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Molecular Pathways: Targeting *MYC*-induced Metabolic Reprogramming and Oncogenic Stress in Cancer

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Abstract

MYC is a multi-functional transcription factor that is deregulated in many human cancers. *MYC* impacts a collaborative genetic program that orchestrates cell proliferation, metabolism, and stress responses. Although the progression of *MYC*-amplified tumors shows robust dependence on *MYC* activity, directly targeting *MYC* as a therapeutic method has proven to be technically difficult. Therefore, alternative approaches are currently under development with a focus on interference with *MYC*-mediated downstream effects. To fuel rapid cell growth, *MYC* reprograms cancer cell metabolism in a way that is substantially different from normal cells. The *MYC*-induced metabolic signature is characterized by enhanced glucose and glutamine uptake, increased lactate production, and altered amino acid metabolism. Targeting *MYC*-reprogrammed cancer cell metabolism is considered to be promising based on multiple preclinical studies. In addition, the increased biosynthetic demand of *MYC*-driven tumors coupled with limited nutrient access within tumor microenvironments create multiple levels of oncogenic stress, which can also be utilized as tumor-specific targets for pharmacological intervention. Presumably, the best therapeutic strategy for treating *MYC*-amplified tumors is combined targeting of multiple *MYC*-mediated pathways, especially those involved in regulating cell proliferation, metabolism, and oncogenic stress.

Background

MYC is a pleiotropic transcription factor that participates in many cellular processes, including cell proliferation, apoptosis, differentiation, metabolism and genome stability (1). Upon activation, *MYC* recognizes CACGTG sequences termed “E Boxes”, as a heterodimer paired with its binding partner MAX. *MYC* cofactors such as TRRAP and GCN5 are then recruited to E Boxes within chromatin and contribute to *MYC*-driven transcriptional events (2). Depending on the specific cellular and signaling contexts, *MYC* is able to induce or suppress the expression of up to 15% of all known genes, partly due to the prevalence of *MYC* cognate sites within the genome (1). Interestingly, it was recently revealed that *MYC* is particularly enriched in the promoter regions of active genes, therefore functioning to amplify existing transcriptional signals (3, 4). This breakthrough finding revolutionizes our understanding of *MYC*, expanding the horizon beyond traditional *MYC* target genes to virtually all actively-transcribed genes. The *MYC* gene family comprises three major members: *c-MYC*, *MYCN* and *MYCL*. *c-MYC* is the only isoform expressed ubiquitously in a broad range of tissues and organs, especially during early embryogenesis. In contrast, *MYCN* and *MYCL* are expressed in a more tissue-restricted manner, such as in the central

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nervous system and lung epithelium (2). Nevertheless, it's generally believed that *MYC* family members can be functionally interchangeable, which is partially supported by the fact that knock-in expression of *MYCN* into the c-*MYC* locus does not interfere with normal mouse development and reproduction (5).

Given the pleiotropic role of *MYC* in multiple cellular functions, *MYC* expression and activity need to be tightly regulated. MYC protein is frequently induced in proliferating cells to orchestrate the signaling and metabolic events that drive cell cycle progression, and is quickly targeted for proteasomal degradation after proliferation signals regress (1, 6). In normal differentiated tissues, *MYC* expression levels remain low except in those bearing a high turnover rate. Meanwhile, deregulated *MYC* resulting from genomic amplification or translocation contributes to neoplastic transformation and tumor progression (1, 7). Not surprisingly, high levels of *MYC* expression were found to be hallmark of many cancer types, including Burkitt's lymphoma, neuroblastoma, medulloblastoma, breast cancer, and multiple myeloma (2, 8). Early studies using transgenic mice suggested that tumors with elevated *MYC* expression are frequently addicted to *MYC*, as tumor progression was severely impaired if *MYC* was silenced (1). Moreover, a systematic investigation of possible side effects of inhibiting global *MYC* expression was recently conducted in the KRAS^{G12D} lung cancer model, where a dominant negative form of MYC (OmoMYC) was ubiquitously expressed under the CMV promoter in these mice (9). While KRAS-driven tumor progression was significantly inhibited by the presence of OmoMYC, there were no obvious physiologic changes observed in most organs and tissues except for a reversible growth retardation found in skin, testis and intestinal epithelium (9). These observations provide solid basis for targeting *MYC* as an efficient and tolerable therapy for treating cancers harboring amplified *MYC*.

For the past two decades, numerous attempts have been made to develop strategies to directly target MYC activity or expression. However, little success has been achieved along this route. For instance, inhibiting MYC activity using small molecules to disrupt the specific MYC-MAX interaction has proven to be quite difficult, largely due to the "flat" interface between the MYC-MAX dimer (10, 11). The best IC₅₀ value of currently-identified MYC inhibitors is at the micromolar level, which is not potent enough to be considered for clinical evaluation (12). Lately another promising strategy emerged following the discovery of G-quadruplex motif, which is a transcription module located in the *MYC* promoter region that suppresses *MYC* gene expression (13). Some leading compounds stabilizing the G-quadruplex motif, such as TMPyP4, showed promising effects in inhibiting lymphoma cell proliferation (14). However, the intrinsic complexity of these structures restrains the possibility of targeting a specific gene like *MYC* using this method. Recently, a small molecule bromodomain inhibitor JQ1 was found to efficiently affect *MYC* transcription and block *MYC*-driven tumorigenesis (15–17). Although a JQ1 derivative compound GSK525762 has entered clinical trials (NCT01587703), the specificity of this molecule merits close attention due to the prevalent interaction between bromodomain proteins and acetylated histones. In fact, JQ1 treatment has already been reported to cause infertility in male mice (18).

Continuous difficulties lying in directly targeting *MYC* led to the thoughts of developing alternative methods to circumvent this problem. It is well established that activated *MYC* reshapes cancer cell metabolism in a way that is coordinated with a sustained proliferative signal (6) (Figure 1). *MYC*-induced glucose and glutamine consumption accompanied by enhanced lactate production provide necessary energy and intermediates for the rapid construction of new daughter cells (7). *MYC* also stimulates ribosomal and mitochondrial biogenesis to sufficiently cover an increased metabolic demand (19). In most cases, *MYC* reprograms cell metabolism by promoting the expression of essential enzymes that control

metabolic flux, such as lactate dehydrogenase, glutaminase and phosphoglycerate dehydrogenase (20–22). Targeting these key metabolic enzymes genetically or pharmacologically has proved to be an effective approach to delay tumor progression in many preclinical studies (21–24). Moreover, the selective inhibition of *MYC*-driven transformation can also be achieved by aggravating the oncogenic stress accumulated in fast-growing cancer cells (25). In this article we will focus on several *MYC*-induced oncogenic and metabolic changes that could be vulnerable for molecular targeting, with an emphasis on current translational efforts aiming to develop better therapeutic strategies to treat *MYC*-induced malignancies.

Clinical Translational Advances

Targeting a *MYC*-induced Warburg effect

Cancer cells preferentially generate energy through aerobic glycolysis rather than oxidative phosphorylation, a well-established phenomenon described as the Warburg effect (26). Although glycolysis is an inefficient way of utilizing glucose, it provides essential intermediates for the biosynthesis of macromolecules, including proteins, lipids and nucleotides (26). Glycolysis also produces minimal oxidative stress, a survival obstacle that is often encountered by rapidly-growing cancer cells (27). Activated *MYC* drives the expression of almost all glycolytic enzymes, particularly lactate dehydrogenase (LDH), hexokinase 2 (HK2), and enolase 1 (ENO1), as well as glucose transporter GLUT1 (7) (Figure 1). Unfortunately, inhibiting the early steps of glycolysis often introduces nontolerable toxicity, as evidenced by the failed clinical trials of the hexokinase inhibitors 2-deoxy-D-glucose (NCT00633087) and lonidamine (NCT00435448). However, targeting lactate metabolism via a small molecule FX11 that inhibits LDHA, an LDH isoform that is specifically induced in tumor tissues, blocks *MYC*-driven lymphoma progression without introducing any observable side effects in mice (21). It would be of great interest to follow the effect of FX11 or its optimized derivatives in future clinical trials.

In addition to suppressing LDHA activity, an alternative approach to interfere with lactate metabolism is to block the excretion of lactate from cancer cells through inhibiting monocarboxylate transporter (MCT) activity, given that high levels of intracellular lactate lower cytosolic pH and cause severe cytotoxicity (28). Currently a MCT1 specific inhibitor AZD3965 is being tested for treating prostate cancer, gastric cancer and large B cell lymphoma (NCT01791595).

Another attractive target within the glycolytic pathway is pyruvate dehydrogenase kinase (PDK). PDK inhibits pyruvate dehydrogenase through direct phosphorylation, which prevents central carbon metabolites from entering the TCA cycle, thus ensuring consistent glycolytic flux and the Warburg effect (29). PDK expression can be robustly increased by the cooperation between *MYC* and hypoxia-inducible factor (HIF), a transcription factor frequently induced in solid tumors with poor vascularity (30) (Figure 1). Interestingly, *MYC* opposes HIF activity in the normal physiological condition, while in transformed tissues it often collaborates with HIF to promote glucose-lactate conversion partially through PDK1 co-activation (30–33). Several clinical trials on brain tumors, head and neck carcinoma, and other recurrent/metastatic solid malignancies are ongoing, using a PDK1 inhibiting compound dichloroacetate (DCA) as a single agent or in combination with other therapeutics (NCT00566410, NCT01386632, and NCT01111097).

Targeting *MYC*-induced glutamine metabolism

MYC-induced aerobic glycolysis directs central carbon metabolites away from the mitochondria, resulting in a significant depletion of TCA cycle intermediates (6). To compensate for substrate loss that hinders rapid cell growth, alternative bioenergetic

resources need to be supplemented. Glutamine, the most abundant nonessential amino acid in the human body, represents a critical replenishment for mitochondrial respiration. In addition to its role in protein synthesis, glutamine can also be catabolized to alpha-ketoglutarate and feed into the TCA cycle, a process termed “anapleurosis” (34). This is accomplished by a two-step glutaminolytic reaction: first, glutamine is converted to glutamate via glutaminase (GLS)-mediated deamination; then glutamate dehydrogenase (GDH) or glutamate-dependent transaminases remove the amino group from glutamate to generate alpha-ketoglutarate (6, 34). Cancer cells harboring amplified *MYC* exhibit *MYC*-dependent glutamine addiction, as glutamine depletion or glutaminolysis inhibition triggers dramatic apoptotic responses in *MYC*-overexpressing fibroblasts, lymphoma cells and neuroblastoma cells, but not in *MYC*-nonexpressing counterparts (35–39). The glutamine dependence induced by *MYC* amplification is partially mediated by *MYC*'s ability to upregulate a few glutamine transporters (ASCT2, SN2, etc.) and glutaminases (Figure 1), which opens a therapeutic window for drug targeting (6, 39). Indeed, several glutaminolysis inhibitors have been developed and tested preclinically. 6-diazo-5-oxo-L-norleucine (DON) is a nonspecific GLS inhibitor that showed anti-tumor activities in both cell culture and animal experiments (40, 41). However, its severe side effects such as neuronal toxicity prevented its bedside application (42). BPTES is a specific inhibitor of GLS1, the kidney-isoform of GLS that is frequently activated by c-*MYC* (43). The in vitro and in vivo proliferation of P493 lymphoma cells overexpressing c-*MYC* are significantly inhibited by BPTES treatment, a phenotype that is even more dramatic in hypoxic conditions (37). It's worth noting that the amplified *MYCN* associated with neuroblastoma predominantly induces the expression of GLS2, the liver isoform of GLS that can't be inhibited by BPTES (36, 43). Therefore caution is needed when treating cancers driven by different *MYC* isoforms. Compound 968 is another GLS1 inhibitor identified by screening for molecules that block Rho-GTPase-induced transformation (44). 968 selectively targets a short splicing isoform of GLS1 named GAC, which is presumably accounting for the elevated basal GLS activity detected in transformed cells. Consistent with this finding, 968 administration significantly decreases the growth rate of human breast cancer and lymphoma cells without affecting normal cell growth (44). Although these preclinical results are encouraging, neither BPTES nor 968 have been transferred to clinical examination, and special attention needs to be paid to the neuronal side effects that might be caused by these GLS inhibitors. Meanwhile, glutaminolysis can also be disrupted by inhibition of GDH or transaminases, two groups of enzymes catalyzing the second step of glutaminolysis (34) (Figure 1). It has been reported that even short-term treatment with aminooxyacetate (AOA), a pan-transaminase inhibitor, was sufficient to delay autochthonous neuroblastoma growth in the TH-*MYCN*^{+/+} mouse model (31). Unfortunately, the intolerable side effects of AOA prevent it from being approved to treat human patients (45). More specific and potent transaminase inhibitors are necessary. Moreover, *MYC*-amplified neuroblastoma and glioblastoma cells are also sensitive to GDH inhibition, especially in glucose-depleted conditions (36, 46). Administration of a nonspecific GDH inhibitor EGCG, which is a green tea extract, triggers dramatic apoptosis in these cells and inhibits neuroblastoma xenograft tumor growth (36). EGCG is currently in Phase 2 trials on colorectal cancer (NCT01360320) and multiple myeloma (NCT00942422).

Targeting *MYC*-induced serine, glycine and proline metabolism

Recent studies focusing on cancer cell metabolism highlight the importance of several amino acids to cancer progression. The serine/glycine metabolic pathway has drawn significant attention because it not only contributes to the biosynthesis of two important amino acids, but also provides the essential one-carbon unit for making nucleotides and other biomolecules (47). Phosphoglycerate dehydrogenase (PHGDH) is the first enzyme catalyzing serine biosynthesis and has been established as an important player in

maintaining the oncogenic potential of breast cancer and melanoma cells (23, 24). In *MYC*-induced hepatocellular carcinoma tissues, PHGDH expression is dramatically increased (Figure 1) and correlates with advanced stages of tumor progression (20). Serine hydroxymethyltransferase (SHMT) is another key enzyme in this metabolic pathway, which functions by breaking down serine into glycine and a one-carbon moiety (47). SHMT is also a *MYC* target gene (Figure 1) and able to partially rescue the growth defect of *MYC*-deficient cells (48). It would be particularly interesting to determine whether *MYC*-amplified cancer cells are more sensitive to the blockage of serine/glycine metabolism, particularly through PHGDH and SHMT inhibition. Proline is another amino acid that is closely regulated by the *MYC* signaling cascade. Proline oxidase (POX) is the first enzyme functioning in proline catabolism whose activity inhibits *MYC*-mediated cancer cell proliferation and survival (49) (Figure 1). POX knockdown partially rescues the growth defect of lymphoma and prostate cancer cells where *MYC* has been inhibited, largely due to a decrease in ROS production which is associated with proline catabolism. *MYC* also markedly increases the biosynthesis of proline from glutamine through upregulation of pyrroline-5-carboxylate synthase (P5CS) and pyrroline-5-carboxylate reductase 1 (PYCR1) (49) (Figure 1). The increased glutamine-proline flux presumably contributes to the glutamine dependence of *MYC*-amplified cells, which leads to the possibility of targeting proline metabolism as an alternative approach to treat *MYC*-driven malignancies.

Targeting *MYC*-induced oncogenic stress and apoptosis

Upon its oncogenic activation, *MYC* elicits a massive transcriptional program that supports cancer cell proliferation and tumor progression. The rapid cell growth and biomass synthesis create an unfavorable cellular environment, a situation termed “oncogenic stress”, and multiple stress defensive responses are activated to overcome this issue (25). In *MYC*-induced lymphoma tissues, elevated protein synthesis leads to the accumulation of unfolded proteins in the ER, which initiates the unfolded protein response (UPR) through activation of the PERK/eIF2 α pathway (50) (Figure 1). Loss of UPR signaling resulting from PERK deletion triggers a caspase-dependent apoptosis in *MYC*-overexpressing cells, which raises interest in using PERK inhibitors to treat *MYC*-amplified tumors. Recently, a small molecule GSK2656157 was developed as a specific PERK inhibitor, which successfully inhibited pancreatic cancer and multiple myeloma xenograft tumor growth, although a drug-induced pancreatic damage was also observed (51). To reduce the amount of unfolded proteins in the ER, PERK/eIF2 α activation blocks global protein synthesis, while simultaneously increasing the expression of selective genes, such as ATF4 (50). Upon activation by PERK, ATF4 protects cells from UPR-induced apoptosis partially through its connection to autophagy (50, 52). However, amino acid deprivation, a metabolic stress that frequently occurs in poorly-vascularized tumors, also activates ATF4 via a PERK-independent kinase GCN2. In this case ATF4 functions as a pro-apoptotic factor that mediates stress-induced cell death (36) (Figure 1). It has been reported that in *MYC*-amplified lymphoma and neuroblastoma cells, glutamine starvation triggers apoptosis via the activation of ATF4-PUMA/NOXA/TRB3 pathway, and *MYC*-induced xenograft tumor growth is significantly inhibited by injection of a nonspecific ATF4 agonist 4-hydroxyphenyl retinamide (4-HPR, also known as fenretinide) (36). Fenretinide is currently in clinical trials to treat neuroblastoma (NCT00646230), B-cell lymphoma (NCT00288067) and ovarian cancer (NCT01535157). Given that *MYC*-induced oncogenic stress sensitizes cancer cells to apoptosis, anti-apoptotic factors would be another group of intriguing targets to consider. Increased glutamine flux elicited by high levels of *MYC* can activate mTOR (53), and transgenic activation of the mTOR downstream effector eIF4E antagonizes *MYC*-dependent apoptosis in vivo (54) (Figure 1). Consistent with these findings, *MYC*-driven lymphoma progression in mice is significantly delayed by administration of a specific mTORC1 inhibitor Everolimus (55), a promising anti-cancer compound that is undergoing

numerous clinical trials (56). Interestingly, an uncontrolled, hyperactivated mTOR signaling event is also detrimental to *MYC*-induced transformation. A Kinome siRNA screen revealed that AMPK-related kinase 5 (ARK5), an upstream inhibitory regulator of mTORC1, contributes to *MYC*-induced hepatocellular carcinoma progression (57). ARK5-restrained mTOR activity is necessary to maintain *MYC*-driven glutaminolysis, suggesting that ARK5 may be a potential drug target for tumors with deregulated *MYC*.

Conclusions and Future Perspective

Cancer cell metabolism is an “antique” research field that has recently been revisited and gained increasing momentum over the past decade. Newly-developed biotechnologies and better understanding of signaling networks will elucidate the mechanisms whereby metabolic changes are induced in cancer cells. *MYC* is a “master regulator” oncogene that orchestrates multiple levels of cancer cell activities, including proliferation, apoptosis, stress responses and metabolism. The multifaceted function of *MYC* opens up exciting possibilities for combined targeting strategies that may achieve better therapeutic responses. Consistent with this idea, co-administration of the apoptosis-inducing fenretinide and glutaminolysis inhibitor EGCG in a preclinical neuroblastoma model resulted in better outcomes than individual application (36). Fenretinide and EGCG are both clinically-approved drugs and can be quickly translated into trials for testing their cooperative effect in human patients. In addition to *MYC*-primed apoptosis and metabolism, *MYC*-induced cell cycle progression can be a third option to consider for combined therapeutic targeting. A list of proliferation-related effectors have been reported to be essential for *MYC*-driven tumorigenesis, including Cyclin-dependent kinases 1/2 (CDK1/2), polyamine synthetic enzyme ornithine decarboxylase 1 (ODC1) and sumoylation-activating enzyme 1/2 (SAE1/2) (58–62). Several compounds that selectively inhibit these enzymes have entered clinical trials, such as eflornithine (NCT01586260, NCT01059071, NCT00983580), AT7519M (NCT01183949, NCT01652144, NCT01627054), and seliciclib (NCT00999401). We believe that the evolving knowledge about *MYC* will keep providing intriguing targets for treating *MYC*-amplified malignancies.

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Figure 1.

The pleiotropic transcription factor MYC reprograms cancer cell metabolism to fuel rapid cell growth. MYC increases glycolytic flux by inducing the expression of glucose transporter GLUT1 and glycolytic enzyme LDH. MYC in cooperation with HIF increases PDK expression to inhibit PDH and prevents central carbon metabolites from entering the TCA cycle (the Warburg effect). Glutaminolysis is stimulated upon activation of several glutamine transporters (ASCT2, SN2, etc.) and GLS in *MYC*-amplified cells. MYC is also capable of enhancing serine, glycine, and proline metabolism by modulating several related enzymes, including PHGDH, SHMT, POX, P5CS, and PYCR1. In addition to MYC's role in metabolic regulation, MYC activation results in multiple cellular responses mediating oncogenic stress that is often present in rapidly-growing cancer cells, such as the UPR and apoptosis. The *MYC*-regulated downstream targets/effects that facilitate cancer progression are highlighted in **red**, while those antagonizing *MYC*-induced tumorigenesis are highlighted in **green**. A number of compounds that directly target MYC or downstream pathways emanating from MYC are also highlighted in **green**. GLUT1, glucose transporter 1; 3-PG, 3-phosphoglycerate; LDH, lactate dehydrogenase; PDK, pyruvate dehydrogenase kinase; PDH, pyruvate dehydrogenase; ASCT2, also known as solute carrier family 1, member 5 (SLC1A5); SN2, also known as solute carrier family 38, member 5 (SLC38A5); GLS, glutaminase; GDH, glutamate dehydrogenase; PHGDH, phosphoglycerate dehydrogenase; SHMT, serine hydroxymethyltransferase; POX, proline oxidase, also known as proline dehydrogenase (PRODH); P5C, pyrroline-5-carboxylate; GSA, glutamic gamma-semialdehyde; P5CS, P5C synthase; PYCR1, P5C reductase 1; HIF, hypoxia inducible factor; UPR, unfolded protein response; FRT, fenretinide, also known as 4-hydroxyphenyl

retinamide (4-HPR); EGCG, epigallocatechin gallate; AOA, aminooxyacetate. DON, 6-diazo-5-oxo-L-norleucine; DCA, dichloroacetate.