Transcriptional Regulation of the c-Myc Promoter by NFAT1 Involves Negative and Positive NFAT-Responsive Elements

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A number of physiological processes in both normal and cancer cells are regulated by the proto-oncogene c-Myc. Among them, processes such as cell cycle regulation, apoptosis and angiogenesis are also controlled by the nuclear factor of activated T cells (NFAT) family of transcription factors. It is already known that NFAT upregulates c-Myc expression by binding to an element located in the minimal c-Myc promoter. However, the importance of other NFAT sites in the context of the full promoter has not been evaluated. In this work, we demonstrate that the regulation of c-Myc by NFAT1 is more complex than previously conceived. In addition to the proximal site, other six NFAT elements were found in the c-Myc promoter by bioinformatics analysis. An electrophoretic mobility shift assay (EMSA) showed that NFAT1 directly binds to three elements in the c-Myc promoter with different affinities and NFAT1 binding to the distal sites was further confirmed by chromatin immunoprecipitation (ChIP). Promoter deletions and site-directed mutagenesis of NFAT binding sites in luciferase reporter gene assays suggested that in NFAT1-mediated transactivation, some NFAT elements are negative and dominant and others are positive and recessive. Furthermore, we demonstrated that cooperation with nuclear partner proteins such as p300 enhances NFAT1-mediated transactivation of the c-Myc promoter. Collectively, our data suggest that the contribution of NFAT1 to the regulation of c-Myc expression may depend on the balance between binding of NFAT1 to positive and negative NFAT-responsive elements and cooperation with transcriptional cofactors, which may differ according to the cellular context and/or microenvironment.

Keywords: c-Myc, NFAT, Gene expression.

Financial support: FAPERJ, CAPES, CNPq, ICGEB, INCT-Cancer.