Review

MYBL2 (B-Myb): a central regulator of cell proliferation, cell survival and differentiation involved in tumorigenesis

Julian Musa¹, Marie-Ming Aynaud², Olivier Mirabeau², Olivier Delattre² and Thomas GP Grünewald*,¹,³,⁴

Limitless cell proliferation, evasion from apoptosis, dedifferentiation, metastatic spread and therapy resistance: all these properties of a cancer cell contribute to its malignant phenotype and affect patient outcome. MYBL2 (alias B-Myb) is a transcription factor of the MYB transcription factor family and a physiological regulator of cell cycle progression, cell survival and cell differentiation. When deregulated in cancer cells, MYBL2 mediates the deregulation of these properties. In fact, MYBL2 is overexpressed and associated with poor patient outcome in numerous cancer entities. MYBL2 and players of its downstream transcriptional network can be used as prognostic and/or predictive biomarkers as well as potential therapeutic targets to offer less toxic and more specific anti-cancer therapies in future. In this review, we summarize current knowledge on the physiological roles of MYBL2 and highlight the impact of its deregulation on cancer initiation and progression.

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Facts

- MYBL2 is a highly conserved member of the MYB family of transcription factors.
- MYBL2 is an important physiological regulator of cell cycle progression, cell survival and cell differentiation.
- Deregulation of MYBL2 expression is involved in cancer initiation and progression.
- High MYBL2 expression is significantly correlated with poor patient outcome in numerous cancer entities.

Open questions

- What are further players of the MYBL2 downstream transcriptional network mediating its cancer-promoting properties?
- How can MYBL2 and players of its downstream transcriptional network be exploited as therapeutic targets to improve patient outcome?
- Which additional cancer entities are also affected by MYBL2 deregulation and which patients could specifically benefit from using MYBL2 as a biomarker or therapeutic target?

Limitless replicative potential, evading apoptosis, tissue invasion and metastasis: these classical hallmarks of cancer, as originally proposed by Hanahan and Weinberg,¹ characterize the malignant phenotype of a cancer cell. MYBL2 (V-Myb avian myeloblastosis viral oncogene homolog-like 2), a transcription factor of the MYB family of transcription factors, contributes to these properties of a cancer cell. MYBL2 is a physiological regulator of cell cycle progression, cell survival and cell differentiation, but due to its frequently found deregulation in cancer, it significantly drives cancer initiation and/or progression.

The MYB family of transcription factors comprises three members: MYB (c-Myb), MYBL1 (A-Myb) and MYBL2 (B-Myb). MYB was the first discovered family member and is the mammalian homolog of the retroviral v-Myb oncogene that causes acute leukemia in birds and can transform hematopoietic cells.¹² MYB1 and MYBL2 have been cloned based on the homology to MYB.¹⁴ In mammals, MYB expression is mainly restricted to hematopoietic cells, colonic crypts and brain,¹³ whereas MYBL1 is expressed in several regions of the developing central nervous system, germinal B-lymphocytes and reproductive systems of both genders.⁷,⁸ In contrast, MYBL2 is expressed in basically all proliferating cells,³ which is a possible explanation for the lethal phenotype of MYBL2 knockout mice showing early embryonal death as a result of impaired inner cell mass formation,⁹ whereas MYBL1 deletion results in viable mice and MYB deletion leads to late embryonal death by cause of lacking erythropoiesis.⁷,¹⁰

According to their tissue-specific expression, MYB and MYBL1 deregulations have been associated with certain specific cancer entities: MYB was shown to be involved in several types of leukemia, colon and breast cancer,¹¹ whereas MYBL1 has been associated with Burkitt’s lymphoma and several types of leukemia.¹² In contrast, MYBL2 deregulations occur in a broad spectrum of cancer entities as it is a central...
regulator of cell cycle progression, cell survival and cell differentiation in many tissue types (see ‘MYBL2 in cancer’ section). In this review, we summarize the physiological roles of MYBL2 in cell cycle regulation, cell survival and cell differentiation, and describe its deregulation as well as the resulting functional and clinical implications in cancer.

### MYBL2 in Cell Cycle Regulation

**MYBL2** is a cell cycle regulated and a cell cycle regulating gene. Its expression is controlled by the DREAM multiprotein complex (Dimerization partner, RB-like proteins, E2Fs and MuvB core), which is crucial in coordinating cell cycle-dependent gene expression and represses most cell cycle genes during cellular quiescence.\(^{13}\) This complex consists of the dimerization partner (DP1, -2, -3), the RB-like proteins p130 or p107, E2F (E2F4 or E2F5) and the multi-vulval class B core (MuvB, itself consisting of LIN9, LIN37, LIN52, LIN54 and RBBP4).\(^{13}\) Upon cell cycle entry, p130 or p107 dissociate from the MuvB core and from repressor E2Fs (E2F4, E2F5) due to loss of DYRK1A-dependent phosphorylation of LIN52, allowing activator E2Fs (E2F1 or E2F2 or E2F3) to transactivate early G1/S cell cycle genes, including **MYBL2**.\(^{13}\) Accordingly, MYBL2 is repressed by the DREAM complex during cellular quiescence and becomes subsequently expressed in late G1 and in S phase.\(^{13}\) Additionally, at a post-transcriptional level, MYBL2 expression can be suppressed by microRNAs.\(^{14–19}\)

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### Table 1 Selected target genes transactivated by MYBL2

| Gene symbol | Protein name | Reference(s) |
|-------------|--------------|--------------|
| **Cell cycle regulation** | | |
| AURKA | Aurora A kinase | Sadasivam et al.\(^{36}\) |
| CCNA1 (Sp1-mediated) | Cyclin A1 | Bartusel et al.\(^{35}\) |
| CCNA2 | Cyclin A2 | Zhu et al.\(^{34}\); Osterloh et al.\(^{37}\) |
| CCNB1 | Cyclin B1 | Bartusel et al.\(^{35}\); Sadasivam et al.\(^{36}\); Osterloh et al.\(^{37}\) |
| CCNB2 (repression) | Cyclin-dependent kinase 1 | Papetti et al.\(^{38}\); Zhu et al.\(^{34}\); Osterloh et al.\(^{37}\) |
| CENPF | Centromere protein F | Iltszche et al.\(^{42}\) |
| CEP55 | Centrosomal protein 55 | Iltszche et al.\(^{42}\) |
| FGFR4 | Fibroblast growth factor 4 | Johnson et al.\(^{40}\) |
| FOXM1 | Forkhead box M1 | Guerra et al.\(^{44}\); Sala et al.\(^{45}\) |
| KIF1C; KIF2C; KIF4A; KIF14; KIF20A; KIF23 | | Nakagoshi et al.\(^{46}\) (activation); Lorvellec et al.\(^{41}\) (activation); Papetti et al.\(^{38}\) (repression) |
| MYB (repression) | c-Myb | Iltszche et al.\(^{42}\) |
| MYB2 (Sp1-mediated) | c-Myc | Iltszche et al.\(^{42}\) |
| NUSAP1 | Nuclear- and spindle-associated protein 1 | Iltszche et al.\(^{42}\) |
| PLK1 | Polo-like kinase 1 | Sadasivam et al.\(^{36}\); Osterloh et al.\(^{37}\) |
| PRC1 | Protein regulator of cytokinesis 1 | Wolter et al.\(^{43}\); Brandt et al.\(^{39}\) |
| TOP2A | DNA topoisomerase II | | |
| **Cell survival** | | |
| BCL2 | Bcl-2 | Grassilli et al.\(^{37}\) |
| BCL2L11 | Bim | Greene et al.\(^{48}\) |
| BIRC5 | Survivin | Knight et al.\(^{49}\) |
| CFLI | ApolipoproteinJ/Clusterin | Cervellera et al.\(^{50}\) |
| FGFR4 | Fibroblast growth factor 4 | Johnon et al.\(^{40}\) |
| MYB (repression) | c-Myb | Guerra et al.\(^{44}\); Sala et al.\(^{45}\) |
| MYB2 (Sp1-mediated) | c-Myc | Nakagoshi et al.\(^{46}\) (activation); Lorvellec et al.\(^{41}\) (activation); Papetti et al.\(^{38}\) (repression) |
| MYC | B-Myc | Sadasivam et al.\(^{36}\); Osterloh et al.\(^{37}\) |
| PLK1 | Polo-like kinase 1 | Yuan et al.\(^{51}\) |
| VDAC2 | Voltage-dependent anion channel 2 | | |
| **Differentiation** | | |
| NANOG | Homeobox protein NANOG | Zhan et al.\(^{52}\) |
| POU5F1 | Oct-4 | Tarasov et al.\(^{53}\) |
| SOX2 | Sox2 | Zhan et al.\(^{52}\) |
| **Invasion/metastasis** | | |
| SNAI1 | Snail (Zinc-finger protein SNAI1) | Tao et al.\(^{120}\) |
CDH1-dependent FOXM1 degradation during M phase

Motifs co-occur in the promoters of these genes. A model sites (MBS), cell cycle genes homology region (CHR, bound promoter binding. These results clearly indicate a dependency of both factors to one another in transactivating late cell cycle genes in early and mid S phase. Afterwards, the FOXM1 complex dissociates due to increasing APC/C-CDH1-dependent FOXM1 degradation during M phase.

Mechanistically, it was proposed that Cyclin D1 abolishes the transactivation activity of MYBL2 through direct interaction. However, contrary to Cyclin A, Cyclin D1 strongly inhibits progression, the major role of MYBL2 in G2/M progression became increasingly clear over the recent years: RNAi-mediated MYBL2 knockdown in human cell lines and experiments in Drosophila with knockout of the MYB2 Drosophila homolog dMyb reduces cell proliferation, expression of G2/M genes and decreases the amount of cells in G2/M phase. Although dMyb is the only gene of the MYB transcription factor family in Drosophila, it is functionally and phylogenetically equivalent to vertebrate MYBL2 and can therefore be seen as a suitable model. The results from Drosophila experiments are remarkable, as they indicate that an adequate proliferative capacity mediated by MYBL2 is necessary to maintain genomic stability.
function mutation of dMyb causes abnormal mitoses that are associated with multiple functional centrosomes, unequal chromosome segregation, micronuclei formation and failure to complete cell division. These are frequent in the later cell cycles with resulting nuclei that often show aneuploidy and/or polyploidy. It was also shown that MYBL2 can contribute to genomic stability by forming complexes with Clathrin and Filamin. This is required for proper localization of Clathrin at the mitotic spindle and is thereby stabilizing kinetochore fibers. Consistently, in embryonic stem cells (ESC) MYBL2 depletion leads to stalling of replication forks, disorganization of the replication program and an increase in double-strand breaks. It has been shown that these effects are, at least in part, mediated by deregulation of MYC and FOXM1 transcription, which are important for normal S phase progression, indicating that MYBL2 protects cells from genomic damage during S phase by promoting proper cell cycle progression. Chromosomal fragmentation, shorter and thicker chromatids, end-to-end fusion and chromatid loss upon MYBL2 knockdown indicates that reduced activity of MYBL2 is also associated with structural chromosomal instability.

**MYBL2 in Cell Survival**

An association between MYBL2 and cell survival has already been reported in early studies. However, over the years, the role of MYBL2 in the regulation of cell survival became increasingly clear and is mainly mediated via transcriptional regulation of specific target genes, but can also be mediated by direct protein–protein interaction. The transcriptional regulation by MYBL2 seems to depend on the cell type: In most cell types MYBL2 appears to have pro-survival functions, whereas it mainly has anti-survival functions in cells of neural origin when exposed to apoptotic stimuli (Figure 2).

**Pro-survival function via transcriptional regulation.** Grassilli et al. showed that MYBL2 overexpression in interleukin 2-dependent murine T cells is associated with enhanced transactivation of the anti-apoptotic Bcl-2, and hence diminished cytokine dependence and enhanced resistance to apoptosis induced by doxorubicin, ceramide and dexamethasone. Consistently, the transfection of a Bcl-2-non-expressing human B-cell line with a MYBL2 expression vector induced the expression of Bcl-2 and vice versa, antisense depletion of MYBL2 decreases Bcl-2 levels and enhances apoptosis. Furthermore, results of Cervellera et al. indicate that ApolipoproteinJ/Clusterin is a MYBL2 target gene, whose expression mediates resistance to apoptosis induced by the chemotherapeutic drug doxorubicin in neuroblastoma. Santilli et al. further confirm these results: under conditions of thermal stress, MYBL2-dependent ApolipoproteinJ/Clusterin expression is enhanced due to redox modification of MYBL2 and constitutes a protective response mechanism to thermal injury in MEFs. MYBL2 has also been shown to suppress autophagy and to promote cell survival of ovarian oocytes by binding the promoter and directly activating the transcription of VDAC2.

**Anti-survival function via transcriptional regulation.** However, in contrast to these findings, MYBL2 seems to have a contrary role concerning cell survival predominantly in neural cells. MYBL2 knockdown protects pheochromocytoma cells, sympathetic neurons and cortical neurons against cell death elicited by NGF withdrawal or DNA damage. This indicates a required role for MYBL2 in neuronal apoptosis after E2F de-repression due to apoptotic stimuli. A model has been proposed by which E2F4–p130 protein complexes protect neurons from cell death by occupying the MYBL2 promoter under basal conditions, whereas under conditions of cell stress these complexes are lost and replaced by E2F1 transactivating MYBL2 and thus promoting cell death.

**Direct protein–protein interactions.** Independent of the transactivation capabilities of MYBL2, it is further able to regulate cell survival by direct interaction with the serine–threonine kinase receptor-associated protein (STRAP), for which MYBL2 can serve as a positive regulator. On the one hand, MYBL2 can enhance STRAP-mediated inhibition of
TGF-β signaling pathways, such as apoptosis and growth inhibition, by inhibiting TGF-β receptor association with SMAD3 and enhancing TGF-β receptor association with SMAD7, and thereby prevent translocation of SMAD3 in the nucleus in response to TGF-β1 (pro-survival function). On the other hand, co-expression of MYBL2 results in increased STRAP-mediated stimulation of p53 nuclear translocation, p53-induced apoptosis and cell cycle arrest via reduction of p53–MDM2 association (anti-survival function).

**MYBL2 in differentiation and maintenance of stem cell properties**

Several lines of evidence indicate that MYBL2 contributes to the maintenance of an undifferentiated and/or stem cell-like phenotype of a cell. Especially in stem cells, the balance between cellular quiescence on the one hand, and cell division in order to generate more stem cells (self-renewal) or to give rise to mature cells (differentiation) on the other hand, is important for the maintenance of the stem cell pool. Early results showed that MYBL2 protein levels decrease upon differentiation of human myeloid cell lines. Later on, in neuroblastoma cells, MYBL2 expression was found to be downregulated during retinoic acid-induced neural and glial differentiation and conversely, constitutive expression of MYBL2 prevents retinoic acid-induced neural differentiation. Compatible with this, levels of p130, a member of the DREAM complex (see ‘MYBL2 in cell cycle regulation’ section) that is able to suppress the MYBL2 promoter upon transfection, was shown to be strongly upregulated during mid/late differentiation stages, whereas MYBL2 levels decrease. Comparable results indicating a role for MYBL2 to maintain cells in an undifferentiated state have also been shown for several different cell types, such as leukemic cell lines, male gonocytes, intestinal epithelial cells and keratinocytes. Mechanistically, for the maintenance of a pluripotent and undifferentiated phenotype of ESC, it was proposed that MYBL2 may regulate a transcriptional network that controls cell cycle progression and cell fate to sustain self-renewal and pluripotency. Especially for the maintenance of pluripotency, MYBL2 directly regulates the expression of POU5F1, SOX2 and NANOG, which are critical mediators of differentiation and pluripotency in ESC. Similarly, MYBL2 was shown to control self-renewal and differentiation of hematopoietic stem cells, possibly by downregulating ID1 and CEBPα, which promote cellular differentiation, while upregulating GATA2, a transcription factor shown to promote proliferation at the expense of differentiation. Thus, MYBL2 helps the cell to maintain in an undifferentiated, pluripotent, but proliferative state.

**MYBL2 in Cancer**

The roles of MYBL2 in cell cycle progression, cell survival and cell differentiation suggest that deregulation of MYBL2 may have an oncogenic potential. It can contribute significantly to cancer progression by promoting cancer cell proliferation, therapy resistance and metastatic spread (Figure 4). Indeed, MYBL2 is frequently found to be overexpressed in several cancer entities and associated with poor patient outcome.

Mechanistically, the role of MYBL2 in regulation of differentiation was mainly investigated in embryonic stem cells (ESC) and hematopoietic stem cells (HSC): In ESC, MYBL2 was shown to directly control the expression of POU5F1, SOX2 and NANOG, which are critical regulators of differentiation and maintenance of pluripotency. In HSC, MYBL2 was shown to downregulate ID1 and CEBPα, which promote cellular differentiation, and to upregulate GATA2, a transcription factor shown to promote proliferation at the expense of differentiation. Thus, MYBL2 helps the cell to maintain in an undifferentiated, pluripotent, but proliferative state.
cycle progression and cell survival in p53-mutated cancers.\textsuperscript{102,103} This is in accordance with results from Parikh et al.\textsuperscript{102} showing that MYBL2 is disproportionately upregulated in many p53 mutant cancers. MYBL2 has even been shown to overcome DNA damage-induced G2 checkpoint arrest in p53 mutant cells and constitutive expression of MYBL2 has been shown to overcome p53-induced G1 checkpoint arrest.\textsuperscript{103} Furthermore, the oncoviral HPV16 E7 protein is able to deregulate DREAM complex assembly and to thereby drive MYBL2 expression.\textsuperscript{104} Consistent to this, HPV16-immortalized cells show upregulated expression of MYBL2.\textsuperscript{105} Mechanistically, the HPV16 E7 oncogene can bind to p130, promote its proteasomal degradation and thereby disassemble the DREAM complex.\textsuperscript{106} E7 in addition directly binds to the MYBL2–MuvB–FoxM1 complex, leading to cooperative transcriptional activation of mitotic genes.\textsuperscript{106} MYBL2 moreover mediates abrogation of DNA damage-induced G1 checkpoint arrest, via regulation of CDK1 expression in E7 transformed cells,\textsuperscript{107} and was shown to rescue oncogene-induced cellular senescence,\textsuperscript{14,108} a permanent cell cycle arrest that cells must bypass during cancer development,\textsuperscript{14,109} probably by suppressing p16\textsuperscript{INK4A} expression.\textsuperscript{14,108,110}

### MYBL2 in deregulation of proliferation.

As described for non-malignant cells (see ‘MYBL2 in cell cycle regulation’ section), MYBL2 has also been shown to drive cell proliferation and/or cell cycle progression in cancer cells, such as breast cancer,\textsuperscript{111} cervical cancer,\textsuperscript{112} colorectal cancer,\textsuperscript{113} hepatocellular carcinoma,\textsuperscript{91} leukemic cells,\textsuperscript{15} lung adenocarcinoma\textsuperscript{42} and neuroblastoma (in MYCN-amplified cell lines).\textsuperscript{113}

### MYBL2 in cancer therapy resistance.

Resistance to chemo- and radiotherapy is one of the main properties of a cancer that determines cancer progression and patient outcome. MYBL2 overexpression in interleukin 2-dependent murine T cells was shown to be associated with enhanced resistance to drug-induced apoptosis by doxorubicin, ceramide and dexamethasone, due to increased transactivation of the anti-apoptotic Bcl-2 by MYBL2.\textsuperscript{47} These results from Grassilli et al. are in accordance with results from Levenson et al.,\textsuperscript{114} showing that MYBL2 is upregulated upon genetic suppressor element-induced drug resistance to DNA-interactive agents, such as aphidicolin, hydroxyurea, cytarabine, etoposide, doxorubicin and mafosfamide in fibrosarcoma cells. In neuroblastoma, MYBL2 directly regulates expression of ApolipoproteinJ/Clusterin and thereby mediates resistance to apoptosis induced by doxorubicin.\textsuperscript{50}

However, MYBL2 was not only shown to mediate resistance to chemotherapeutic agents, but also resistance to DNA damage, as, for example, caused by radiation. Under physiological conditions, such as in p53 wild-type cells, DNA damage results in p53-dependent binding of p130 and E2F4 to MuvB and the dissociation of the MYBL2–MuvB complex.\textsuperscript{99–101} Also, upon ionizing radiation, Cyclin F suppresses the MYBL2-regulated transcriptomic program by directly interacting with MYBL2 and thereby suppressing Cyclin A-mediated phosphorylation of MYBL2.\textsuperscript{115} On the contrary, under non-physiological conditions, such as in p53 mutant cells, MYBL2 fails to dissociate from MuvB, which contributes to increased G2/M gene expression in response to DNA damage.\textsuperscript{103} In accordance, DT40 chicken B cells lacking MYBL2 show increased sensitivity to DNA damage elicited by UV irradiation and alkyllylation.\textsuperscript{116} Consistently, in Ewing sarcoma cells, MYBL2 can be destroyed quickly upon UV irradiation, leading to induction of apoptosis,\textsuperscript{117} whereas this is not the case in neuroblastoma, where MYBL2 levels do not change upon irradiation, making the cells resistant to UV-induced apoptosis.\textsuperscript{117} Interestingly, in neuroblastoma cells MYBL2 is found to be hypophosphorylated and overexpression of a non-phosphorylatable MYBL2 mutant in HEK 293 cells can protect cells from UV-induced apoptotic cell death, suggesting that decreased Cyclin A-dependent phosphorylation, accompanied by decreased activation but also decreased proteasomal degradation, can facilitate the survival promoting activity of MYBL2.\textsuperscript{117}

Consistent with these results, a pro-survival role for MYBL2 has also been shown in several cancer cell lines, such as colorectal cancer,\textsuperscript{93} hepatocellular carcinoma\textsuperscript{51} and leukemia cells.\textsuperscript{118}
MYBL2 in invasion and metastasis. Early results of Iwai et al. have shown that the introduction of an inducible dominant interfering Myb protein into ESC lead to dissociation of ESC colonies into dispersed single cells and to reduced adhesion of the ESC to the culture dish. Cell adhesion analyses have shown that MYBL2 suppression decreased the adhesion with extracellular matrix proteins, such as Laminin, Collagen and Fibronectin, probably due to reduced cell surface expression of Beta1 Integrin.

However, in contrast to these early findings, a role for MYBL2 in epithelial-to-mesenchymal transition (EMT), a process in which epithelial cells lose their polarity and gain migratory and invasive properties, has been proposed: In breast cancer cells, MYBL2 knockdown is able to restore the expression of the epithelial marker E-Cadherin, the formation of cell–cell junctions and to suppress cell invasion, anchorage-independent growth and tumor formation. Conversely, MYBL2 overexpression decreased the expression of the E-Cadherin, but increased expression of mesenchymal markers. Mechanistically, it was proposed that MYBL2 upregulates the expression of the major EMT regulator SNAIL, thereby mediating activation of EMT and cancer cell invasion.

In accordance with this, MYBL2 protein levels have been shown to be significantly upregulated in matched breast cancer metastases compared to the primary tumor. Similar results were shown for prostate cancer and renal cell carcinoma: MYBL2 is overexpressed in prostate cancer (xenograft) metastases, whereas in renal cell carcinoma MYBL2 was found to be expressed in metastases from primary tumors being MYBL2 negative.

Conclusions
MYBL2 is a central regulator of cell cycle progression, cell survival and cell differentiation. Deregulation of MYBL2 expression can contribute significantly to cancer progression by promoting cancer cell proliferation, therapy resistance, metastatic spread and is correlated with poor patient outcome in several cancer entities. Therefore, MYBL2 and/or players of its downstream transcriptional network could serve as effective targets for cancer treatment. Although no direct MYBL2 inhibitor is available yet, CDK2 inhibition could be used to reduce MYBL2 activity in MYBL2 high-expressing cancers. Yet, highly specific CDK2 inhibitors are lacking, but several more or less specific CDK inhibitors have already been in clinical trials for cancer treatment. Also, several inhibitors interfering with players of the downstream transcriptional network of MYBL2, such as inhibitors against Aurora kinases, FGF receptors, Kinesins, Bcl-2 and BIRC5 (Survivin) have already been in clinical trials and may serve as an effective, more specific and less toxic future anti-cancer therapy in cancers highly expressing MYBL2.

Conflict of Interest
The authors declare no conflict of interest.

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