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The Paradox of c-Myc Proto-oncogene and its Diverse Functions

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Abstract

c-Myc is one of the most extensively studied genes in contemporary biomedical research. A number of studies have suggested that in response to the external and internal signals, c-Myc interacts with other small protein such as Max, Mad etc. and modulates the expression of several target genes. Intriguingly, it has been estimated that c-Myc regulate ~10-15% of the global transcriptome, and therefore, influence the major cellular functions like cell cycle, cell adhesion, cellular apoptosis, metabolism, protein biosynthesis, etc. Functioning as a regulator of global gene expression, aberrant expression of c-Myc has been implicated as the major cause of several human diseases including cancer. Therefore, understanding the diverse functions of c-Myc is not only essential to answer some key questions related to developmental biology but also to develop novel therapeutic strategies against some fatal human diseases.

Keywords: c-Myc; Transactivation; Cell cycle; Tumorigenesis

Introduction

The proto-oncogene Myc family is one of the most profoundly studied groups of genes in contemporary biology. Associated with the characteristic of neoplastic potential, this group includes multiple members such as c-Myc, L-Myc and N-Myc [1]. Among these, in view of the possible involvement of c-Myc in major cellular functioning as well as in tumorigenesis; global efforts have been made to understand the enigma of the functioning of c-Myc in development and cancer biology with the emphasis on developing novel therapeutic approaches. The present article attempts to provide a brief overview of the various aspects of c-Myc in cellular functioning and development.

c-myc was discovered as the cellular homolog of the retroviral *v-myc* oncogene [2]. Comprising with three exons, human *c-myc* gene is located on chromosome 8 [3]. Depending upon the selection of translation start site, c-Myc transcripts may translate either shorter polypeptides of ~62kDa (major product) or longer polypeptides with ~66kDa in low quantity [4]. c-Myc protein consists of two important domains: a basic Helix-loop-Helix Leucine Zipper (bHLH-LZ) at its C-terminal and a potential transactivation domain at N-terminal end. With the help of its bHLH-LZ domain, c-Myc heterodimerises with another small bHLH-LZ protein called Max and bind to the E-box sequences (5'-CACGTG-3') and transactivates the target genes [5]. Intriguingly, in spite of its notable role in transactivation, c-Myc along with its interacting partners may also function as repressor of gene expression [6].

Temporal regulation of c-Myc protein plays important role in regulating various aspects of cellular activities. It has been demonstrated that multiple Ras effector pathways responses to the mitogenic signals and regulates the stability of c-Myc through two conserved pathways: the Raf-MEK-ERK kinase cascade and the phosphatidylinositol-3-OH kinase (PI3K)-Akt pathway, which inhibits the function of glycogen synthase kinase-3β (GSK-3β) [7]. Interestingly, ERK kinase phosphorylates Ser 62 of c-Myc to prevent it from degradation; on the other hand, GSK-3β kinase phosphorylates at Thr 58 to promote ubiquitin-proteasome mediated degradation of c-Myc. Early in the G1 phase of cell cycle, Ras activates ERK and inhibits GSK-3β; however, in the later phase of G1, reduced functioning of Ras-PI3K-Akt pathway leads to activation GSK-3β which is essential for the c-Myc turnover. Moreover, GSK-3β mediated ubiquitination of c-Myc is further regulated/ enhanced by the posttranslational modification of several players like PP2A phosphatases, PIN1 prolyl isomerase, Fbw7 etc. [8]. It appears that the temporal accumulation of c-Myc is a vital factor for regulation of global gene expression; however, comprehensive analysis is needed to generate further insights regarding regulation of c-Myc.

c-Myc in Global Transcriptional Regulation

Despite being an oncogene and its implication in several aspects of cellular functioning, recent findings suggested indispensable role(s) of c-Myc as global regulator of gene expression. Moreover, advances in high throughput based technologies such as microarray gene profiling, Serial Analysis of Gene Expression (SAGE), Chromatin Immunoprecipitation (ChIP) etc. have facilitated in identification of target genes of c-Myc. It has been estimated that c-Myc could regulate the expression of ~10-15% of all the genes in the genome from *Drosophila* to human [9,10]. It has been suggested that c-Myc mediated activation of gene expression is generally achieved through numerous mechanisms which include recruitment of histone acetylases, chromatin modulating proteins, DNA methyltransferases and several other factors [6]. Additionally, binding of Myc/Max heterodimer to the E-box consensus sequences facilitate recruitment of multiple co-activator complexes and transcription machinery to initiate transactivation network. Some of the major targets of c-Myc include the genes involved in protein biosynthesis, metabolism, cell cycle entry etc.

In addition to the c-Myc mediated transactivation of genes; the role of c-Myc in trans-repression is also essential to maintain the cellular homeostasis. Interaction of Max with Mad protein family could

modulate the transactivation ability of c-Myc protein. Mad protein family including Mad 1, 2, 3, 4 and Mix 1 binds to Max and compete with Myc/Max heterodimers to bind with E-box consensus sequence of the target genes. Following the Max/Mad binding, several chromatin modifying co-repressor complexes such as Sin3, N-CoR and histone deacetylase 1 and 2 are recruited to the promoters of the target genes. Consequently, deacetylation of histone tails results in closed chromatin conformation in order to inhibit transcriptional activation [11]. Above phenomenon is well supported with the fact of tight regulation of Myc and Mad family protein unlike ubiquitous expression of Max. Interestingly, ChIP analysis has revealed that Myc/Max binding is switched to Max/Mad binding during the process of cellular terminal differentiation [12]. Furthermore, c-Myc also represses certain genes through inhibiting the transcriptional activator Miz 1. The binding of c-Myc to Miz 1 repress target genes which are otherwise transactivated by Miz1 [13]. Taken together, c-Myc play a key role in maintenance of cellular homeostasis, i.e. high level of c-Myc is essential for cell growth, cellular proliferation and metabolism, and low level of c-Myc is also necessary to achieve terminal differentiation in multiple lineages. Therefore, functional role of c-Myc is tightly regulated and emerged as a critical factor for cellular activities and major developmental decisions.

c-Myc in Cell Cycle Regulation, Metabolism and Cellular Apoptosis

Although some of the functional variations have been attributed to cell type specificity, studies in mammalian and *Drosophila* systems revealed that c-Myc influences various classes of genes directly or indirectly, which are involved in cell cycle regulation, protein biosynthesis, metabolism and cellular apoptosis [6,14]. Moreover, c-Myc also has the ability to promote cell proliferation by attenuating the progression of cell cycle through inhibition of Cyclin Dependent Kinases (CDK) inhibitors such as p21 and p151NK4A, as well as genes which are responsible for cell adhesion and cell-cell communication [15-17]. In addition, active roles of c-Myc in ribosome biogenesis and protein synthesis have also been established. c-Myc, in order to compensate the increase demand of protein synthesis due to increase cell proliferation, consistently regulates the process of protein biosynthesis at various stages. It has been demonstrated that a sub-group of c-Myc target genes encodes for tRNA and rRNA, which are transcribed by RNA polymerase III and II [18]. Therefore, c-Myc mediated regulation of cell cycle, cellular differentiation and protein biosynthesis are some very crucial aspect of development and cellular functioning.

In *Drosophila* to vertebrates, c-Myc regulates many of the important pathways which are involved in cellular metabolism. Earlier studies have demonstrated that several of the c-Myc target genes encode for key enzymes such as glucose transporter, hexokinase II, lactate dehydrogenase A, enolase A etc., which are involved in glucose metabolism [19]. Above findings suggest a role of c-Myc in modulation of glucose uptake and glycolysis [19]. In addition, involvement of c-Myc in energy metabolism has been postulated by some earlier reports in which a sub group of c-Myc targets were found to be involved in mitochondrial biogenesis and function [20]. It was proposed that c-Myc promotes oxidative phosphorylation and glycolysis through the coordinated transcriptional network [20]. A subgroup of c-Myc target genes include enzymes like Ornithine Decarboxylase (ODC), carbamoyl phosphate synthase, aspartate transcarbamylase etc. as well as endonucleases which are involved in DNA biosynthesis and repair [21]. In view of above, an active role of c-Myc was proposed in DNA metabolism and modulation of G1/S transition during cell cycle entry [21].

Role of c-Myc in cellular apoptosis has been discovered recently. It has been demonstrated in myeloid progenitor cell line and fibroblast that c-Myc overexpression during serum or nutrient deprivation results in p53 dependent extensive cell death [22]. c-Myc was also found to induced cellular apoptosis through transcriptional induction of Egr1 but independent to p53 [23]. Therefore, further studies are required in order to establish the precise role of c-Myc in cellular apoptosis.

c-Myc in Tumorigenesis

In view of the broad operative spectrum of c-Myc, any abnormality in the regulation may lead to devastating impact on cell proliferation, cellular activities and development. Functioning as a proto-oncogene, c-Myc is one of the most frequently activated oncogenes involved in ~20% of the total human cancers. Expression of c-Myc has been found to be amplified in several human cancer types including lung carcinoma, breast carcinoma, prostate cancer, Burkiitt's lymphomas and very rare cases of colon carcinoma [24]. Some of the factors leading to abrupt activation of c-Myc include abnormal regulation of c-Myc by compromised signal transduction, various mutations that increase the half-life of c-Myc protein as well as abnormal translocation of *c-Myc* gene near to some highly transcribed regions [25]. Though single oncogenic mutation in c-Myc may not be enough to induce tumorigenesis and may requires some additional accessory mutations. However, in view of the crucial role of c-Myc in majority of human cancers, it is important to investigate various aspects of c-Myc in cellular function and development. This may potentially help in designing novel therapeutic approaches against cancer.

c-Myc in Cell Reprogramming

Interestingly, c-Myc has also been demonstrated as a potent inducer of the cell reprogramming. c-Myc, in combination with other embryonic transcription factors such as Oct-4, Sox-2 and Klf-4, revert terminally differentiated somatic fibroblasts in induced pluripotent stem cells (iPSCs) [26]. Providing the insight role of c-Myc in cell reprogramming, it was found that ectopic expression of c-Myc promotes Embryonic Stem (ES) cell-like transcription pattern when expressed individually in fibroblasts [27]. Moreover, c-Myc inhibits differentiation of mouse ES cells into the primitive endoderm lineage, through the repression of Gata-6 expression, a master regulator of primitive endoderm differentiation [28]. It appears that c-Myc mediates cellular reprogramming and establishment of pluripotent stem cells by activating several pluripotent genes along with inhibiting those genes which mediate differentiation of ES cells. In addition, inherent properties of c-Myc in cell proliferation, cellular metabolism and its ability to modulate chromatin structures for easy accessibility for other reprogramming factors further helps the ES cells to maintain its pluripotency. However, in spite of its ability to induced iPSCs, the tumorigenic property of c-Myc may increase the risk of tumor formation in transformed cells. Therefore, by minimising the transforming ability and increasing the efficiency of iPSCs induction, several approaches such as replacement of wild type c-Myc with mutant c-Myc or L-Myc and the temporal induction of c-Myc expression has succeeded in reducing its tumorigenic effect [29,30].

Concluding Remarks

As stated earlier, c-Myc has emerged as a master regulator for several distinct genetic programmes as well as a key molecule for cancer biology. Intriguingly, up-regulation of c-Myc promotes cell cycle machinery; on the other hand down-regulation of this protein is essential to achieve terminal differentiation of various cell lineages. Interestingly, a recent finding suggests that targeted upregulation of Myc can mitigates poly(Q) induced neurodegeneration in *Drosophila* [31]. Therefore, understanding the Myc biology is necessary to understand some unanswered questions dealing with developmental biology and also to design novel strategies to combat several devastating human diseases.

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