## Tumorigenesis

**Major finding:** The glutathione and thioredoxin pathways protect cells against ROS to promote tumorigenesis.

**Clinical relevance:** Dual targeting of the glutathione and thioredoxin pathways may be an effective therapeutic strategy.

**Impact:** Glutathione is required for tumor initiation, and inhibition of antioxidants may be chemopreventive.

### ANTIOXIDANT PATHWAYS COOPERATE TO INDUCE TUMORIGENESIS

Highly proliferative cancer cells are subjected to increased levels of reactive oxygen species (ROS), which have been shown to promote mutagenesis, suggesting that antioxidants such as glutathione (GSH) may prevent tumor formation. However, high levels of ROS induce oxidative stress, resulting in senescence and cell death, and recent studies have suggested that antioxidants instead protect cancer cells from ROS accumulation and enhance tumor progression. To further clarify the role of antioxidants in tumorigenesis, Harris and colleagues assessed the effects of inhibiting the GSH pathway on tumor initiation and progression. Genetic deletion of glutamate-cysteine ligase, modifier subunit (*Gclm*), which mediates GSH synthesis, impaired tumor initiation and progression in several mouse models of spontaneous tumor development. Similarly, early treatment with the GSH synthesis inhibitor buthionine-[S, R]-sulfoximine (BSO) prior to tumor development increased ROS levels and reduced tumor burden, indicating that ROS accumulation impairs malignant transformation and that GSH is required for tumor initiation. In contrast, administration of BSO after tumor onset did not affect ROS levels or diminish tumor burden, suggesting that alternate mechanisms may buffer ROS levels in established tumors. Consistent with this idea, *Gclm*-deficient cells exhibited increased expression of the antioxidant transcription factor nuclear factor (erythroid-derived 2)–like factor 2 (NFE2L2, also known as NRF2), which may compensate for decreased GSH synthesis to facilitate cell survival. In addition, inhibition of GSH synthesis increased intracellular cystine levels and expression of genes in the thioredoxin (TXN) antioxidant pathway, which were also upregulated in human breast cancers. Combined genetic or pharmacologic blockade of the GSH and TXN antioxidant pathways resulted in elevated ROS levels and synergistically increased cell death and reduced xenograft tumor growth *in vivo*. These results highlight a critical role for the GSH and TXN pathways in controlling ROS levels to enable tumor progression, and suggest that inhibition of antioxidant synthesis may be chemopreventive. ■

*Harris IS, Treloar AE, Inoue S, Sasaki M, Gorrini C, Lee KC, et al. Glutathione and thioredoxin antioxidant pathways synergize to drive cancer initiation and progression. Cancer Cell 2015;27:211–22.*

## Metabolism

**Major finding:** The MYC superfamily member MONDOA is essential in MYC-overexpressing cancer cells.

**Concept:** MONDOA loss disrupts MYC-driven transcriptional reprogramming of metabolism and kills MYC-dependent cells.

**Impact:** Strategies to disrupt MONDOA activity or MONDOA-dependent pathways may be effective in MYC-driven cancers.

### MONDOA IS REQUIRED FOR MYC-DRIVEN METABOLIC CHANGES

Upregulation of MYC proteins in cancer cells alters transcription of genes that enact the widespread metabolic changes necessary to support biosynthesis for increased growth and proliferation. MYC proteins are part of a larger network of basic-helix-loop-helix–leucine zipper proteins that regulate gene expression in response to various environmental cues, but it is not clear how or whether components of this extended network contribute to MYC-driven tumorigenesis. Carroll, Diolaiti, and colleagues performed an RNAi screen of MYC network genes and found that MONDOA (also known as MLX-interacting protein, or MLXIP) knockdown was selectively lethal to fibroblasts and cancer cell lines overexpressing MYC or MYCN. In MYCN-overexpressing cells, MONDOA loss attenuated changes in expression of MYCN target genes, particularly those involved in metabolism. Many of these metabolic pathway genes were required for the survival of MYCN-overexpressing neuroblastoma cells, suggesting that the synthetic lethality between MONDOA loss and MYC overexpression was due to disruption of MYC-driven metabolic reprogramming. Metabolomic profiling of MYCN-overexpressing cells indicated that MONDOA knockdown reduced glutamine uptake in association with a reduction in both glutamine-derived tricarboxylic acid cycle intermediates and glutamine-derived lipid biosynthetic pathway intermediates. MYCN-overexpressing cells were also hypersensitive to inhibitors of lipid biosynthesis, underscoring the significant role of lipogenesis in the metabolic reprogramming that supports the growth and proliferation of MYC-driven cancers. High expression of MYC and MONDOA metabolic pathway target genes was associated with shorter overall survival in several cancer types, further pointing to cooperation between MYC and MONDOA in cancer metabolism. The observation that oncogenic MYC activity is dependent on MONDOA raises the possibility that disrupting MONDOA function or targeting MONDOA-regulated metabolic pathways may be an effective approach for treatment of MYC-driven tumors. ■

*Carroll PA, Diolaiti D, McFerrin L, Gu H, Djukovic D, Du J, et al. Deregulated Myc requires MondoA/Mlx for metabolic reprogramming and tumorigenesis. Cancer Cell 2015;27:271–85.*