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Review Article

C-Myc (Oncogenic) Transcription Factor

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ABSTRACT

In this review, we correlate C-MYC transcription factor with cancer. The C-MYC proto-oncogene is associated with the direct cell proliferation, growth, differentiation and apoptosis. As an oncogene, C-MYC is a high-ranking member. C-MYC protein is a transcription factor that regulates a variety of cellular processes including cell growth and production, cell-cycle progression, transcription, differentiation, apoptosis, and cell motility. Prospective strategies that either inhibit the growth promoting effect of C-MYC or activate its pro-apoptotic function are presently being explored.

Key word: C-MYC transcription factor

INRTODUCTION

Molecular aspects of C-MYC protein a transcription factor that activates expression of a great number of genes through binding on consensus sequences have been studied by several researchers. By modifying the expression of its target genes, C-MYC activation results in numerous biological effects. The first to be discovered was its capability to drive cell proliferation, but it also plays a very important role in regulating cell growth, apoptosis, differentiation and stem cell self-renewal. C-MYC is a very strong proto-oncogene and it is very often found to be up regulated in many types of cancers. The C-MYC gene is to be found on human chromosome 8q24; it was discovered soon after its identification that activated C-MYC oncogene instrumental in the progression of human Burkitt's lymphoma, as a result of a translocation between chromosome 8. The findings that human cancers frequently display altered expression of human C-MYC gene draw attention to the importance of this gene in the cause of human cancers. C-MYC proteins emerged as transcription factors, able to regulate gene expression. Prominent or deregulated expression of C-MYC has been detected in a wide range of cancer. Meanwhile several studies were discovering how Myc functioned as an oncogenic transcription factor Myc was discovered to actually trigger rapid apoptosis (Evan et al., 1992), an endogenous and conserved program of cell suicide. Further, what rapidly became clear was that Myc was the rule, rather than the exception, as other oncogenes such as E1A (Lowe and Ruley, 1993) and E2F-1 (Kowalik et al., 1995). Myc-induced apoptosis requires its DNA binding functions and dimerization with Max (Evan et al., 1992; Amati et al., 1993).The term genomic instability refers to genetic changes that affect the normal organization and function of genes and chromosomes. The advent of technologies to study in vivo DNA-binding sites of Myc has yielded a number of important advances as well as surprises in the field. The known gene targets of MYC, however, have been far more difficult to assign to pathways that have obvious links to cell cycle progression or malignant transformation. Furthermore, none of the known targets of Myc, including the gene encoding cyclin D2, are able to completely substitute for any specific Myc function (Berns *et al.*, 2000). Myc has been shown to control many genes encoding products that regulate ribosome biogenesis and protein translation, which can ultimately affect cell mass and proliferation. No monomeric Myc proteins have been found in vivo. Instead, Myc is bound to a partner protein, Max, through a basic-region/helix–loop–helix/leucine-zipper (BR/HLH/LZ) domain (Blackwood *et al.*, 1991, 1992). Max is present in stoichiometric excess to Myc, due to e constitutive gene expression and high stability at mRNA and protein level. Max is now recognized as the central and shared dimerization partner of a rather large network of related b-HLH-Zip transcription factors that function, as transcriptional repressors (Grandori et al., 2000**)** Indeed it can also form homodimers or heterodimers with several related proteins, known as Mad1, Mxi1 (also known as Mad2), Mad3, Mad4 and Mnt (also known as Rox), as shown by in vitro binding experiments (Ayer and Eisenman., 1993; Hurlin et al., 1996,1997). The dimers all bind directly to the same DNA sequence

(CACA/GTG), which is a subset of the general E-box sequence (CANNTG) that is bound by all bHLH proteins (Blackwell *et al.,* 1990)**.**

The c-Myc

Four transcriptional promoters have been identified, but RNA initiated at the P2 promoter usually contributes to 80-90% of total c-myc steady-state RNA in normal cells (Taub *et al*., 1984). A shift in the transcription starting point has been documented in Burkitt's cell lines, where transcription of the translocated c-myc is preferentially initiated further upstream at promoter P1 instead of at P2 (Strobl and Eick, 1992; Strobl et al., 1993; Taub *et al.,* 1984). The cause of this promoter shift is not known. The c-myc gene comprises three exons. Exon 1 contains two promoters and is non coding. Exons 2 and 3 encode the Myc protein resulting in the the major 64-kDa.polypeptide with translation initiation at the canonical AUG start codon nucleotide 16 of exon 2. A longer polypeptide of 67 kDa results from translation initiated 15 codons upstream of the AUG at a CUG codon (exon 1) (Hann *et al*., 1992). An internal translationally initiated c-Myc 45-kDa polypeptide was recently recognized (Spotts *et al*., 1997).

c-Myc molecular associates

Several proteins can bind directly to MycboxII, raising the question of whether they bind simultaneously or whether Myc forms separate complexes with each of these proteins. One is TRRAP, which is a core subunit of the TIP60 and GCN5 Histone Acetyl Transferase (HAT) complexes (McMahon et al., 1998) and the recruitment depends on the integrity of MycboxII (Bouchard et al., 2001; Frank et al., 2001). The undertaking of C-MYC in normal cellular function, particularly in proliferation and differentiation, will be examined. Specific mechanisms for C-MYC over expression in cancer and the effect of this over expression on the cell cycle, apoptosis, differentiation, cellular metabolism and genomic instability discussed. One of the most striking findings of the past years has been the discovery that the enhanced expression of C-MYC proteins contributes to almost every aspect of tumor cell biology. Considerable movement has been made over the last two decades in our perceptive of the function of C-MYC in normal cells and in cancer cells. In contrast to the tightly regulated C-MYC gene in normal cells, which only express the gene when cells actively divide, cancer cells may express the gene in an uncontrolled fashion as the result of genetic aberrations. The C-MYC protein or the C-MYC gene is over expressed in a wide variety of human cancers with 80% of breast cancers, 70% of colon cancer, 90% of gynecological cancers, 50% of hepatocellular carcinomas and a variety of hematological tumors possessing abnormal C-MYC expression. On the basis of these frequencies, it is estimated that approximately 100,000 US cancer deaths per year are associated with changes in the C-MYC gene or its expression.

CONCLUSION

Apoptosis is an important safeguard that protects the organism from tumor cells: At its most basic level, apoptosis is controlled by intrinsic survival pathways that are necessary to block the cell death program, and those invoked by extrinsic signals that actively trigger the demise of the cell. Extrinsic apoptotic pathways are direct and efficient signals that provoke cell suicide, and are induced following ligation of the Fas/TNF-a family of death receptors with their ligands. The C-MYC structure and comparison of different biological and cellular systems, under a variety of circumstances, will be tracing the connections of the C-MYC network through the densely intertwined metabolic, regulatory, and structural of the cell. There are numbers of bioinformatics programs that classify expression of C-MYC gene with diverse approach. These programs become effortless and user-friendly. The large numbers of C-MYC targets participate in numerous pathways with different ranges. Scientifically the C-MYC gene network may expose links that can be therapeutically manipulated to induce the therapy of C-MYC gene.

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REFERENCES

Abrahams V.M, Kamsteeg M and Mor G (2003). Molecular Biotechnology **25** 19–30.

Adams JM, Harris AW, Pinkert CA, Corcoran LM, (1985). Nature, **318** 533–538.

Alarcon-Vargas D, Tansey WP and Ronai Z. (2002). Oncogene, **21** 4384–4391.

Amanullah A, Liebermann DA and Hoffman B (2002). Oncogene, **21** 1600–1610.

Antonsson B, Montessuit S, Sanchez B and Martinou JC (2001). *J. Biol. Chem*., 276, 11615–11623.

Ar-Rushdi A, **Nishikura K**, **Erikson J**, **Watt R**, **Rovera G**, **Croce CM. (1983).** *Science***.** Oct 28; 222(4622):390-3.

Ashe PC and Berry MD. (2003). Prog. Neuropsychopharmacol. Biol. Psychiatry,

Ayer DE, Eisenman RN. (1993). A switch from Myc:Max to Mad:Max heterocomplexes accompanies monocyte/macrophage differentiation. **Genes Dev.** Nov **7** (11)2110-9.

Blackwell TK, **Kretzner L**, **Blackwood EM**, **Eisenman RN**, **Weintraub H (1990).** Sequence-specific DNA binding by the c-Myc protein. **Science.** Nov 23;250 (4984):1149-51.

Blackwood EM, Luscher B, Eisenman RN (1992). Myc and Max associate in vivo. **Genes Dev.** Jan; **6** (1)71-80.

Blackwood EM, **Luscher B**, **Kretzner L**, **Eisenman RN (**1991). The Myc:Max protein complex and cell growth regulation. **Cold Spring Harb Symp Quant Biol.56** 109-17.

Dalla-favera r, **gelmann ep**, **martinotti s**, **franchini g**, **papas ts**, **gallo rc**, **wong-staal f (1982). Proc natl acad sci u s a.** 1982 nov; **79**(21) 6497-501.

Evan GI, **Wyllie AH**, **Gilbert CS**, **Littlewood TD**, **Land H**, **Brooks M**, **Waters CM**, **Penn LZ**, **Hancock DC**. Induction of apoptosis in fibroblasts by c-myc protein. **Cell.** 1992 Apr **3** 69(1) 119-28.

Gomez-Roman, N, Grandori, C., Eisenman, RN & White, RJ(2003). Nature 421,

Grandori C, **Cowley SM**, **James LP**, **Eisenman RN (2000).** The Myc/Max/Mad network and the transcriptional control of cell behavior. **Annu Rev Cell Dev Biol.16** 653-99.

Hann SR, **Sloan-Brown K**, **Spotts GD (1992).** Translational activation of the non-AUG-initiated c-myc 1 protein at high cell densities due to methionine deprivation. **Genes Dev.** Jul **6** (7) 1229-40.

Hurlin PJ, **Queva C**, **Eisenman RN (1997).** Mnt, a novel Max-interacting protein is coexpressed with Myc in proliferating cells and mediates repression at Myc binding sites.*Genes Dev.* Jan 111(1) 44-58.

Kowalik TF, **degregori J**, **Schwarz JK**, **Nevins JR (1995)**. E2F1 overexpression in quiescent fibroblasts leads to induction of cellular DNA synthesis and apoptosis. **J Virol.** Apr;**69** (4) 2491-500.

Lowe SW, **Ruley HE (1993).** Stabilization of the p53 tumor suppressor is induced by adenovirus 5 E1A and accompanies apoptosis. **Genes Dev.** Apr **7** (4)535-45.

Spotts GD, **Patel SV**, **Xiao Q**, **Hann SR(1997).** Identification of downstream-initiated c-Myc proteins which are dominant-negative inhibitors of transactivation by full-length c-Myc proteins. *Mol Cell Biol.* Mar;**17** (3) 1459-68.

Strobl LJ, **Eick D (1992).** Hold back of RNA polymerase II at the transcription start site mediates down-regulation of c-myc in vivo. *EMBO J.* Sep **11**(9) 3307-14.

Taub R, **Kelly K**, **Battey J**, **Latt S**, **Lenoir GM**, **Tantravahi U**, **Tu Z**, **Leder P (1984)**. A novel alteration in the structure of an activated c-myc gene in a variant t(2;8) Burkitt lymphoma. *Cell.* Jun; **37**(2) 511-20.

Taub R, **Moulding C**, **Battey J**, **Murphy W**, **Vasicek T**, **Lenoir GM**, **Leder P (**1984). Activation and somatic mutation of the translocated c-myc gene in burkitt lymphoma cells. **Cell.** Feb; 3**6** (2) 339-48.