

Keywords: Myc; MondoA; cancer metabolism; transcription; TXNIP; tumourigenesis

Interactions between Myc and MondoA transcription factors in metabolism and tumourigenesis

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Metabolic reprogramming towards aerobic glycolysis is a common feature of transformed cells and can be driven by a network of transcription factors. It is well established that c-Myc and hypoxia-inducible factor-1 α (HIF-1 α) contribute to metabolic reprogramming by driving the expression of glycolytic target genes. More recently, the c-Myc-related transcription factor MondoA has been shown to restrict glucose uptake and aerobic glycolysis via its induction of thioredoxin-interacting protein (TXNIP). Three recent studies demonstrate that complex and cancer type-specific interactions between c-Myc, MondoA and HIF-1 α underlie metabolism, tumourigenesis and drug response. In triple-negative breast cancer, c-Myc blocks MondoA-dependent activation of TXNIP to stimulate aerobic glycolysis. In contrast, in neuroblastoma, N-Myc requires MondoA for metabolic reprogramming and tumourigenesis. Finally, the therapeutic response of BRAF^{V600E} melanoma cells to vemurafenib requires downregulation of c-Myc and HIF-1 α and upregulation of MondoA-TXNIP, and the subsequent reprogramming away from aerobic glycolysis. In this minireview we highlight the findings in these three studies and present a working model to explain why c-Myc and MondoA function cooperatively in some cancers and antagonistically in others.

THE PLAYERS AND THEIR ROLES

The MYC family of proto-oncogenes (c-Myc, L-Myc, N-Myc or collectively Myc) encode basic helix-loop-helix leucine zipper (bHLHZip) transcription factors that have roles in normal and oncogenic physiology (Eilers and Eisenman, 2008; Meyer and Penn, 2008). Aberrant Myc activity leads to increased cell proliferation and growth and Myc family members are commonly dysregulated in cancer. Cancers of many different tissue types have dysregulated Myc and, when paired with other mutations, Myc can drive tumourigenesis. Myc's normal and pathological functions have been the subject of many excellent reviews and will not be discussed here. Rather, we focus on the interplay between Myc and related bHLHZip factors that comprise an extended Myc network. This extended Myc network functions to match nutrient availability with nutrient utilisation, supporting cell growth and tumourigenesis.

Myc requires dimerisation with another bHLHZip transcription factor, Max, for DNA binding and the recruitment of transcriptional machinery. All Myc paralogues dimerise with Max and the different heterocomplexes have many common target genes, although each heterocomplex has a unique subset of target genes and expression patterns. Generally, Myc/Max complexes influence cell growth by driving the expression genes involved in key biosynthetic pathways and by supporting glycolysis and glutaminolysis (Dang, 2012b). Myc can also act as a transcriptional repressor at certain promoters that is critical to its function in driving cell growth and proliferation (Walz *et al*, 2014).

A complete functional characterisation of Myc proteins is difficult because they do not function in isolation (O'Shea and Ayer, 2013). Rather, their activity is potentially regulated by a dizzying array of additional protein partnerships mediated by families of related bHLHZip transcription factors. The first level of regulation is mediated by the Mad family of transcriptional repressors (Mxd1, Mxi1, Mxd3, Mxd4) that also interact with Max.

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Received 31 July 2015; revised 10 September 2015; accepted 15 September 2015; published online 15 October 2015

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Furthermore, Max can also interact with Mnt, which is related to the Mad family, and Mga, which has a T-Box DNA-binding domain in addition to its bHLHZip domain (Hurlin and Huang, 2006). The Mxd/Max complexes repress many of the same targets that are activated by Myc/Max complexes (Iritani *et al*, 2002); however, no comprehensive genome-wide occupancy studies have been conducted. The second level of regulation is mediated by a Max-like bHLHZip protein called Mlx. Mlx can interact with Mxd1 and Mxd4 and potentially Mnt. Mxd/Mlx, Mxd/Max and Myc/Max all bind similar DNA sites *in vitro*, suggesting overlapping transcriptional targets *in vivo*, but again no comprehensive genome-wide study is available (O'Shea and Ayer, 2013). The third level of regulation is that Mlx interacts with the Mondo family of bHLHZip transcriptional activators. There are two Mondo paralogs, MondoA (or MlxIP) and carbohydrate response element-binding protein (ChREBP, MondoB or MlxIPL) (Figure 1). Mondo/Mlx complexes are important nutrient sensors and share a similar DNA-binding sequence with the rest of the network heterocomplexes (O'Shea and Ayer, 2013). The existence of multiple Myc-related bHLHZip factors, their assembly into different heterocomplexes and the participation of these heterocomplexes in potentially overlapping networks suggests that functional output of Myc/Max complexes is likely dictated by many mechanisms: (1) competitive or collaborative interactions with other network complexes at shared targets, (2) competition for limiting Max or Mlx or (3) different complexes may regulate distinct effector pathways that compete or collaborate to control cell growth and tumourigenesis. In this review we focus on the last possibility as three recent papers demonstrate that Myc/Max and MondoA/Mlx complexes play critical roles in matching the cellular demand for nutrients with nutrient availability (Parmenter *et al*, 2014; Carroll *et al*, 2015; Shen *et al*, 2015).

THE MONDO FAMILY

In normal physiology, MondoA and ChREBP are ubiquitously expressed with the highest expression in skeletal muscle and liver, respectively, and are important regulators of glucose-dependent transcription (Peterson and Ayer, 2011). MondoA/Mlx localise

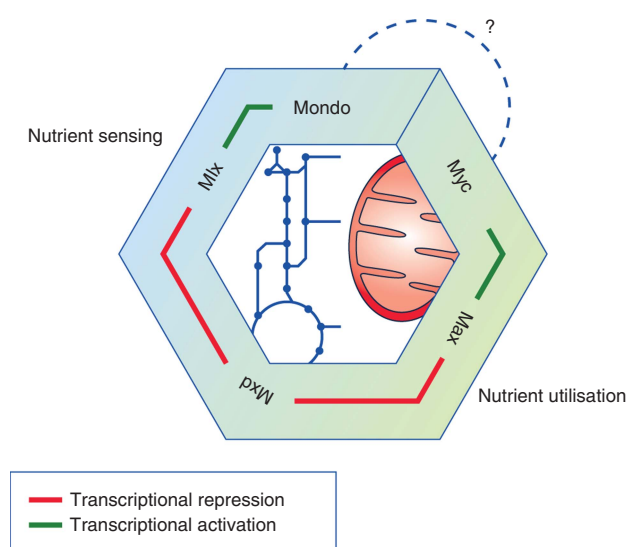


Figure 1. The extended Myc network. Transcriptional activation and repression mediated by Myc/Max and Max/Mxd respectively drive a transcriptional profile that coordinates nutrient utilisation. Transcriptional activation and repression by Mondo/Mlx make up a nutrient sensing branch of the network.

primarily to the cytoplasm and translocate to the nucleus in response to increased extracellular glucose concentrations. The mechanistic details of how the heterocomplex senses extracellular glucose are still being worked out, but current data suggest that MondoA/Mlx complexes sense intermediates in the upper portion of the glycolytic pathway (O'Shea and Ayer, 2013). For MondoA, an allosteric mechanism where a glucose-derived metabolite binds directly to the conserved N-terminus to trigger nuclear accumulation, promoter binding and transcriptional activation of target genes seems to be key (Peterson *et al*, 2010). The transcriptional activity of MondoA/Mlx complexes also requires mitochondrial electron transport (Yu *et al*, 2010) that enables their nuclear import and promoter binding. Thus, MondoA/Mlx complexes sense the status of two key bioenergetic pathways, allowing cells to adapt to changes in glycolytic flux or mitochondrial activity.

The most well-characterised direct and glucose-dependent target gene of MondoA/Mlx is thioredoxin-interacting protein (TXNIP), a member of the α -arrestin family (O'Shea and Ayer, 2013). TXNIP has pleiotropic functions in different cellular stress response pathways, with one of its most striking features being a potent negative regulator of glucose uptake. It can suppress both insulin-dependent and insulin-independent glucose uptake by limiting the localisation of glucose transporters to the plasma membrane (Wu *et al*, 2013). Furthermore, in some cell types TXNIP can drive degradation of hypoxia-inducible factor-1 α (HIF-1 α) (Shin *et al*, 2008), a central regulator of glycolytic gene expression under hypoxic growth conditions. Thus, the glucose-stimulated and MondoA-dependent induction of TXNIP triggers a negative feedback loop that restricts glucose uptake until glucose homeostasis can be restored. Furthermore, the dependence of the MondoA/TXNIP axis on electron transport ensures that cells with defective oxidative phosphorylation maintain a high glycolytic rate to support cellular bioenergetics.

Given that TXNIP is a potent negative regulator of glucose uptake and aerobic glycolysis, it is not surprising that its expression is reduced in many cancer types and low TXNIP expression correlates with poor clinical outcome in several cancers including breast and gastric cancer (Shin *et al*, 2008; Chen *et al*, 2010; Shen *et al*, 2015). MondoA is absolutely required for TXNIP expression, yet MondoA is not a frequent target for mutational inactivation in cancer. Rather, the activity of MondoA at the TXNIP promoter is suppressed by activation of common oncogenic or pro-growth pathways, for example Ras, PI3K and mTOR (Elgort *et al*, 2010; Kaadige *et al*, 2015). The prevalence of Ras, PI3K and mTOR activation across cancer types suggests broad suppression of the MondoA/TXNIP axis in tumourigenesis.

THE EXPANDED NETWORK IN TRIPLE-NEGATIVE BREAST CANCER

The triple-negative breast cancer (TNBC) accounts for 15–20% of breast cancer cases. Typically, TNBCs occur earlier in life, reoccur more frequently and have decreased overall survival. The TNBCs lack expression of the oestrogen receptor (ER), progesterone receptor (PR) and HER2, and hence the 'triple-negative' nomenclature (Foulkes *et al*, 2010). The TNBCs are more metabolic than other breast cancer subclasses, and thus understanding how nutrients support their growth and survival may provide pathways for therapeutic development. Consistent with Myc's role in regulating aerobic glycolysis, c-Myc expression correlates with the glycolytic phenotype of TNBCs (Palaskas *et al*, 2011). In contrast, there is no general correlation between c-Myc levels or Myc activity and glutamine utilisation or glutamine-dependence in TNBC (Timmerman *et al*, 2013; Shen *et al*, 2015). These findings prompted us to study how c-Myc controls glucose metabolism in TNBC (Shen *et al*, 2015). As expected, c-Myc knockdown reduced

glucose uptake in multiple TNBC cell lines. Surprisingly, TXNIP was induced in c-Myc knockdown TNBC cells and its induction was required for the reduction in glucose uptake resulting from c-Myc knockdown. This finding suggests that in addition to its canonical function of driving the expression of glycolytic target genes, c-Myc can also drive glucose metabolism by repressing TXNIP. Mechanistically, c-Myc can bind to proximal double E-box carbohydrate response element (ChoRE) in the TXNIP promoter, also the known MondoA/Mlx binding site. Furthermore, TXNIP induction following c-Myc knockdown is entirely dependent on MondoA. Thus, either c-Myc recruits dominant transcriptional repression machinery to the TXNIP promoter or displaces strongly activating MondoA/Mlx complexes from the TXNIP promoter by direct competition. MondoA levels increase at the TXNIP promoter following c-Myc knockdown, supporting the second model.

In the TNBC line MDA-MB-157, Myc-driven expression of glycolytic target genes and its repression of TXNIP contribute to Myc-driven glucose metabolism to approximately the same extent (Shen *et al*, 2015). Further studies are needed to determine whether these mechanisms are similarly balanced in other cancer types or whether cancer type-specific mechanisms dictate their relative contributions. Elevated c-Myc drives expression of genes that encode many biosynthetic pathways placing a demand on biosynthetic precursors such as glucose and glutamine (Dang, 2012a). In TNBC, c-Myc-dependent repression of TXNIP increases glucose uptake that helps to match nutrient demand with nutrient availability. A c-Myc_{high}/TXNIP_{low} gene signature correlates with reduced overall survival and reduced metastasis-free survival in breast cancer, particularly in TNBC, highlighting the clinical significance of c-Myc-dependent repression of TXNIP (Shen *et al*, 2015).

It is striking that the c-Myc_{high}/TXNIP_{low} signature only correlates with poor clinical outcome in TNBC and not in other subtypes of breast cancer. Furthermore, the gene signature only correlates with poor clinical outcome in tumours that also harbour mutations in the tumour suppressor gene TP53 (Shen *et al*, 2015). TP53 is mutated in between 60% and 90% of TNBCs (Turner *et al*, 2013), and this may explain why c-Myc_{high}/TXNIP_{low} only correlates with poor clinical outcome in this breast cancer subtype. Thus, there may be functional cooperation between c-Myc_{high}/TXNIP_{low} and mutation of TP53. Importantly, this cooperation does not appear to depend on established connections between dysregulated c-Myc expression and TP53 mutation (Shen *et al*, 2015). Thus, in TNBC, c-Myc and MondoA, via their opposing regulation of TXNIP expression, function antagonistically.

THE EXPANDED NETWORK IN BRAF^{V600} MELANOMA

c-Myc and MondoA antagonism also appears to be at play in melanomas that harbour the activated alleles of the BRAF kinase (Parmenter *et al*, 2014). The BRAF-mutant melanomas are highly glycolytic and their sensitivity to the BRAF inhibitor vemurafenib correlates with a dramatic suppression of glucose uptake and aerobic glycolysis. Vemurafenib treatment reduces the membrane expression of the GLUT1 and GLUT3 glucose transporters and decreases expression of hexokinase II, the first rate-limiting enzyme in glycolysis. Importantly, BRAF^{V600} melanomas rendered resistant to vemurafenib by expression of NRAS^{Q61K} do not reprogramme their metabolism in response to drug treatment.

Vemurafenib treatment of BRAF^{V600} melanomas drives upregulation of TXNIP and its paralogue ARRDC4 that contributes to its suppression of glucose uptake and aerobic glycolysis (Parmenter *et al*, 2014). MondoA occupancy at the TXNIP and ARRDC4 promoters increases in response to vemurafenib treatment and this

increase is blocked by expression of NRAS^{Q61K}. As expected, MondoA is required for upregulation of TXNIP in response to vemurafenib. MondoA is also required for the decrease in glucose uptake and cell proliferation driven by vemurafenib. These results strongly implicate the MondoA/TXNIP axis as a key effector of the vemurafenib therapeutic response.

Vemurafenib treatment also results in dramatic downregulation of c-Myc and HIF-1 α . Furthermore, functional experiments show that downregulation of c-Myc and HIF-1 α is required for vemurafenib to suppress glucose metabolism in BRAF^{V600} melanomas. Unlike TNBCs, where c-Myc knockdown is sufficient to upregulate TXNIP, c-Myc knockdown in one BRAF^{V600} melanoma cell line only increases TXNIP slightly (Parmenter *et al*, 2014). Thus, other mechanisms, in addition to c-Myc downregulation, must also contribute to vemurafenib-dependent induction of TXNIP. Together, these experiments establish that activation of the MondoA/TXNIP axis along with reduction of c-Myc and HIF-1 α are required in combination for vemurafenib to reprogramme metabolism away from glucose metabolism and suppress growth in BRAF^{V600} melanomas. Given these findings, it is not surprising that vemurafenib-treated melanomas become dependent on glutamine (Hernandez-Davies *et al*, 2015). Together, these studies suggest that c-Myc and MondoA work in opposition in these cancers.

THE EXPANDED NETWORK IN NEUROBLASTOMA

In contrast to TNBC and BRAF^{V600} melanomas, c-Myc and MondoA cooperate in reprogramming metabolism and supporting tumourigenesis in neuroblastoma (Carroll *et al*, 2015). Neuroblastoma is the most common extracranial solid tumour in children. Approximately 20% of neuroblastomas have N-Myc amplification that co-relates with advanced-stage disease and poor clinical outcome (Louis and Shohet, 2015). In N-Myc-overexpressing neuroblastomas, loss of MondoA or Mlx results in cell death, demonstrating that the MondoA/Mlx heterodimer is required for N-Myc-dependent cell growth and tumourigenesis. This finding extends to other Myc-amplified cells including human B-cell leukaemia and transformed neural stem cells. In contrast, neuroblastoma cells that lack N-Myc amplification do not require MondoA for viability; however, overexpression of N-Myc in these cells drives MondoA dependence. Together, these data suggest that neuroblastoma cells with high N-Myc expression depend on MondoA/Mlx for their growth and survival.

There are over 1000 Myc/Max and MondoA/Mlx co-regulated genes in neuroblastoma cells including many metabolic genes (Carroll *et al*, 2015). Multiple MondoA-dependent pathways are required for N-Myc-driven survival/growth, providing the mechanistic basis of the dependence of N-Myc-overexpressing cells on MondoA. For example, MondoA depletion reduces N-Myc-driven expression of genes involved in glutamine uptake and utilisation, resulting in reduced global cellular biosynthesis, reduced mitochondrial metabolic capacity and a subsequent reduction in oxygen consumption. MondoA loss results in reduced activity of many nutrient utilisation and biosynthetic pathways. These findings suggest that MondoA supports the metabolic changes driven by and required by N-Myc overexpression. Furthermore, cells driven by N-Myc overexpression have an increased demand for biosynthetic and bioenergetic substrates that cannot be met by low MondoA levels. This mismatch eventually leads to apoptosis and a blockade of tumourigenesis. The pathological significance of the cooperation between N-Myc and MondoA is highlighted by the finding that the highest expression of a seven-gene signature comprising MondoA and six metabolic genes correlates with poor clinical outcome in neuroblastoma and hepatocellular carcinoma. Reflecting the

apparent functional differences in the extended Myc network in TNBC and neuroblastoma, this same gene signature does not correlate with clinical outcome in invasive breast carcinoma.

CONCLUSIONS

These three studies highlight the complex interactions between the members of the extended Myc network in metabolism and tumourigenesis (Parmenter *et al*, 2014; Carroll *et al*, 2015; Shen *et al*, 2015). The studies in TNBC and BRAF^{V600} melanoma suggest that MondoA and Myc function antagonistically in controlling glucose uptake/glycolysis. In contrast, in neuroblastoma, N-Myc amplification drives a dependence on MondoA and Mlx (Figure 2). These findings seem contradictory, but we suggest that the activities of Myc and MondoA function principally to match the demand for biosynthetic precursors with their availability. We speculate that in TNBC, TXNIP suppression by Myc increases the availability of glucose to support Myc-driven biosynthetic reactions. In contrast, in neuroblastoma, N-Myc increases MondoA levels that in turn activate glutaminolysis and lipogenesis to support N-Myc-driven biosynthetic reactions. Together, these data suggest that in cells or tumours that depend primarily on glucose catabolism to fuel biosynthesis, Myc and MondoA will function antagonistically. In contrast, in cells or tumours that depend primarily on catabolism of glutamine and lipids to fuel biosynthesis, Myc and MondoA will function collaboratively.

How broadly the complex interplay between Myc and MondoA extends across tumourigenesis remains to be explored. Current data suggest that the primary function of the MondoA/TXNIP axis is in growth and tumour suppression. For example, TXNIP is downregulated in many tumour types and is only infrequently upregulated in tumours (O'Shea and Ayer, 2013). Furthermore, MondoA is not strongly downregulated in tumours, but several common oncogenic drivers suppress its transcriptional activity at the TXNIP promoter. It will be interesting to determine whether tumours that show suppression of the MondoA/TXNIP axis are particularly dependent on glucose. MondoA has been proposed to function as an oncogene in B-cell acute lymphoblastic leukaemia (Wernicke *et al*, 2012). The function of c-Myc in B-ALL is not well studied, but elevated c-Myc levels do associate with increased risk of persistent disease (Allen *et al*, 2014). Whether MondoA is required for B-ALL growth and tumourigenesis or is required to support other c-Myc-driven B-cell lymphomas such as Burkitt's

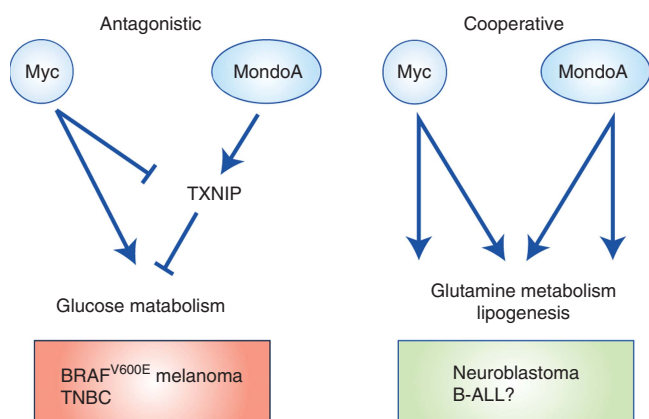


Figure 2. Myc and MondoA coordinate nutrient utilisation. In triple-negative breast cancer and melanoma, Myc and MondoA competitively influence glucose metabolism, whereas in neuroblastoma and possibly B-ALL, MondoA and Myc cooperatively drive glutamine metabolism and lipogenesis.

and diffuse large B-cell should be investigated (Slack and Gascoyne, 2011). As argued above, these Myc-driven tumours may be particularly dependent on glutamine or lipid catabolic pathways.

The highlighted studies indicate that Myc/Max complexes have cell-type differences in their transcriptional targets. For example, in neuroblastoma, N-Myc/Max increases the expression of MondoA and TXNIP (Carroll *et al*, 2015), whereas in TNBC/ c-Myc represses TXNIP without influencing MondoA levels (Shen *et al*, 2015). These cell-type differences may reflect differences in the pallet of co-activators/co-repressors available in a given cell type, or they may reflect more indirect mechanisms such as c-Myc- or MondoA-driven changes in cell metabolism. Furthermore, the relationship between MondoA and Myc may be influenced by the relative level of Myc amplification and/or the specific Myc homologue that is deregulated (Murphy *et al*, 2008). With the discovery of Max almost 25 years ago and the demonstration that Myc/Max complexes functioned as transcriptional activators, there was hope that determining 'how' c-Myc functioned in normal and pathological settings would follow directly from determining the cohort of Myc/Max transcriptional targets. However, as many studies now highlight, studying Myc in isolation provides only partial answer to what is a complex multidimensional puzzle.

ACKNOWLEDGEMENTS

We thank members of the Ayer lab for helpful discussions. DEA is supported by R01GM055668 and W81XWH1410445 from the Department of Defense.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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