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REVIEW ARTICLE

The implication of MYC oncogene in cancer and its therapy

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ABSTRACT

MYC is a proto-oncogene that has been linked to the development of almost all malignancies in humans. Multiple processes are imperative to checkpoints concerning cellular aging, cell death, and arrest of cell proliferation, which are genetically and epigenetically controlled, prevent MYC activation from causing cancer in many normal cells. MYC bypasses these mechanisms when triggered pathologically, under genetic or epigenetic conditions, enforcing many of cancer's "hallmark" features, such as constant growth of tumors associated with the replication and transcription of DNA, proliferation of cells, and modified cellular metabolism. MYC directs dictates the destiny of tumor cells by increasing stemness and inhibiting the senescence and differentiation of cells. MYS also orchestrates alterations in the vicinity of the tumor, that include the formation of blood vessels and inhibition of the host's body defense mechanisms. MYC activation is required for the progression and persistence of many human malignancies. It might be feasible to anticipate when tumors may become dependent on MYC using multiscale mathematical models. MYC is a significant molecular component that participates in initiating and maintaining tumorigenesis. As deep pockets are absent and their broad protein interfaces lack marked features, MYCs are challenging to prey with standard small-molecule medicines, despite being a crucial player in oncogenesis. Large biomolecules are also unable to access them, due to their inability to cross cell membranes. With recent technological advancements, a variety of options to target MYC in tumors are available, that range from lowering MYC levels directly to suppressing certain housekeeping functions in cells that overexpress MYC to further tailored techniques targeting MYC-induced downstream events. There are currently no approved direct inhibitors of MYC; nevertheless, various therapeutic compounds that target MYC are in development.

Keywords – MYC, proto-oncogene, tumor, apoptosis, targeting, cancer therapy.

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INTRODUCTION

Myelocytomatosis (MYC) gene family is a group of three gene products (cellular MYC or c-MYC; neuroblastoma derived MYC or n-MYC; and lung carcinoma derived MYC or l-MYC) which act as transcription factors governing growth and progression into the cell cycle by inducing the expression of thousands of genes [38,32]. Cell differentiation, self-renewal, cellular metabolism, cell cycle, growth, and survival along with protein synthesis are all regularly coordinated by the MYC proto-oncogenes, usually present downstream of many membrane receptor-ligand complexes and at the junction of numerous signal transduction pathways [5,14,39].

In cells, c-MYC expression is generally strictly regulated, but in most human malignancies, it becomes dysregulated and overexpressed, thus illustrating it to be an important oncogene in humans [20]. Changes at the molecular levels of DNA, RNA, or proteins can lead to this change, however, direct mutation of *c-myc* seems rare. Overexpression of *c-myc* might escalate E-box contacts having lower

affinity that otherwise keep off at normal physiological conditions, causing carcinogenesis through alterations in the activation of genes that control the growth and proliferation of cells [30].

MYC serves as a potent transcription factor that promotes the expression of a wide range of target genes to coordinate cellular proliferation, metabolism, and death. The expression of the genes belonging to the MYC family is strictly regulated in immune cells during development or in response to immunological activation. According to the latest research, they have emerged to be crucial modulators of immune cell development, differentiation, and activation. MYC controls gene product expression via directly activating or inhibiting gene transcription [48], transcriptional amplification [26,51], stimulating microRNA and chromatin regulators [21] and controlling the synthesis [31]. MYC knockout is embryonic lethal and inhibits the survival, proliferation, and differentiation of adult cells [3]. MYC is thus an important protein that is crucial to embryonic development as well as adult mature cell proliferation.

MYC participates in different physiological processes, such as immunology and its related disorders, in addition to cancer. MYC performs multi-faceted roles in regulating cell differentiation and proliferation. Additionally, events like transformation, angiogenesis, genomic instability, and apoptosis have been reported to be MYC controlled [5]. New information about the role of MYC as a gene transcription regulator has revealed several pathways for the initiation and suppression of various downstream genes. In addition, the list of MYC-controlled genes has risen in recent years, demanding an emphasis on identifying and separating genuine targets. Finally, discovering MYC-binding proteins has been challenging, despite the field's recent expansion with a flood of novel interactors. The identification of these proteins, as well as their budding impact on MYC, exemplifies the velocity and breadth of modern MYC research.

MYC AS AN ONCOGENE

MYC regulates the transcription of a large number of genes involved in the cell cycle, self-renewal, survival, cell growth, metabolism, protein and ribosomal biogenesis, and differentiation, all of which are crucial for normal as well as neoplastic growth and proliferation of cells [5]. MYC controls these programs in a manner that is in sync with the immunological response of the host. MYC participates in carcinogenesis via tumor cell-intrinsic effects [2].

Recent findings have revealed that MYC expression in tumor cells influences both the innate as well as adaptive immune systems to control the tumor microenvironment [29]. In a permissive environment, the *myc* oncogene deregulates the checkpoints involved in cell growth and senescence, accelerating the carcinogenic process for the afflicted clone. MYC is associated with the development of almost all human malignancies. MYC activation does not cause cancer in many normal cells because of multiple genetic and epigenetically regulated checkpoint mechanisms such as proliferative arrest, apoptosis, and cellular senescence. [12].

There have been exceptional advancements that help to detect activated *myc* in its unregulated, carcinogenic form in primary human malignancies owing to breakthrough advances in molecular diagnostic techniques. These advancements provide new avenues for understanding tumor subgroups with dysregulated MYC expression, identifying critical collaborating lesions, and realizing the therapeutic potential of targeting MYC. Progress has also been made in understanding the range and depth of the myriad biological activities regulated by MYC.

Function of MYC in various cancers

Proto-oncogenes in the MYC family play a significant role in the development of varied human cancers. They function as transcription factors causing continuous cell-cycle progression and blocking differentiation by binding to a specific target sequence (12). While much of recent research on the *c-myc* oncogene has resulted in some significant improvements, it has also revealed a great quantity of contradicting data regarding the gene product's method of action.

Studies demonstrate that *c-myc* can act both as an activator or a repressor of transcription, as well as, function in both programmed cell death (apoptosis) and cell-cycle progression [2]. Furthermore, specific functions of the alternative translation products of the *c-myc* gene, namely, *c-myc*1 and *c-myc*2, have piqued curiosity [12]. The discovery that c-MYC1: c-MYC2 increases dramatically during cellular aging stemmed from the surprising fact that *c-myc*2 boosts cell growth while *c-myc*1 appeared to limit cell development [20] when forced expression of these two proteins was performed separately under experimental conditions.

Two recent studies imply that MYC may play a crucial role in the regulation of immune response. The proteins RAS and MYC interact through impacts on the tumor microenvironment in lung cancer [23]. The authors used Cre-lox to conditionally activate *KRAS* and *MycER* to conditionally activate MYC. MYC activation causes an inflow of macrophages, as well as a loss of CD3+ T cells, NKp46+ natural killer (NK)

cells, and B220+ B cells, and has been linked to angiogenesis induction within 24 hours [3]. The removal of NKp46+ NK cells slowed tumor development significantly. T cells were returned to the microenvironment by anti-PD-L1 therapy, however, tumor regression did not occur. CCL9 and IL-23 have been linked to the import of F4/80+ PD-L1+ macrophages and the depletion of PD-L1+ macrophages [3]. The discrepancies in *c-myc* activities, together with the frequent incidence of *c-myc* mutations in human cancers, indicate that, while comprehending the activities of the *myc* gene family is difficult, it is worthwhile to explore.

MYC in the regulation of metabolism in cancer

Oncogenes like *myc* may promote tumor growth both through their intrinsic influence on the proliferation of cells and modulation of immunological checkpoints, allowing immune surveillance to be circumvented. MYC is necessary for tumors induced by other oncogenic events involving the WNT and RAS signaling pathways [43,40], and is typically triggered by these signaling pathways, implying that MYC activity is essential in all cancers. When MYC is overexpressed, it promotes and restricts a large variety of target genes, among which must be the oncogenic effectors [43]. c-MYC is a transcription factor that links cellular metabolism to carcinogenesis by regulating the genes involved in ribosome and mitochondria biosynthesis along with glucose and glutamine metabolism [7]. As a result, it is suggested that MYC, MYC-activated gene products, or related biological processes have been identified as potential targets for cancer therapy [6]. The biological processes driven by MYC are outlined in the figure below, followed by a table that lists the genes that c-MYC targets and the downstream processes affected.

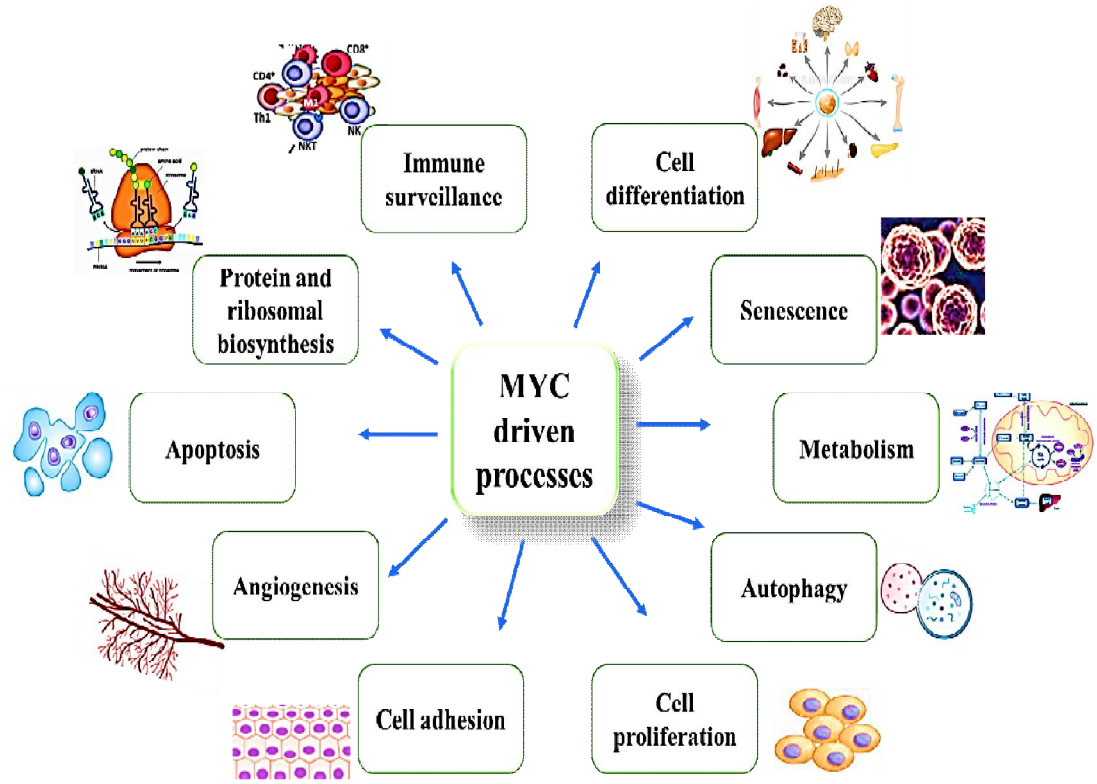

Figure: MYC driven biological processes – MYC has been shown to operate as transcription factors, causing cell-cycle progression, cellular immortalization, cell differentiation, and participation in various cellular processes as described above. [Adapted from (2,3). Created using Microsoft PowerPoint. Image source: https://www.google.com/images]

Table: 1: Target genes of c-MYC and the subsequent biological processes affected. (Dang, 1999)

Target Genes	*Change in expression*	*Processes affected*	*References*
ARF or p19	Upregulated	Apoptosis	[52]
CAD	Upregulated	Growth and metabolism	[30]
Cdc2	Upregulated	Growth-related	[1]
Cdc25A	Upregulated	Growth-related	[13]
Collagens *α1(I), α2(I), α3(VI), α1(III)*	Downregulated	Adhesion	[44, 50]
Cyclin A	Upregulated	Growth-related	[17, 18]
Cyclin D1	Up or down-regulated	Growth-related	[16, 34]
Cyclin E	Upregulated	Growth-related	[25, 34]
DHFR	Upregulated	Growth and metabolism	[28]
eIF2α	Upregulated	Growth and metabolism	[37]
eIF4E	Upregulated	Growth and metabolism	[37, 19]
LDH-A	Upregulated	Growth and metabolism	[41, 44]
MHC class I	Downregulated	Immune surveillance	[46]
MrDb	Upregulated	Metabolism	[15]
p53	Upregulated	Growth-related	[44]
Thrombospondin	Downregulated	Metastasis	[45]

ONCOGENE ADDICTION AND ITS IMMUNE MECHANISM

Genes that repress tumor-suppressors or activate proto-oncogenes are frequently involved in the initiation of cancer. Oncogene addiction is a phenomenon that occurs when these processes are required for the survival and proliferation of tumor cells [29]. Additionally, emerging data suggest that oncogenes also directly control immune responses, resulting in immunosuppression (19). The expression of proteins such as PD-L1, that regulate the immune response, is induced by various oncogenes or the loss of tumor suppressors. Oncogenes, specifically MYC, inhibit immune surveillance, and oncogene-targeted therapy may restore the immune response to malignancies [47].

Targeted oncogene inactivation combined with therapy might help in restoring immune response to tumors. When the driver oncoprotein is targeted or removed, cancers frequently demonstrate "oncogene addiction," which is associated with rapid and long-term tumor regression [33,11]. Following the elimination of the driving oncoprotein, oncogene addiction is divided into two "phases." Proliferative arrest and apoptosis are two fundamental tumor cell processes that cause oncogene addiction in the initial phase. The final phase of oncogene addiction, on the other hand, is dependent on the host and necessitates a healthy host immune system to ensure the complete elimination of tumor cells.

Oncogene addiction is common in tumors caused by unregulated *c-myc*, which are responsive to c-MYC protein suppression or inhibition. Immune checkpoint expression is causally regulated by the *myc* oncogene. PD-L1 expression appears to be regulated by other oncogene proteins such as EGFR, STAT3, BRAF, -catenin, and AKT/mTOR, as well as tumor-suppressor genes such as PTEN loss [29].

MYC in immune evasion

MYC regulates the immune system of the host through immunological checkpoints, specific receptors, and released cytokines, which leads to cancer start and maintenance (14). MYC controls the expression and synthesis of MHC class I and class II, CD47, NKG2D, and PD-L1, among other immune ligands and effector molecules [3]. Apoptosis may enhance the immune response by recruiting the innate immune cells. The inactivation of MYC reduces immunological checkpoints and activates macrophages and CD4+ T cells, resulting in an adaptive immunity-dependent response [8]. The engagement of T-cell mediated immune response, along with the production of additional cytokines, are believed to be involved in the last phase of tumor eradication. Immune activation has been linked to changes in the tumor microenvironment alteration, including the induction of cellular senescence and angiogenesis inhibition [9]. TSP-1 is involved in some of these processes.

Targeting MYC in cancer therapy

One of the most common "hallmarks of cancer" cells is the aberrant activation of the *c-myc* (*myc*) oncogene, which can be caused by transcriptional overexpression (gene amplification, translocation, or changes in upstream signaling pathways) and/or protein stabilization [10]. Indeed, high MYC protein levels are not only capable of driving the start of a tumor, but they are also obligatory for its maintenance. Cancer cells require persistent MYC overexpression, proliferation arrest, apoptosis, and differentiation to occur when MYC levels are reduced [7]. This has been observed not just in MYC-driven animal tumor models, but also in tumors driven by other oncogenes, making c-MYC a promising anti-cancer target [46]. Unfortunately, due to a lack of enzymatic activity and a large pocket that may be targeted by small molecule inhibitors, MYC is not an easily "druggable" protein. As a result, inhibiting MYC co-factors and/or downstream effectors which might be essential for tumor formation and maintenance is one of the field's top targets.

MYC is a key regulator of cancer cell proliferation, regulating cell growth, cell cycle, metabolism, and cell survival through a transcriptional program. Many attempts have been made to target MYC specifically for cancer treatment. Several chemicals have been developed to either directly or indirectly disrupt MYC function or stability. The most potent inhibitors go after the MYC-MAX interaction [15], which is needed for DNA binding. Unfortunately, the pharmacokinetics and pharmacodynamics of these drugs are insufficient for in vivo use. Indirect inhibition of MYC has been reported in recent research thanks to the development of two drugs, JQ1, and THZ1, which target factors engaged in different phases of transcription [36].

Although certain actions are MYC-independent, some drugs elucidate substantial therapeutic potential concerning malignancies having elevated MYC levels. These methods will be used to produce new medicines that will pharmacologically target MYC-driven malignancies. Immune checkpoints have been demonstrated to be regulated by oncogenes that control MYC. As a result, MYC may prevent highly proliferative cells from generating an immunological response in general. MYC-driven cancer cells have taken use of this method to avoid immune detection. Inactivation of MYC can thereby restore the immune response to a tumor. MYC-induced cancers could be particularly vulnerable to immuno-oncology treatment.

MYC is a transcription factor that affects multiple steps of RNA metabolism, including constitutive and alternative splicing, the efficiency of translation, and stability of the mRNA, as well as directly modulating several stages of transcription and co-transcriptional processing (e.g. RNA-Polymerase II initiation, elongation, and mRNA capping) [22,24,19]. Since MYC is an oncoprotein with unregulated expression in several human cancers, recognizing its major downstream functions in tumors is critical for developing successful therapeutic options. With this information and recent technical improvements, we now have a variety of options for targeting MYC in tumors, ranging from lowering MYC levels directly to suppressing certain housekeeping functions in MYC-over expressing cells to more focused techniques based on MYC-induced downstream effects.

The MYC oncogene has a role in the development of several human malignancies. New cancer therapy prospects have arisen as a result of recent discoveries about its expression and function. Drug-like compounds could block MYC activation by bromodomain proteins, resulting in tumor suppression *in vivo* [42]. Tumor growth can also be slowed by pharmacologically decoupling MYC-induced cellular biomass increase from bioenergetic pathways involving glucose or glutamine metabolism [4,7]. Targeting MYC-MAX dimerization or MYC-induced microRNA production are two further ways to stop MYC from leading to cancer [36,7].

CONCLUSION AND PROSPECTS

MYC holds the promise to serve as an effective therapeutic target in oncology. It is one of the few proteins that are most elevated in cancers of all types [10]. It also serves as a signaling hub, which is expected to be necessary for the initiation and development of tumors. Genetic models of *myc* inactivation have conclusively demonstrated that inactivating this critical molecule with negligible adverse effects on normal cells is conceivable [49]. The present understanding of the mechanisms behind the regulation of MYC abundance and its downstream pathways, along with novel pharmacological alternatives, provides various avenues for inhibiting this important transcription factor [27].

In patients with MYC-driven malignancies, treatments that target the MYC pathway will be critical for reverting malignant growth and boosting anti-tumor immune responses (10). In the recent decade, a wide variety of MYC inhibitors have been produced, some of which are relatively potent and selective compared to others. Although direct inhibitors of MYC, particularly those that target the MYC-MAX interaction, are more precise for MYC, as they target the bHLH-LZ domain common to most transcription

factors [15,31]. A better-tailored approach to inhibit MYC could involve the chemical inhibition of specific MYC domains. The mechanisms of action of indirect MYC inhibitors like JQ1 and THZ1 work are still being studied [36]. Furthermore, more research is needed to test the effectiveness of these molecules to treat cancers in humans. Finally, newer strategies should be formulated to target MYC from varied aspects leveraging its strengths as the prime controller of transcription in tumor cells.

REFERENCES

1. Born, T. L., Frost, J. A., Schönthal, A., Prendergast, G. C., & Feramisco, J. R. (1994). C-Myc cooperates with activated Ras to induce the cdc2 promoter. *Molecular and Cellular Biology*, *14*(9), 5710–5718. PubMed. https://doi.org/10.1128/mcb.14.9.5710-5718.1994
2. Casey, S. C., Baylot, V., & Felsher, D. W. (2017). MYC: Master Regulator of Immune Privilege. *Trends in Immunology*, *38*(4), 298–305. https://doi.org/10.1016/j.it.2017.01.002
3. Casey, S. C., Baylot, V., & Felsher, D. W. (2018). The MYC oncogene is a global regulator of the immune response. *Blood*, *131*(18), 2007–2015. https://doi.org/10.1182/blood-2017-11-742577
4. D'Andrea, A., Gritti, I., Nicoli, P., Giorgio, M., Doni, M., Conti, A., Bianchi, V., Casoli, L., Sabò, A., Mironov, A., Beznoussenko, G. V., & Amati, B. (2016). The mitochondrial translation machinery as a therapeutic target in Myc-driven lymphomas. *Oncotarget*, *7*(45), 72415–72430. PubMed. https://doi.org/10.18632/oncotarget.11719
5. Dang, C. V. (1999). C-Myc target genes involved in cell growth, apoptosis, and metabolism. *Molecular and Cellular Biology*, *19*(1), 1–11. PubMed. https://doi.org/10.1128/MCB.19.1.1
6. Dang, C. V. (2012). MYC on the path to cancer. *Cell*, *149*(1), 22–35. PubMed. https://doi.org/10.1016/j.cell.2012.03.003
7. Dang, C. V., Le, A., & Gao, P. (2009). MYC-induced cancer cell energy metabolism and therapeutic opportunities. *Clinical Cancer Research : An Official Journal of the American Association for Cancer Research*, *15*(21), 6479–6483. PubMed. https://doi.org/10.1158/1078-0432.CCR-09-0889
8. de Jonge, A. V., Mutis, T., Roemer, M. G. M., Scheijen, B., & Chamuleau, M. E. D. (2020). Impact of MYC on Anti-Tumor Immune Responses in Aggressive B Cell Non-Hodgkin Lymphomas: Consequences for Cancer Immunotherapy. *Cancers*, *12*(10), 3052. PubMed. https://doi.org/10.3390/cancers12103052
9. Dhanasekaran, R., Deutzmann, A., Mahauad-Fernandez, W. D., Hansen, A. S., Gouw, A. M., & Felsher, D. W. (2022). The MYC oncogene—The grand orchestrator of cancer growth and immune evasion. *Nature Reviews Clinical Oncology*, *19*(1), 23–36. https://doi.org/10.1038/s41571-021-00549-2
10. Duffy, M. J., O'Grady, S., Tang, M., & Crown, J. (2021). MYC as a target for cancer treatment. *Cancer Treatment Reviews*, *94*, 102154. https://doi.org/10.1016/j.ctrv.2021.102154
11. Felsher, D. W. (2010). MYC Inactivation Elicits Oncogene Addiction through Both Tumor Cell-Intrinsic and Host-Dependent Mechanisms. *Genes& Cancer*, *1*(6), 597–604. PubMed. https://doi.org/10.1177/1947601910377798
12. Gabay, M., Li, Y., & Felsher, D. W. (2014). MYC activation is a hallmark of cancer initiation and maintenance. *Cold Spring Harbor Perspectives in Medicine*, *4*(6), a014241. PubMed. https://doi.org/10.1101/cshperspect.a014241
13. Galaktionov, K., Chen, X., & Beach, D. (1996). Cdc25 cell-cycle phosphatase as a target of c-myc. *Nature*, *382*(6591), 511–517. https://doi.org/10.1038/382511a0
14. Gnanaprakasam, J. N. R., & Wang, R. (2017). MYC in Regulating Immunity: Metabolism and Beyond. *Genes*, *8*(3). https://doi.org/10.3390/genes8030088
15. Grandori, C., Mac, J., Siëbelt, F., Ayer, D. E., & Eisenman, R. N. (1996). Myc-Max heterodimers activate a DEAD box gene and interact with multiple E box-related sites in vivo. *The EMBO Journal*, *15*(16), 4344–4357. PubMed.
16. Hanson, K. D., Shichiri, M., Follansbee, M. R., & Sedivy, J. M. (1994). Effects of c-myc expression on cell cycle progression. *Molecular and Cellular Biology*, *14*(9), 5748–5755. PubMed. https://doi.org/10.1128/mcb.14.9.5748-5755.1994
17. Hoang, A. T., Cohen, K. J., Barrett, J. F., Bergstrom, D. A., & Dang, C. V. (1994). Participation of cyclin A in Myc-induced apoptosis. *Proceedings of the National Academy of Sciences of the United States of America*, *91*(15), 6875–6879. PubMed. https://doi.org/10.1073/pnas.91.15.6875
18. Jansen-Dürr, P., Meichle, A., Steiner, P., Pagano, M., Finke, K., Botz, J., Wessbecher, J., Draetta, G., & Eilers, M. (1993). Differential modulation of cyclin gene expression by MYC. *Proceedings of the National Academy of Sciences of the United States of America*, *90*(8), 3685–3689. PubMed. https://doi.org/10.1073/pnas.90.8.3685
19. Jones, R. M., Branda, J., Johnston, K. A., Polymenis, M., Gadd, M., Rustgi, A., Callanan, L., & Schmidt, E. V. (1996). An essential E box in the promoter of the gene encoding the mRNA cap-binding protein (eukaryotic initiation factor 4E) is a target for activation by c-myc. *Molecular and Cellular Biology*, *16*(9), 4754–4764. PubMed. https://doi.org/10.1128/MCB.16.9.4754
20. Kalkat, M., De Melo, J., Hickman, K. A., Lourenco, C., Redel, C., Resetca, D., Tamachi, A., Tu, W. B., & Penn, L. Z. (2017). MYC Deregulation in Primary Human Cancers. *Genes*, *8*(6). https://doi.org/10.3390/genes8060151
21. Knoepfler, P. S., Zhang, X., Cheng, P. F., Gafken, P. R., McMahon, S. B., & Eisenman, R. N. (2006). Myc influences global chromatin structure. *The EMBO Journal*, *25*(12), 2723–2734. PubMed. https://doi.org/10.1038/sj.emboj.7601152
22. Koh, C. M., Sabò, A., & Guccione, E. (2016). Targeting MYC in cancer therapy: RNA processing offers new opportunities. *BioEssays*, *38*(3), 266–275. https://doi.org/10.1002/bies.201500134

23. Kortlever, R. M., Sodir, N. M., Wilson, C. H., Burkhart, D. L., Pellegrinet, L., Brown Swigart, L., Littlewood, T. D., & Evan, G. I. (2017). Myc Cooperates with Ras by Programming Inflammation and Immune Suppression. *Cell*, *171*(6), 1301-1315.e14. https://doi.org/10.1016/j.cell.2017.11.013
24. Kress, T. R., Sabò, A., & Amati, B. (2015). MYC: connecting selective transcriptional control to global RNA production. *Nature Reviews Cancer*, *15*(10), 593–607. https://doi.org/10.1038/nrc3984
25. Leone, G., DeGregori, J., Sears, R., Jakoi, L., & Nevins, J. R. (1997). Myc and Ras collaborate in inducing accumulation of active cyclin E/Cdk2 and E2F. *Nature*, *387*(6631), 422–426. https://doi.org/10.1038/387422a0
26. Lin, C. Y., Lovén, J., Rahl, P. B., Paranal, R. M., Burge, C. B., Bradner, J. E., Lee, T. I., & Young, R. A. (2012). Transcriptional amplification in tumor cells with elevated c-Myc. *Cell*, *151*(1), 56–67. PubMed. https://doi.org/10.1016/j.cell.2012.08.026
27. Madden, S. K., de Araujo, A. D., Gerhardt, M., Fairlie, D. P., & Mason, J. M. (2021). Taking the Myc out of cancer: Toward therapeutic strategies to directly inhibit c-Myc. *Molecular Cancer*, *20*(1), 3. https://doi.org/10.1186/s12943-020-01291-6
28. Mai, S., & Jalava, A. (1994). c-Myc binds to 5' flanking sequence motifs of the dihydrofolate reductase gene in cellular extracts: Role in proliferation. *Nucleic Acids Research*, *22*(12), 2264–2273. PubMed. https://doi.org/10.1093/nar/22.12.2264
29. Marinkovic, D., & Marinkovic, T. (2021). The new role for an old guy: MYC as an immunoplayer. *Journal of Cellular Physiology*, *236*(5), 3234–3243. https://doi.org/10.1002/jcp.30123
30. Miltenberger, R. J., Sukow, K. A., & Farnham, P. J. (1995). An E-box-mediated increase in cad transcription at the G1/S-phase boundary is suppressed by inhibitory c-Myc mutants. *Molecular and Cellular Biology*, *15*(5), 2527–2535. PubMed. https://doi.org/10.1128/MCB.15.5.2527
31. Orian, A., van Steensel, B., Delrow, J., Bussemaker, H. J., Li, L., Sawado, T., Williams, E., Loo, L. W. M., Cowley, S. M., Yost, C., Pierce, S., Edgar, B. A., Parkhurst, S. M., & Eisenman, R. N. (2003). Genomic binding by the Drosophila Myc, Max, Mad/Mnt transcription factor network. *Genes & Development*, *17*(9), 1101–1114. PubMed. https://doi.org/10.1101/gad.1066903
32. Oster, S. K., Ho, C. S. W., Soucie, E. L., & Penn, L. Z. (2002). The myc Oncogene: MarvelouslY Complex. In *Advances in Cancer Research* (Vol. 84, pp. 81–154). Academic Press. https://doi.org/10.1016/S0065-230X(02)84004-0
33. Pagliarini, R., Shao, W., & Sellers, W. R. (2015). Oncogene addiction: Pathways of therapeutic response, resistance, and road maps toward a cure. *EMBO Reports*, *16*(3), 280–296. PubMed. https://doi.org/10.15252/embr.201439949
34. Pérez-Roger, I., Solomon, D. L., Sewing, A., & Land, H. (1997). Myc activation of cyclin E/Cdk2 kinase involves induction of cyclin E gene transcription and inhibition of p27Kip1 binding to newly formed complexes. *Oncogene*, *14*(20), 2373–2381. https://doi.org/10.1038/sj.onc.1201197
35. Philipp, A., Schneider, A., Väsrik, I., Finke, K., Xiong, Y., Beach, D., Alitalo, K., & Eilers, M. (1994). Repression of cyclin D1: A novel function of MYC. *Molecular and Cellular Biology*, *14*(6), 4032–4043. PubMed. https://doi.org/10.1128/mcb.14.6.4032-4043.1994
36. Posternak, V., & Cole, M. D. (2016). Strategically targeting MYC in cancer. *F1000Research*, *5*, F1000 Faculty Rev-408. PubMed. https://doi.org/10.12688/f1000research.7879.1
37. Rosenwald, I. B., Rhoads, D. B., Callanan, L. D., Isselbacher, K. J., & Schmidt, E. V. (1993). Increased expression of eukaryotic translation initiation factors eIF-4E and eIF-2 alpha in response to growth induction by c-myc. *Proceedings of the National Academy of Sciences of the United States of America*, *90*(13), 6175–6178. PubMed. https://doi.org/10.1073/pnas.90.13.6175
38. RYAN, K. M., & BIRNIE, G. D. (1996). Myc oncogenes: The enigmatic family. *Biochemical Journal*, *314*(3), 713–721. https://doi.org/10.1042/bj3140713
39. Sabò, A., Kress, T. R., Pelizzola, M., de Pretis, S., Gorski, M. M., Tesi, A., Morelli, M. J., Bora, P., Doni, M., Verrecchia, A., Tonelli, C., Fagà, G., Bianchi, V., Ronchi, A., Low, D., Müller, H., Guccione, E., Campaner, S., & Amati, B. (2014). Selective transcriptional regulation by Myc in cellular growth control and lymphomagenesis. *Nature*, *511*(7510), 488–492. PubMed. https://doi.org/10.1038/nature13537
40. Sansom, O. J., Meniel, V. S., Muncan, V., Phesse, T. J., Wilkins, J. A., Reed, K. R., Vass, J. K., Athineos, D., Clevers, H., & Clarke, A. R. (2007). Myc deletion rescues Apc deficiency in the small intestine. *Nature*, *446*(7136), 676–679. https://doi.org/10.1038/nature05674
41. Shim, H., Dolde, C., Lewis, B. C., Wu, C. S., Dang, G., Jungmann, R. A., Dalla-Favera, R., & Dang, C. V. (1997). C-Myc transactivation of LDH-A: implications for tumor metabolism and growth. *Proceedings of the National Academy of Sciences of the United States of America*, *94*(13), 6658–6663. PubMed. https://doi.org/10.1073/pnas.94.13.6658
42. Sorolla, A., Wang, E., Golden, E., Duffy, C., Henriques, S. T., Redfern, A. D., & Blancafort, P. (2020). Precision medicine by designer interference peptides: Applications in oncology and molecular therapeutics. *Oncogene*, *39*(6), 1167–1184. PubMed. https://doi.org/10.1038/s41388-019-1056-3
43. Soucek, L., Whitfield, J. R., Sodir, N. M., Massó-Vallés, D., Serrano, E., Karnezis, A. N., Swigart, L. B., & Evan, G. I. (2013). Inhibition of Myc family proteins eradicates KRas-driven lung cancer in mice. *Genes & Development*, *27*(5), 504–513. PubMed. https://doi.org/10.1101/gad.205542.112
44. Tavtigian, S. V., Zabludoff, S. D., & Wold, B. J. (1994). Cloning of mid-G1 serum response genes and identification of a subset regulated by conditional myc expression. *Molecular Biology of the Cell*, *5*(3), 375–388. PubMed. https://doi.org/10.1091/mbc.5.3.375

45. Tikhonenko, A. T., Black, D. J., & Linial, M. L. (1996). Viral Myc Oncoproteins in Infected Fibroblasts Down-modulate Thrombospondin-1, a Possible Tumor Suppressor Gene *. *Journal of Biological Chemistry*, *271*(48), 30741–30747. https://doi.org/10.1074/jbc.271.48.30741
46. Versteeg, R., Noordermeer, I. A., Krüse-Wolters, M., Ruiter, D. J., & Schrier, P. I. (1988). C-myc down-regulates class I HLA expression in human melanomas. *The EMBO Journal*, *7*(4), 1023–1029. PubMed.
47. von Eyss, B., & Eilers, M. (2011). Addicted to Myc—But why? *Genes & Development*, *25*(9), 895–897. PubMed. https://doi.org/10.1101/gad.2053311
48. Walz, S., Lorenzin, F., Morton, J., Wiese, K. E., von Eyss, B., Herold, S., Rycak, L., Dumay-Odelot, H., Karim, S., Bartkuhn, M., Roels, F., Wüstefeld, T., Fischer, M., Teichmann, M., Zender, L., Wei, C.-L., Sansom, O., Wolf, E., & Eilers, M. (2014). Activation and repression by oncogenic MYC shape tumour-specific gene expression profiles. *Nature*, *511*(7510), 483–487. PubMed. https://doi.org/10.1038/nature13473
49. Whitfield, J. R., Beaulieu, M.-E., & Soucek, L. (2017). Strategies to Inhibit Myc and Their Clinical Applicability. *Frontiers in Cell and Developmental Biology*, *5*. https://www.frontiersin.org/article/10.3389/fcell.2017.00010
50. Yang, B. S., Geddes, T. J., Pogulis, R. J., de Crombrugghe, B., & Freytag, S. O. (1991). Transcriptional suppression of cellular gene expression by c-Myc. *Molecular and Cellular Biology*, *11*(4), 2291–2295. PubMed. https://doi.org/10.1128/mcb.11.4.2291-2295.1991
51. Zeid, R., Lawlor, M. A., Poon, E., Reyes, J. M., Fulciniti, M., Lopez, M. A., Scott, T. G., Nabet, B., Erb, M. A., Winter, G. E., Jacobson, Z., Polaski, D. R., Karlin, K. L., Hirsch, R. A., Munshi, N. P., Westbrook, T. F., Chesler, L., Lin, C. Y., & Bradner, J. E. (2018). Enhancer invasion shapes MYCN-dependent transcriptional amplification in neuroblastoma. *Nature Genetics*, *50*(4), 515–523. https://doi.org/10.1038/s41588-018-0044-9
52. Zindy, F., Eischen, C. M., Randle, D. H., Kamijo, T., Cleveland, J. L., Sherr, C. J., & Roussel, M. F. (1998). Myc signaling via the ARF tumor suppressor regulates p53-dependent apoptosis and immortalization. *Genes & Development*, *12*(15), 2424–2433. PubMed. https://doi.org/10.1101/gad.12.15.2424