Myc Requires Mondoa to Reprogram Cancer Metabolism

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Overexpression of Myc-family transcription factors (TFs) is a hallmark of the majority of human cancers (Dang, 2012). Overexpression of Myc-family TFs leads to alterations in gene transcription that influence numerous cellular processes, including metabolism, to facilitate increased cellular growth. Myc TFs function in the context of a larger transcriptional network in which they dimerize with the Max protein to bind specific DNA sequences, called E-boxes, to exert effects on gene expression. Mxd proteins antagonize Myc transcriptional activity by competing for Max and E-box binding, and their expression is often correlated with arrested growth and cellular differentiation. An additional Myc-like network, centered on the Mlx protein, operates in parallel to the Myc network and involves dimerization with MondoA. MondoA senses intermediates in glycolysis, which in turn promotes translocation of MondoA to the nucleus, where it increases the transcription of genes involved in glucose metabolism. Interestingly, Mlx can associate with Mxd proteins, indicating a point of contact between the Myc arm of this network, which utilizes nutrients to promote cellular growth and proliferation, and the nutrient sensing abilities of MondoA. To understand potential roles of Myc network TFs in facilitating cellular transformation by Myc proteins, postdoctoral fellows Dr. Patrick Carroll and Dr. Daniel Diolaiti in the lab of Dr. Robert Eisenman (Basic Sciences Division) and colleagues at the Universities of Washington and Utah undertook an siRNA screen of Myc network factors. They found that depletion of MondoA, previously implicated in metabolic sensing, severely reduced the viability of Myc-overexpressing cells, suggesting a potential metabolic vulnerability of Myc-transformed cells.

In an siRNA screen targeting Myc network members, the authors found that knockdown of MondoA, and to a lesser extent its dimerization partner Mlx, in the context of increased c-Myc levels strongly reduced the viability of mouse fibroblasts. MondoA depletion also reduced the viability of several human cancer cell lines overexpressing c-Myc, indicating a general requirement for MondoA in c-Myc-induced cell growth. Extending these observations to n-Myc, which is overexpressed in ~25% of neuroblastomas, the authors found that MondoA knockdown strongly reduced viability of neuroblastoma cell lines with N-Myc overexpression but not those with normal N-Myc levels.

To gain insight into the reliance of N-Myc overexpression on MondoA, the authors made use of a neuroblastoma cell line enabling inducible expression of N-Myc known as Tet21N. Knockdown of

MondoA in Tet21N cells following N-Myc induction impaired proliferation and also increased apoptosis. Furthermore, increased levels of the cell cycle inhibitors p21 and p53 were detected after MondoA knockdown, suggesting that MondoA dampens cellular stress associated with N-Myc overexpression to ensure continued cell survival and proliferation. Indeed, MondoA knockdown impaired the ability of N-Myc-overexpressing Tet21N cells to form colonies in soft agar and to form tumors in mouse xenograft models.

As N-Myc and MondoA are TFs, the authors next asked if loss of MondoA altered the transcriptional properties of N-Myc. While MondoA knockdown did not substantially alter the set of genes altered by N-Myc, the magnitude of these changes was significantly attenuated. N-Myc required MondoA for maximal expression of genes involved in promoting cell growth and proliferation, including many genes involved in nucleotide biosynthesis, amino acid metabolism, mitochondrial function, and lipid biosynthesis. The expression of these genes was also dependent on the MondoA dimerization partner Mlx, indicating a requirement for MondoA-Mlx heterodimers in upregulating metabolism in the context of N-Myc overexpression. Lastly, the researchers found that knockdown of a number of metabolic genes induced by MondoA substantially reduced cell viability in N-Myc overexpessing cells. Metabolic profiling of neurolastoma cells revealed broad alterations in cellular metabolism upon N-Myc activation and shows that these cells depended on lipid biosynthesis for survival.

To assess the relevance of metabolic upregulation to human cancers, the authors identified a gene expression signature consisting of Myc/MondoA-regulated metabolic genes and assessed the expression of this signature in patients with six distinct cancers: neuroblastoma, lung squamous cell carcinoma/lung adenocarcinoma, liver hepatocellular carcinoma, colon adenocarcinoma, acute myeloid leukemia, and breast invasive carcinoma. High expression of the signature was significantly correlated with poor prognosis in all cases to differing degrees.

This study defines a mechanism through which deregulated Myc is able to hijack cellular metabolism to promote tumorigenic cell growth and proliferation. "Our synthetic lethal condition represents an imbalance of metabolic economics; a failure of supply in the context of insatiable (or increased) demand," said Dr. Carroll. These findings also open new possibilities for therapy of Myc-overexpressing cancers. "Our findings have clear implications for the therapeutic treatment of Myc over-expressing malignancies and suggest that inhibiting MondoA/Mlx transcriptional activity or blocking lipid metabolism could be an effective therapeutic strategy to selectively target these cancers," said Dr. Diolaiti.

Carroll PA, Diolaiti D, McFerrin L, Gu H, Djukovic D, Du J, Cheng PF, Anderson S, Ulrich M, Hurley JB, Raftery D, Ayer DE, Eisenman RN. 2015. Deregulated Myc Requires MondoA/Mlx for Metabolic Reprogramming and Tumorigenesis. *Cancer Cell*27(2):271-285.

Also see: Dang CV. 2012. MYC on the path to cancer. *Cell* 149(1):22-35.

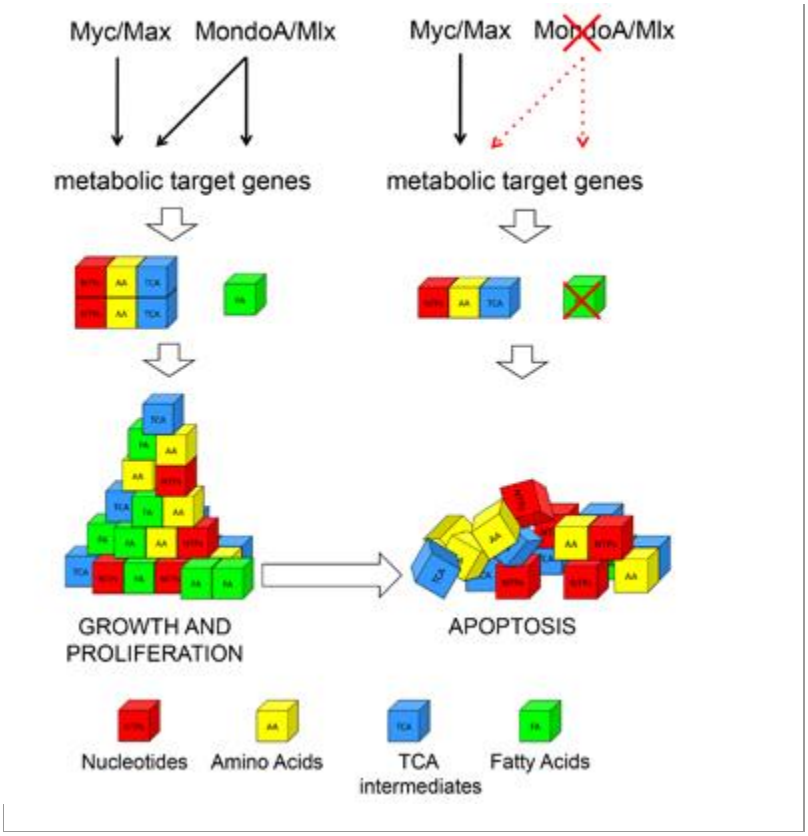

Image provided by Dr. Daniel Diolaiti

Myc/Max and MondoA/Mlx, both separately and cooperatively, influence the expression of genes involved in the metabolism of the cell's building blocks, leading to increased cell growth and proliferation. When MondoA is lost, fatty acid metabolism is impaired, leading to a failure of growth and subsequent cell death.