

Mechanism of MYC Oncogene in Tumor Cell Proliferation

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Abstract

MYC proto-oncogene (MYC) is a well-known oncogene that can act as a transcription factor. Its abnormal activation can be observed in nearly all types of human malignant tumors. Inside tumor cells, MYC controls multiple biological events including cell cycle progression, DNA replication, glycolysis and glutamine metabolism. By regulating these processes, it pushes tumor cells to divide continuously and reshapes cellular metabolism, making it a viable target for cancer therapy. This paper first introduces MYC's protein structure and core biological roles, then explores its mechanisms driving tumor formation and progression. Previous studies results have identified two main ways for MYC to drive tumor proliferation. First, MYC binds MYC-associated factor X (MAX) to form protein dimers, then regulates target genes to speed up the shift from G1 to S phase and DNA replication. In this way, tumor cells break the growth limits that normal cells follow. Second, MYC rewrites glucose and glutamine metabolism to supply enough energy and raw materials for cell division. Scientists have come up with several ways to block MYC's activity that cause cancer. These include disrupting the MYC-MAX binding, lowering MYC levels, speeding up MYC protein degradation, and interfering with glycolysis and glutamine metabolism controlled by MYC. Recent studies also indicate that MYC can alter the nutrient composition inside tumor microenvironment, which provides new research direction for combining MYC inhibitors with immunotherapy. MYC links uncontrolled tumor growth and metabolic changes in tumors, so therapies targeting this gene shows great clinical potential. However, most relevant research only stays at cell and animal preclinical stages. Future research needs to focus on improving drug selectivity and safety, exploring how MYC works differently in various tissue cells, and advancing lab discoveries into clinical treatments.

Key words

MYC oncogene; cell cycle; metabolic reprogramming; tumor proliferation.

1. Introduction

Cancer has become one of the most serious public health challenges in the world. Malignant tumors are distinguished by uncontrolled, continuous cell division. The development of tumors involve the mutation and abnormal activation of genes and signal pathways. MYC oncogene occupies an essential position. The protein encoded by the MYC gene acts as a transcription factor, controlling vital cellular behaviors including cell expansion, cell cycle switching, metabolic processes, cell differentiation and apoptotic death. Normal tissues tightly limit MYC expression. The protein is only appears in a short period after cells receive growth signals. But most tumor cells have abnormally high MYC activity. Three primary mechanisms, gene amplification, chromosomal translocation, and dysregulated upstream signaling, trigger abnormal MYC activity. Persistent MYC activation drives constant tumor cell proliferation and speeds up disease progression [1].

MYC carries out most of its biological functions by forming heterodimers with MAX. This MYC-MAX complex recognizes specific DNA sequences named E-boxes, thereby activating or repressing the transcription of downstream target genes. Through adjusting these genes, MYC can change cell cycle speed, DNA replication efficiency, ribosome synthesis and protein translation.

These processes are particularly critical for tumor cells, as rapidly dividing cells need constant energy supply and raw materials for cell structure construction. Apart from regulating cell cycle progression, MYC also reshapes tumor cell metabolism. It can raise the absorption speed of glucose, enhance glycolysis, promote glutamine decomposition and stimulate nucleotide synthesis. These metabolic changes offer sufficient energy and biomolecular precursors for tumor cell growth and division. MYC links tumor cell proliferation and metabolic transformation together closely [2]. Due to its core role in tumor development, many researchers regard MYC as an ideal target for new anti-tumor drugs.

However it is difficult to design small-molecule drugs that directly inhibit MYC. As a transcription factor, MYC has no obvious enzyme active region and its protein surface lacks stable pockets for small molecules to bind. Thus, researchers have developed various indi-

rect intervention plans such as preventing MYC-MAX binding, lowering MYC expression, accelerating MYC protein degradation, or blocking signal pathways controlled by MYC [3]. A series of preclinical experiments have proved that these strategies can effectively slow down tumor growth. But all MYC-targeted treatment methods are still in the early research stage. Later work needs to solve problems including weak drug selectivity, serious toxic side effects, and screening patient groups that are most likely to respond to MYC inhibition treatment.

Therefore, this paper will review MYC protein structure and its basic biological functions, analyzes how upstream and downstream regulatory networks of MYC affect tumor cell division.

2. Structure and Functions of MYC

MYC is a transcription factor that controls various cell activities, covering cell growth, proliferation, substance metabolism, differentiation and apoptosis. Its functional activity is controlled by a complicated regulatory network formed by intracellular and extracellular signals together decides MYC activity. Under physiological conditions, MYC expression only rises briefly after cells receive growth stimulation. However in tumor cells, MYC can stay active for a long time, leading to continuous activation of growth promoting genes and accelerating tumor formation [1].

2.1 Structure of MYC and the MYC-MAX Complex

The MYC protein consists of about 439 amino acid residues, and its sequence can be divided into two functional domains. The N-terminal region contains transcriptional activation domain and several highly conserved fragments called MYC boxes. These MYC boxes help MYC connect with other regulatory proteins and control MYC protein stability. For example, the MYC-box II (MBII) fragment can recruit transcription cofactors, which activate downstream genes including cyclin D1 (CCND1) and lactate dehydrogenase A (LDHA) [1]. Therefore, the N-terminal domain plays a dual role in controlling MYC transcriptional activity and

protein stability.

The C-terminal domain contains a basic helix-loop-helix leucine zipper (bHLH-LZ) structure. This structure makes MYC able to interact with MAX protein. Single MYC protein cannot bind DNA efficiently, so MYC usually forms heterodimers with MAX first and the whole complex recognizes E-box sequences on target gene DNA [4].

When MYC-MAX heterodimers attach to E-box sites near target genes, they can recruit other proteins responsible for chromatin modification and transcription regulation. These auxiliary proteins loosen compact DNA structure, allowing transcriptional machinery to combine with gene promoters and increase the expression level of MYC target genes. Most of these target genes participate in cell growth, protein synthesis and substance metabolism.

MAX protein can also bind other proteins in the MYC regulatory network, such as MAX-dimerization protein (MXD) and MAX-binding protein, transcription repressor (MNT). The heterodimers formed by MAX and MXD/MNT usually suppress gene transcription, which counteracts the growth-promoting effect of MYC-MAX complex. In normal cells, the balance between MYC-MAX activation and MAX-MXD/MNT inhibition maintains steady cell growth speed. Tumor cells over-produce MYC protein, breaking this balance and causing excessive expression of growth related genes [4].

2.2 Upstream Regulation of MYC

Cells modulate MYC level through multiple biological steps, including gene transcription, mRNA translation, post-translation protein modification and protein degradation. Under normal conditions, extracellular growth factors activate intracellular signal pathways to raise MYC expression. So cells can adjust growth state according to external nutrient and signal conditions. When growth signals disappear, MYC content will drop back to low levels.

Numerous tumor related signal pathways can change MYC activity. The rat sarcoma viral oncogene homolog (RAS)/mitogen-activated protein kinase (MAPK) pathway can promote MYC gene transcription and slow down MYC protein degradation. The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway

boosts cellular protein synthesis, indirectly increasing MYC production and extending its survival time. Besides, WNT/ β -catenin signal can also activate MYC transcription in specific cell types. All these pathways transmit extracellular growth signals into the cell and regulate MYC expression and activity [1].

The MYC protein is unstable and can be degraded under normal physiological conditions. Post-translational modification determines whether MYC stays active or is marked for degradation by the ubiquitin-proteasome system. This flexible regulatory mechanism enables normal cells to adjust MYC activity in response to surrounding environment. However, gene mutation and abnormal signal transmission in tumor cells make MYC much more stable and the protein remains active far longer than normal conditions [5].

Genetic alterations can also break the steady expression of MYC in tumor tissues. Gene amplification creates multiple copies of MYC gene, which greatly increases intracellular MYC protein level. Statistics show nearly 30% of human breast cancer samples carry MYC amplification, and the accumulation of MYC protein continuously drives tumor cells to divide rapidly [1]. In some lymphoma types, chromosome translocation places MYC gene near highly active strong promoters. Changes in enhancer sequences and other transcriptional regulators can also upregulate MYC expression without changing its coding sequences. Overall, three kinds of mechanisms, gene mutation and amplification, abnormal upstream signal pathways, and weakened protein degradation, can lead to sustained MYC activation in tumors [1,2].

2.3 Downstream Targets and Functions of MYC

After forming heterodimers with MAX, MYC can regulate hundreds of different target genes. The exact gene set controlled by MYC varies based on cell type, MYC protein concentration and cell physiological state. That means MYC does not produce same regulatory effects in all tissues. However, most downstream genes controlled by MYC are related to cell growth and proliferation [4].

One core function of MYC is adjusting cell cycle progress. MYC increases the expression of genes that

drive cells from G1 phase to S phase where DNA replicates. Meanwhile, MYC weakens the inhibitory effect of cell cycle suppressor proteins. These two changes make it easier for cells to start DNA duplication and continuous division. For normal tissues, this function supports embryonic development and wound repair. However in tumors, unrestricted MYC activity results in uncontrolled cell proliferation [6].

MYC also accelerates intracellular protein synthesis. It controls genes involved in rRNA transcription, ribosomal protein production, RNA processing and protein translation. By promoting ribosome assembly, MYC helps tumor cells generate more structural proteins, expand cell volume and accelerate division. Thus, MYC connects cell cycle progress with the production of cellular components [4].

MYC also takes part in regulating cellular metabolism. Rapidly dividing cells consume large amounts of energy and raw materials used to synthesize DNA, protein and cell membrane structures. MYC upregulates genes related to glucose intake, glycolysis, glutamine metabolism, mitochondrial respiration and nucleotide synthesis. Increased glucose uptake and glycolysis trigger the Warburg effect, producing carbon intermediates for biosynthesis. Glutamine metabolism provides nitrogen elements needed for nucleotide production. These metabolic changes fully meet the energy and material demands of tumor cell growth [2,7].

MYC also has complex dual regulatory effects on cell survival. Under specific conditions, high MYC activity can initiate cell apoptosis, especially when cells lack enough survival signals. This mechanism acts as self-protection for tissues to clear abnormally proliferating cells. But tumor cells often produce extra gene mutations to block apoptosis pathways. As a result, tumor cells can retain the growth-promoting function of MYC while escaping MYC-induced programmed cell death [1,8].

3. Mechanisms of MYC in Cancer Cell Proliferation

MYC is a key transcription factor that drives unlimited division of tumor cells. For healthy cells, MYC expression only rises temporarily after receiving growth signals, and its activity drops rapidly once cell growth

finishes. In most malignant tumors, gene amplification, chromosome translocation or disordered upstream signal pathways lead to permanent high MYC expression. After combining with MAX to form heterodimers, MYC binds E-box sequences on target genes and regulates cell cycle progress and intracellular metabolic processes at the same time. These two sets of regulatory pathways coordinate with each other, providing enough raw materials and energy for continuous tumor cell division, and this is the core molecular mechanism through which MYC induces malignant proliferation [1].

3.1 Regulation of the Cell Cycle and DNA Replication

3.1.1 Accelerating G1/S phase transition

The most direct way for MYC to speed up tumor cell proliferation is to push static cells out of resting state and enter S phase ahead of schedule. MYC-MAX complex activates transcription of cyclin D, cyclin E and related cyclin-dependent kinase (CDK). These proteins assemble into kinase complexes and phosphorylate retinoblastoma (Rb) protein. After phosphorylation, Rb protein loses its ability to suppress E2F transcription factors, and E2F then activates a batch of genes required for DNA replication [4].

At the same time, MYC combines with MSP-retrovirus integration site 1 protein (MIZ1) to reduce the expression of cell cycle inhibitory proteins p21 and p27. These two proteins can block the activity of cyclin-CDK complexes and stop cells entering S phase. For normal cells, MYC level drops rapidly once external growth factors disappear, so p21 and p27 accumulate to block cell cycle progress. Tumor cells with abnormal MYC always maintain high MYC concentration, which makes G1/S checkpoint lose its monitoring function. Tumor cells can divide repeatedly even without growth factor stimulation [6]. Long-term excessive activation of MYC shortens the whole cell cycle and greatly raises the proliferation rate of tumor cells [1].

3.1.2 Regulation of DNA replication

Complete DNA replication is the prerequisite for one cell to split into two daughter cells, and MYC participates in every stage of genome duplication. MYC increases the expression of cell division cycle 6 (CDC6),

chromatin licensing and DNA replication factor 1 (CDT1), proliferating cell nuclear antigen (PCNA) and other components that form pre-replication complexes. These proteins assemble on DNA replication starting points during G1 phase to prepare for DNA synthesis in S phase [4]. Apart from transcriptional regulation, MYC protein gathers near DNA replication forks and activates more silent replication origins, accelerating overall DNA synthesis speed.

Excessively fast DNA replication leads to replication stress and double-strand fracture of DNA. Under normal conditions, cells will activate DNA repair pathways and stop proliferation after DNA damage happens. But MYC simultaneously upregulates multiple DNA damage repair genes, so tumor cells can tolerate unstable genomes without cell cycle arrest or apoptosis [1]. Besides, MYC raises telomerase reverse transcriptase (TERT) expression to maintain telomere length, helping tumor cells avoid replicative aging and realize long-term unlimited proliferation.

3.2 Metabolic Reprogramming in MYC-Driven Cancer

Continuous cell cycle progress and DNA replication consume large amounts of glucose, amino acids, nucleotides and energy substances. Through transcriptional regulation, MYC changes cellular metabolism, which researchers define as metabolic reprogramming. These metabolic transformations fulfill the material needs of fast tumor cell growth and are essential for malignant proliferation [2].

3.2.1 Rewiring central carbon and nitrogen metabolism

MYC changes glucose and glutamine metabolism to provide carbon and nitrogen sources needed for tumor growth. In terms of glucose metabolism, MYC increases glucose transporter 1 (GLUT1), glucose transporter 3 (GLUT3) and key glycolytic enzymes including HK2, PKM2 and LDHA.

For nitrogen supply, MYC increases alanine-serine-cysteine transporter 2 (ASCT2) and glutaminase 1 (GLS1), which increases the uptake and breakdown of glutamine in tumor cells. Glutamate produced from glutamine decomposition enters tricarboxylic acid cycle

to generate carbon skeletons. Normal cells can adjust glutamine intake based on external nutrient levels. In contrast, tumor cells with high MYC rely heavily on glutamine. As a result, insufficient glutamine supply inhibits cell proliferation, and this phenomenon is defined as glutamine addiction [4].

3.2.2 Macromolecular biosynthesis and crosstalk with cell cycle

To support fast cell division, MYC activates ribosome assembly, protein synthesis and nucleotide production synchronously. It increases the transcription of rRNA and ribosomal protein genes to raise cellular protein synthesis efficiency. Meanwhile, MYC upregulates key enzymes involved in de novo nucleotide synthesis, such as dihydrofolate reductase (DHFR) and thymidylate synthase (TYMS), which continuously provide raw materials for DNA replication [7]. Glucose provides carbon skeletons and glutamine offers nitrogen elements. Blocking any of these metabolic pathways can remarkably inhibit the proliferation of tumor cells [2].

MYC connects metabolic transformation and cell cycle progress to form a positive feedback loop. Fast cell division consumes more nutrients, which further activates MYC-controlled metabolic genes. Metabolites produced by enhanced metabolism stabilize MYC protein through mTOR pathway and speed up cell cycle transition. Unlike normal cells that lower MYC expression after finishing growth, tumor cells keep this feedback loop operating all the time, resulting in out-of-control cell growth [6]. In addition, tumor cells absorb large quantities of glucose and glutamine, which depletes nutrients inside tumor microenvironment and restrains anti-tumor immune cell activity. This creates a suitable living environment for tumor cells to escape immune elimination [9,10].

4. Conclusion

In short, MYC relies on two interrelated molecular regulatory mechanisms to push tumor cells to divide endlessly. First, MYC breaks the restriction function of G1/S checkpoint and accelerates DNA duplication, removing the growth limits that control normal cell division. Second, MYC reshapes the whole metabolic mode of tumor cells. It rearranges glucose and glutamine met-

abolic pathways to produce enough carbon, nitrogen and energy substances required for large biomolecule synthesis. Cell cycle acceleration and enhanced metabolism promote each other, forming a stable positive feedback cycle unique to MYC-driven tumors.

MYC is widely recognized as a promising target for anti-tumor drug development. However, MYC protein has no enzyme active pocket, so researchers cannot easily design small-molecule drugs to directly inhibit its activity. Most existing treatment ideas take indirect intervention methods: stopping MYC from binding MAX protein, reducing MYC stability inside cells, or suppressing glycolysis and glutamine metabolism regulated by MYC. Apart from that, MYC changes nutrient composition inside tumor microenvironment to help tumor cells escape immune clearance. This research finding opens new research directions for combining MYC inhibitors with tumor immunotherapy.

Up to now, nearly all treatment plans targeting MYC are still limited to preclinical research. Weak drug selectivity and severe systemic toxic side effects become two major obstacles restricting clinical transformation. More follow-up research is needed to explore how MYC regulates downstream genes in different tissue cells, screen low-toxicity specific inhibitors, and identify patient subgroups sensitive to MYC inhibition treatment. Fully exploring the regulatory mechanism of MYC in cell cycle and metabolism can provide sufficient theoretical support for developing new precise treatment schemes for tumors with MYC overexpression.

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