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European Journal of Cancer 41 (2005) 2479–2484

European Journal of Cancer

www.ejconline.com

B-MYB, a transcription factor implicated in regulating cell cycle, apoptosis and cancer

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Available online 29 September 2005

Abstract

B-MYB belongs to the MYB family of transcription factors that include A-MYB and c-MYB. While A-MYB and c-MYB are tissue-specific, B-MYB is broadly expressed in rapidly dividing cells of developing or adult mammals. B-MYBs liaisons with important players of the cell cycle and transcription machinery, such as E2F and retinoblastoma proteins, suggest that its essential function in stem cell formation and mammalian development could be related to its ability to directly or indirectly impinge on gene expression. Besides its role in the cell cycle, B-MYB has been shown to promote cell survival by activating antiapoptotic genes such as ApoJ/clusterin and BCL2. Here, we discuss how B-MYB could be implicated in tumourigenesis by regulating gene expression.
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Keywords: MYB; E2F; Retinoblastoma; Cell cycle; BCl2; Clusterin; Apoptosis; Neuroblastoma

1. Introduction

B-MYB (MYBl2) is a transcription factor that belongs to the *MYB* gene family. C-MYB, the prototype family member, is the mammalian homologue of v-MYB, the oncogene carried by E26 and AMV retroviruses that causes acute leukaemia in birds. In mammals, expression of c-MYB is mainly restricted to cells of the haematopoietic lineage with some notable exceptions, such as the epithelial cells of colonic crypts and the brain [1,2]. A-Myb is expressed in germinal B lymphocytes and in male and female reproductive systems, where it plays a role [3,4]. B-MYB gene expression is found in all cell types and protein level is proportional to the degree of cell proliferation. This explains the strong expression of B-MYB in embryonal stem cells, in developing mammalian tissues and in adult haematopietic precursor cells [5–7]. The broad expression of B-MYB in proliferating cells at least in part explains the striking phenotype of B-MYB knockout mice, which show early embryonal death due to impaired inner cell mass formation [6]. This is in stark contrast with A-MYB and c-MYB deletion, which results in either viable mice or late embryonal death due to lack of erythropoiesis, respectively [3,8].

2. B-MYB is the ancestral progenitor of the MYB family

The early lethal phenotype of B-MYB-deleted mice indicates that other MYB family members cannot rescue B-MYB function, favouring the hypothesis that B-MYB plays a unique role in cell homeostasis. This idea is supported by studies conducted in the drosophila system where vertebrate B-MYB, but not c-MYB or A-MYB, complements Drosophila MYB (dMYB) in hemocytes, which are specialised cells involved in insect haematopoiesis [9]. Unlike vertebrates, drosophila and other invertebrates such as sea urchin and *Caenorhabditis elegans* only contain one MYB gene in their genome that is closely related to B-MYB. It is thought that c-MYB and A-MYB have arisen after genome duplications that took place during the 500 million years of vertebrate evolution. dMYB has been shown to promote DNA replication

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doi:10.1016/j.ejca.2005.08.004

and transcriptional activation of genes, such as cyclin B1, essential for G2/M phase progression [10]. Mutations in dMYB lead to centrosome amplification suggesting that its activity is required to maintain genomic integrity [11]. dMYB is found in a high molecular weight complex that include, among many other proteins, E2F and pRB; this protein assemblage control transcription, DNA replication and chromatin structure [12,13]. dMYB and the other dMYB binding partners Mip130 and L(3)MBT form a repressor complex similar to the synMuv of *C. elegans*, implicated in the regulation of developmental processes [12,13]. As discussed below, mammalian B-MYB interacts with E2Fs and the retinoblastoma member p107, suggesting that it is part of a protein machinery that has been conserved throughout evolution. dMYB and its binding partners mainly constitute transcriptional repressor complexes [12,13]. While it cannot be excluded that B-MYB is involved in the formation of repressor complexes, its presence has been detected in the chromatin of actively transcribed mammalian genes, like IGFBP5 and ApoJ/clusterin [14,15]. It is likely that during evolution MYB has acquired a broad range of transcription functions in order to cope with the more complex mechanisms of gene expression in higher species.

3. B-MYB and transcription control: regulation of the cell cycle

B-MYB is a growth-regulated gene. Its expression is barely detectable in G0 and is induced at the G1/S transition of the cell cycle [16,17]. Its protein levels parallel only in part mRNA expression and a pool of stable B-MYB protein is detectable throughout the cell cycle [16,17]. B-MYB, like c-MYB and A-MYB, binds DNA *in vitro* through the consensus sequence C/TAACNG. This reflects the high degree of homology of the DNA-binding domain [18]. There is, though, a clear difference in the ability to transactivate artificial promoters bearing the MYB consensus sequence. In the absence of co-factors, B-MYB is a much worst activator of transcription than c-MYB or A-MYB. This is probably caused by the transcriptional co-repressors N-COR and SMRT, which maintain B-MYB in a repressed state [19]. B-MYB is phosphorylated during S phase by the cyclin-dependent kinase cdk2 and evidence from several laboratories suggests that this modification activates B-MYB [20–23]. B-MYB phosphorylation may interfere with co-repressor binding therefore enhancing B-MYB transcriptional activity [19]. While cyclin/cdk2-directed phosphorylation activates B-MYB, it also induces accelerated protein turnover [24]. B-MYB proteolysis is precipitated by its ubiquitination and subsequent proteosome-induced degradation [24]. The ubiquitin ligase SKP2 binds to phosphorylated substrates and has been shown to interact with B-MYB and direct its destruction [24]. Interestingly, SKP2 is oncogenic and its transforming ability has been shown to be related to its ability to ubiquitinate c-MYC [25,26]. In quite a counter-intuitive fashion, SKP2 marks c-MYC for destruction but also activates transcription of relevant MYC target genes, leading to cell transformation [25,26]. One could speculate that, in a similar manner, B-MYB transactivating activity could be modulated by SKP2 ubiquitination. It would be interesting to assess whether SKP2 and B-MYB co-operate in activating B-MYB-target genes and cell transformation. This hypothesis could be easily tested in cells with genetic deletion of SKP2.

Transcriptional co-factors have been shown to bind to B-MYB to either enhance or suppress its transcriptional activity, such as CBP/P300, cyclinD1, PARP1, p107 and p57kip2. CBP/p300 is a prototypical co-activator, involved in facilitating the activity of a plethora of transcription factors. Whether or not phosphorylation is required to promote interaction of B-MYB with CBP/p300 is not entirely clear [27,28]. However, it has been reported that B-MYB phosphorylation promotes CBP-dependent acetylation, which is required for full stimulation of its transcriptional activity [29]. The mechanism of PARP1 co-activation has been analysed in some detail and depends on the integrity of cdk2 phosphorylation sites on B-MYB [30]. Protein–protein interaction facilitates cyclin/cdk2 phosporylation/activation, explaining the synergistic transactivation of MYB-binding site-bearing promoters in the presence of exogenous levels of B-MYB and PARP1 [30].

Cyclin D1 interacts with the B-MYB transcriptional domain, quenching B-MYB transactivation by interfering with CBP/p300 [28,31]. When cells exit quiescence in response to growth factors they generate a burst of Cyclin D1, required for further progression along the cell cycle. A plausible hypothesis is that cyclin D1 could co-ordinate B-MYB with the cell cycle, maintaining it in a repressed state until cyclin D1 destruction in late G1. Phosphorylation by mitotic cyclins and cdk2 could then switch-on transcription of relevant B-MYB-target genes in S or later cell cycle phases (Fig. 1).

p107 and p57Kip2 are negative regulators of B-MYB transcriptional activity. *p107* belongs to the retinoblastoma family of tumour suppressor genes, which include *pRB1* and *pRB2-p130*. p107, as well as other RB proteins, keep the cell cycle in check by associating with key cell cycle proteins E2F and cyclins. Aberrant activation of the B-MYB promoter induced by the E7 oncoprotein is caused by displacement of a repressive complex containing p107 in a critical E2F-binding site near the transcription start site [32]. Whilst investigating the role of p107 in the control of B-MYB gene transcription, we found that not only p107 suppresses B-MYB expression, but also inactivates its transcriptional activity *via* protein–protein interaction [33]. It was later

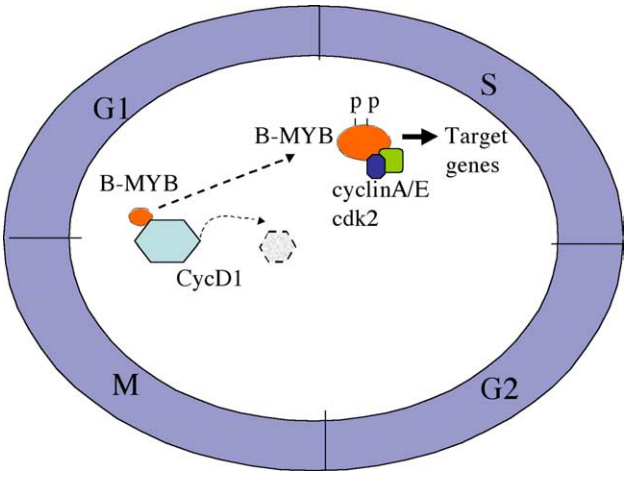

Fig. 1. B-MYB transcriptional activity is regulated during the cell cycle by phosphorylation orchestrated by cyclins. B-MYB transactivation is blocked by direct interaction with cyclin D1 in early G1. In late G1/S, cyclin D1 is down-regulated whereas B-MYB is up-regulated and phosphorylated by cdk2 and mitotic cyclins.

determined that B-MYB binds to the cyclin-binding domain of p107 resulting in activation of cyclin E/cdk2 kinase [34]. Since there is a certain degree of sequence homology between the cyclin-binding domain of p107 and functional domains of the cdk2 inhibitors p21cip-1, p27kip and p57kip2, it was investigated whether these could also interact with B-MYB. Only p57 was shown to efficiently bind to the B-MYB-DNA-binding domain and to suppress its transcriptional activity [35]. Oddly, though, p107 binds to the B-MYB carboxyl terminus, suggesting that the inhibitory effect is not dependent on the same mechanism [35].

Whether or not B-MYB transactivating function is required for regulation of the cell cycle is still debatable. Early experiments conducted by Watson's group showed that a transcriptionally silent B-MYB mutant is similar to WT B-MYB in its ability to overcome the G1 growth arrest imposed by p107 [34]. B-MYB, as suggested above, could promote cell cycle progression by relaxing the inhibitory effects of p107 on mitotic cyclins. However, more recent data point at a role for B-MYB in promoting transcription of genes essential for cell cycle progression. B-MYB in concert with E2F1-3 regulates expression of genes required for the G2/M phase of the cell cycle, like cdc2, cyclin A2 and cyclin B1 [36]. Notably, expression of G2/M genes is dependent not only on MYB-binding sites, but also on the integrity of adjacent E2F sites, leading to the hypothesis that a complex including B-MYB and activator E2Fs orchestrate expression of G2/M genes [36]. This is in accord with our recent experiments showing that down-regulating B-MYB in human fibroblasts by RNAi provokes a partial arrest of cells in the G2/M phase and apoptosis [15].

E2F transcription factors are transformed from activators to inhibitors of gene expression by interacting with retinoblastoma family members. Growth factor-induced activation of cyclinD1 causes cdk4-dependent phosphorylation of retinoblastoma proteins which can no longer bind to E2F, which becomes free to activate transcription. A native E2F/pRB/B-MYB complex in mammalian cells has not yet been identified, however, exogenous expression of p107, but not of pRB1, causes suppression of B-MYB autoregulation [33]. B-MYB transactivates its own promoter indirectly, *via* SP1 binding sites in the promoter region adjacent to the transcription start site [37]. Notably, SP1 and E2F1 have been shown to bind to each other and co-operate in promoter transactivation [38,39]. An interesting hypothesis is that a complex containing B-MYB/E2F/SP1 and retinoblastoma family members like p107 and, perhaps, p130 could coordinate expression of cell cycle-related genes in mammalian cells. This complex would be maintained in a repressed state until further progression of the cell cycle induces detachment of relevant retinoblastoma family members, enabling the synergistic co-operation and transcription of target genes (Fig. 2).

Is B-MYB required for cell cycle progression? RNAi inactivation of B-MYB ablates mitotic gene expression in glioblastoma cells but does not result in growth arrest [36]. In contrast, B-MYB depletion in normal human fibroblasts causes reduced proliferation and apoptosis [15]. It is possible that highly malignant tumour cell lines have a less stringent requirement for B-MYB than normal cells. Alternatively, enhanced expression of other MYB family members in tumour cells could compensate for the loss of B-MYB.

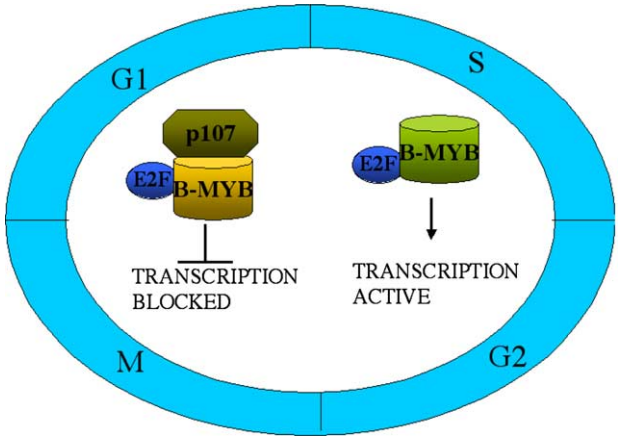

Fig. 2. Hypothetical model of regulation of G2/M genes by B-MYB. A repressive complex, which includes B-MYB, activator E2Fs and the retinoblastoma family member p107, is transformed in a transcriptionally active complex in late G1/S by dissociation of p107. These and other proteins might be the mammalian equivalent of the MYB-MuvB complex recently described in drosophila.

4. B-MYB and transcription control: regulation of apoptosis

MYB family members have been implicated in regulation of apoptosis by transactivating key target genes like BCL2. In a series of landmark papers, different groups have shown that c-MYB and v-MYB can directly or indirectly enhance the activity of the BCL2 promoter and stimulate its transcription [40–42]. This mechanism probably is at the base of the requirement for c-MYB during development of blood cell lineages. A MYB dominant negative molecule constituted by the c-MYB-DNA-binding domain fused to the transcriptional inhibitor Engrailed was developed by Weston and co-workers [43]. Constitutive expression of this fusion protein causes abnormal development of T-cells *in vivo* [43]. While these results were largely confirmed by studies of genetic inactivation of c-MYB in the lymphoid compartment [44–46], it is not possible to exclude the contribution of B-MYB in lymphocyte survival. In fact, overexpression of B-MYB in leukaemic T cells also results in activation of BCL2 and enhanced cell survival [47]. Recently, B-MYB binding sites have been found in the second exon of the *BCL2* gene. Antisense depletion of B-MYB induced a decrease in BCL2 expression and survival of a human B cell line, suggesting that BCL2 is a *bona-fide* B-MYB-target gene [48]. Another B-MYB target gene involved in regulation of apoptosis is *ApoJ/clusterin*. ApoJ/clusterin is a secreted protein that was found to be overexpressed in neuroblastoma cells that were stably transfected with a B-MYB transgene [49]. Interestingly, blockade of ApoJ/clusterin with antibodies enhanced doxorubicin killing of B-MYB-transfected neuroblastoma cells, suggesting that B-MYB could enhance cell survival through regulation of ApoJ/clusterin [49]. Physical and chemical stresses and other apoptotic stimuli greatly induce transcription of the *ApoJ/clusterin* gene. We have recently shown that a B-MYB-binding site in the *ApoJ/clusterin* promoter is critically required for thermal regulation of the gene in mammalian fibroblasts [15]. Heat induces a redox modification of B-MYB that becomes competent to bind to the *ApoJ/clusterin* gene in chromatin immunoprecipitation assays, suggesting that up-regulation of ApoJ/clusterin by heat is a pro-survival response to temperature damage [15]. The role of B-MYB in promoting transcription of survival genes could in part explain its absolute requirement in mouse development and the growth inhibiting effects of B-MYB antisense oligonucleotides in different cell lines.

In stark contrast with the findings described above, MYB proteins have been shown to mediate neuronal death after E2F de-repression. DNA damaging agents or NGF withdrawal cause transcription of E2F-target genes, like c-MYB and B-MYB, and apoptosis in primary cortical neurons or post-mitotic PC12 cells [50]. Suppressing c-MYB or B-MYB expression by antisense constructs or RNAi rescues cell death, demonstrating their direct role in neuron demise [51]. While these results seem to contradict the role of MYB genes in promoting cell survival, previous reports had suggested that B-MYB and c-MYB could induce cell death in certain settings. For example, B-MYB overexpression enhances apoptosis in myeloid cells treated with TGF-beta and c-MYB synergistically interacts with p53 in inducing BAX up-regulation and apoptosis of osteosarcoma or myeloid cells [52,53]. However, MYB proteins become proapoptotic only after forced overexpression or when endogenous gene expression is re-activated in quiescent cells. Indeed, inhibition of c-MYB or B-MYB expression in proliferating, non-terminally differentiated neuronal cells causes cell death [50]. A complication is that transformed neuronal cells show inconsistent induction of MYB in response to apoptotic stimuli like DNA damage, suggesting that the role of MYB in neuronal apoptosis is still unclear [54]. Thus, we may conclude that moderate B-MYB or c-MYB expression is in favour of cell survival. Large overexpression can cause apoptotic death of post-mitotic neurons or of other cells exposed to growth-interfering cytokines or tumour suppressor proteins like p53.

5. B-MYB and cancer

Although the direct role of B-MYB in cancer is not yet fully established, there are several indications that it could be a promoting factor. Cytogenetic analysis revealed that B-MYB at 20q13 is amplified in breast, liver, ovarian carcinomas and in cutaneous T lymphoma [55–58]. Even in the absence of gene amplification, B-MYB expression is increased in testicular and prostate malignancies [59,60]. Notably, B-MYB expression is greatly increased in metastatic *vs*. localised prostate tumours [60]. Advanced neuroblastoma has also been linked to increased B-MYB expression. Neuroblastoma is a childhood malignancy that manifest at diagnosis either as a localised or metastatic disease. Stages 1–2 are characterised by resectable tumours, without metastasis. Stages 3–4 define unresectable tumours with involvement of distant lymphnodes, the bone marrow or liver. Stage 4s is a sub-class of neuroblastoma capable of metastatic spread but that shows little bone marrow involvement, no N-MYC amplification or other adverse prognostic indicators. This class of tumours spontaneously regress and are classified as benign. Raschella *et al*. [61] have shown that B-MYB expression is increased in stages 3–4 compared to stages 1–2 and 4s. Interestingly, c-MYB and A-MYB are broadly expressed in neuroblastoma but are not associated with disease staging. How could B-MYB be involved in promoting aggressive neuroblastoma? Benign tumours have been observed to

spontaneously differentiate and regress, whereas metastatic types are characterised by the absence of differentiated figures and high mitotic index. 13*cis*-Retinoic acid induces differentiation of neuroblastoma cell lines *in vitro* and promotes their transition into a post-mitotic stage. The differentiation process is accompanied by down-regulation of B-MYB, among other proliferation markers [62]. Maintaining high levels of B-MYB by ectopic overexpression leads to resistance to retinoic acid differentiation and failure to arrest neuroblastoma cell proliferation [62]. Another mechanism by which B-MYB could contribute to aggressive behaviour of neuroblastoma cell is by inducing anti-apoptotic genes. As described in the above section, regulation of ApoJ/clusterin by B-MYB could be important to confer a drug-resistant phenotype to neuroblastoma cells [49]. Whether or not B-MYB is a *bona-fide* neuroblastoma oncogene is undetermined and awaits further experiments. Regulated inhibition of endogenous B-MYB expression in neuroblastoma and other relevant cancer models *in vivo* will address its role in the establishment and maintenance of the tumourigenic phenotype.

Conflict of interest statement

None declared.

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