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MYC Transcriptomics

Suresh Peddigari*

Department of Internal Medicine, Hematology and Oncology, University of Cincinnati, USA

MYC is a transcriptional factor and a proto-oncogene that is frequently deregulated in a wide array of cancers. Myc family genes include *MYC, MYCN* and *MYCL1*, which encode nuclear phospho proteins and function as sequence specific transcription factors that regulate large number of genes [1]. All the *MYC* family members have been implicated in a wide variety of human hematological malignancies and solid tumors. Of all the Myc family proteins, the MYC transcription factor is extensively studied and has been defined as a global regulator. The genome wide location analysis and gene expression profiling disclosed that 15% of the genome is regulated by the MYC transcription factor [2,3]. Alterations in MYC expression are induced by multiple mechanisms, including translocations, gene amplification, point mutations, over expression and increased protein stability. The MYC regulated cellular processes include cell growth, proliferation, differentiation, cell cycle progression, cell metabolism and apoptosis. The recent studies demonstrate that MYC is also a master regulator of ribosome biogenesis [4].

Many cancer cells have elevated levels of the MYC transcription factor, and it directly impacts the tumor progression. How does the elevated levels of MYC regulates the transcription of vast number of genes is an interesting question to understand as targeting MYC in MYC dependent tumors appears to be an appealing strategy. Deregulated MYC expression is suggested to induce a transcriptional response network that is different from the response triggered by endogenous level of MYC, which is fully re-strained by feedback loops. Transcriptomic analysis of MYC binding sites can reveal the global regulation of MYC transcription factor. Two recent studies demonstrated that in tumor cells expressing high levels of MYC, the transcription factor accumulates at elevated levels in association with its heterodimer partner, Max at the E-box sequences of core promoter region of the actively transcribed genes and enhances the transcripts levels of the active genes [5,6]. In addition to the core promoter, the MYC also binds to enhancer sequences of active genes. This shows that MYC is not an on-off specifier of specific transcriptional programs, but rather a universal amplifier of gene expression increasing output from all active promoters. The increased transcripts levels were achieved by stimulation of RNA Pol II elongation.

Recent studies have demonstrated MYC as a direct regulator of ribosome biogenesis. Ribosome biogenesis requires the coordinated function of nuclear RNA polymerases I, II and III and MYC has been shown to regulate all three RNA polymerases. The ribosomal proteins, which are transcribed by RNA Pol II are direct transcriptional targets of MYC. Moreover, MYC has been shown to regulate the transcription of 47S rRNA by RNA Pol I and 5S rRNA by Pol III. The direct regulation of MYC on the ribosomal components reveals the link between ribosome biogenesis and cancer progression [4]. This suggests that MYC regulates transcription as well as translation.

MYC's ability to initiate and maintain tumorigenesis may be depended on its regulation of ribosome biogenesis. A modest decrease in these ribosomal protein levels in cancer cells could significantly affect the progression of tumors by two contradicting mechanisms. One study showed that the loss of one allele of RPL24 in *Eμ-Myc* transgenic mice in which the *Eμ* immunoglobulin heavy chain intron transcription enhancer drives the expression of the *Myc* transgene, restores the protein synthesis levels to that of wild type B-cells and suppresses the progression of B-cell lymphoma [7]. In another study, the same rpL24+/- heterozygocity leads to the activation of the tumor suppressor protein p53, by suppressing MDM2, which is the E3-ligase and inhibitor of p53 [8]. This ribosomal haplo-insufficiency leads to impaired ribosome biogenesis and the ribosomal proteins rpL5 and rpL11 along with 5S rRNA as a mutually dependent complex to bind to MDM2 and stabilize p53 [9].

In conclusion, MYC is a global transcription regulator in many cancers and transcriptomic analysis of MYC transcriptional activity as well as understanding MYC's regulation of ribosome biogenesis can provide novel targets to suppress tumor progression.

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***Corresponding author:** Suresh Peddigari, Department of Internal Medicine, Hematology and Oncology, University of Cincinnati, 3125 Eden Ave, Cincinnati, OH 45236, USA, Tel: 513-558-3651; E-mail: peddigsh@ucmail.uc.edu

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