both growth-regulated mitochondrial biogenesis and as a sensor of metabolic stress. Upon exposure of cells to mitochondrial inhibitors, intracellular ROS, or topoisomerase I inhibition, PRC orchestrates an inflammatory program of gene expression associated with the adaptation to cellular stress. Activation of this program is accompanied by the coordinate induction of c-MYC which is linked kinetically to that of PRC in response to multiple stress inducers. PRC and c-MYC exist in a complex and their coordinate induction by mitochondrial inhibitors led to a marked increase in their resistance to proteolysis. The c-MYC inhibitor, 10058-F4, blocked the induction of PRC, c-MYC and the PRC stress genes by CCCP, a result consistent with a requirement for c-MYC in the activation of the stress response. Deletion mapping combined with site-directed mutagenesis demonstrated that PRC steady-state expression is up-regulated upon mutation of two GSK-3 serine phosphorylation sites within the carboxy-terminal domain. The negative control of the PRC stress response by GSK-3 was confirmed by the induction of the phosphor-inactivated form of GSK-3β by CCCP and by the coordinate induction of PRC and c-MYC by the GSK-3 inhibitor, AZD2858. In addition, inhibition of the activated form of Akt by MK-2206 blocked the induction of PRC and c-MYC by CCCP as well as the activation of representative PRC stress genes. Akt is known to up regulate c-MYC through its suppression of GSK-3 activity. Thus, PRC and c-MYC can act in concert through Akt-GSK-3 signaling to reprogram gene expression in response to mitochondrial stress.

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