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Review

Mechanism of transcriptional activation by the Myc oncoproteins

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Abstract

The Myc family proteins are potent oncogenes that can activate and repress a very large number of cellular target genes. The amino terminus of Myc contains a transactivation domain that can recruit a number of nuclear cofactors with diverse activities. Functional studies link transactivation to the ability of Myc to promote normal cell proliferation and for oncogenic transformation. The biochemical mechanism of Myc-mediated transactivation has revealed a wide range of effects on chromatin and basal transcription. This review summarizes recent advances in understanding the function of Myc as a transcriptional activator and the role of this activity in Myc biological activities.

Keywords: Myc; Transcription; Chromatin; Acetyltransferase; Polymerase; Proliferation; Oncogenesis; Cancer; Cofactor

Contents

1. Introduction

The Myc oncoproteins are among the most enigmatic families of transcription factors. Although one or more of the Myc proteins are expressed in all growing cells, a Myc DNA binding complex is not visible using conventional electrophoretic mobility shift assays because the DNA binding activity is too weak. Consequently, transactivation by Myc proteins is inevitably quite wimpy, so these proteins do not stand out as potent transcription factors in transient assays with promoter-reporter fusions. Hence, we might never have known that the Myc proteins exist if they were not shown to be essential for cancer, cell growth, and embryogenesis from classic and compelling genetic experiments in tumor biology and development. What

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is the evidence that Myc functions as a transcription factor and through what mechanism(s) does it regulate transcription? We will address these and other related questions in this review.

1.1. Myc is established as a transcription factor

Since v-Myc was a nuclear protein [1], several groups began to investigate whether Myc was a transcription factor by measuring the transcriptional response of individual genes to Myc expression [2,3]. Around the same time, the Myc C-terminus was found to contain a leucine zipper (LZ) and a helix-loop-helix (HLH) motif, both of which were previously found in sequence specific DNA-binding proteins [4,5]. Myc became firmly established as a transcription factor with the discovery of Max [6]. Max can homodimerize and bind to DNA directly, whereas Myc cannot homodimerize and must form a heterodimer with Max in order to bind to DNA [6]. Max is a small, ubiquitously expressed protein that can bind to a whole collection of B-HLH-LZ proteins [7].

As with other transcription factors, Myc proteins are modular. The Myc N-terminus was found to function as a transactivation domain by the demonstration that a fusion of the Myc N-terminus and the Gal4 DNA-binding domain was a potent transactivator [8]. Following the identification of Max, Myc-Max heterodimers were demonstrated to have relatively weak transactivation activity [9]. Subsequent analysis of a panel of endogenous target genes revealed comparable induction of some promoters, establishing Myc as a relatively weak transcription factor both endogenously and in transient assays [10]. A plethora of microarray studies published recently have concurred that Myc activates the majority of target genes by two-fold [11]. Although Myc is now firmly ensconced as a transcription factor, it is certainly feeble compared to other transcription factors.

It remains a distinct possibility that Myc has transcription independent activity. Mapping of the transactivation domain revealed a discordance between biologically significant domains and those required for transactivation [8]. In addition, it is a mystery why some tumors express Myc at 100-fold over the endogenous level, when a much lower quantity of Myc protein would achieve the same transactivation.

1.2. The Myc transactivation domain has functionally distinct regions

The transactivation domain of Myc can be subdivided into a series of smaller evolutionarily-conserved domains (Fig. 1). Comparing the biological activity of these domains with their transactivation potential has given valuable insight into Myc function. The first comprehensive mapping of the Myc transactivation domain screened for domains necessary for Myc induced cell transformation [12]. Two conserved regions called Myc Homology Boxes I and II (MBI and MBII) were found to be necessary for Myc to co-operate with H-Ras to induce transformation of primary rat embryo fibroblasts. These domains were also found to be necessary for Myc to induce apoptosis and block differentiation [13,14]. Recently two further Myc Homology domains have been characterized. MBIII is necessary for cell transformation and, curiously, deleting MBIII actually potentiates Myc-induced apoptosis [15]. MBIV is also necessary for full Myc transforming activity and apoptosis, and deleting MBIV actually potentiates Myc-induced G2 arrest [16]. MBIII and MBIV mutants have defects in the activation and repression of a variable set of Myc target genes. The Myc transactivation domain was also shown to be necessary for Myc-induced proliferation [17], but further mapping of the domains required for proliferation has been surprisingly difficult. MBI, MBIII and MBIV are not required for cell proliferation [15,16,18]. Although Myc with a MBII deletion is completely defective for transformation, apoptosis, differentiation, and G2 arrest [12–14,16] it is only partially defective for induction of cell proliferation [10,19]. Furthermore, Myc mutants where deletion of MBII is combined with deletions of MBI, MBIII or MBIV do not weaken the proliferative activity of MBII (Cowling and Cole, unpublished observations).

How does deletion of the Myc homology domains impact on transactivation? Can we understand the function of these domains by measuring the number of genes that they regulate and more specifically, which genes they regulate? Commensurate with MBII being essential for most Myc functions, a deletion of the MBII domain dramatically reduces the transactivation function of Myc [16]. In microarray studies, the number of genes upregulated two-fold or more by MycΔMBII was found to be only 10% of the number upregulated by MycWT. Careful examination of the data, however, reveals that MycΔMBII upregulates most of the same genes as MycWT, but slightly more weakly. MycΔMBII may be able to induce proliferation via the combined activity of the weakly activated Myc target genes, or MycΔMBII may drive proliferation by activation of the very few genes that it does transactivate well.

MycS is a naturally-occurring Myc variant that lacks the N-terminal 100 amino acids of Myc, including MBI but not MBII [20]. MycS was found to be largely defective for transactivation by reporter assay [18] and by microarray analysis (Cowling and Cole, unpublished observations), and yet it activates proliferation equivalently to MycWT. This supports the finding made by analysis of MBII, that only weak transactivation is required for cell proliferation. Although Myc-induced repression is out of the scope of this chapter, it is pertinent that MycS is only partially defective for repression of genes and may predominantly induce proliferation via target gene repression [18].

Early studies showed that deletion of MBI was not necessary for transactivation [8], and this has been confirmed for endogenous target genes in subsequent studies [15,17]. Why MBI is necessary for cell transformation but not transcription remains an unsolved mystery of Myc biology, and contributes to the notion that Myc may have transcription-independent functions. Deletion of MBIII or MBIV reduces Myc-dependent transactivation, although by not nearly as much as deletion of MBII [15,16].

1.3. Myc transactivates by binding to nuclear co-factors

Myc protein drives transcription by recruiting co-factors to target gene promoters. Many Myc co-factors have been