We are IntechOpen, the world’s leading publisher of Open Access books
Built by scientists, for scientists

4,200
Open access books available

116,000
International authors and editors

125M
Downloads

154
Countries delivered to

TOP 1%
Our authors are among the most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™
Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com
The Key Role of E2F in Tumor Suppression through Specific Regulation of Tumor Suppressor Genes in Response to Oncogenic Changes

Kenta Kurayoshi, Eiko Ozono, Ritsuko Iwanaga, Andrew P. Bradford, Hideyuki Komori, Keigo Araki and Kiyoshi Ohtani

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.72125

Abstract

E2F, the principal target of the tumor suppressor pRB, plays crucial roles in tumor suppression. Upon dysfunction of pRB, E2F activates tumor suppressor genes such as ARF, an upstream activator of the tumor suppressor p53, resulting in the induction of apoptosis and tumor suppression. The E2F activity that activates the tumor suppressor genes is detected only in cancer cells and not in normal growing cells. The E2F activity can drive selective suicide gene expression and induce apoptosis specifically in cancer cells. Thus, the E2F activity provides a beneficial tool to specifically target cancer cells in cancer treatment.

Keywords: E2F, RB, ARF, apoptosis, cancer specific gene expression

1. Introduction

A human body consists of 37 trillion cells and the cell number is maintained by a balance of cell death and cell proliferation. As aged cells are eliminated by cell death, new cells are supplied by cell proliferation to retain appropriate cell numbers. To maintain homeostasis, cell proliferation is strictly regulated by growth signals. Cell proliferation is also induced by abnormal growth stimulation such as overexpression or constitutive activation of oncogenes, which leads to tumorigenesis [1]. To protect cells from tumorigenesis, mammalian cells harbor tumor suppressor pathways, principally mediated by pRB and p53 [2, 3]. The RB pathway consists of pRB and upstream regulators such as cyclin-dependent kinases (CDKs) and CDK inhibitors.
The p53 pathway consists of p53 and upstream regulators such as HDM2 and ARF. The RB pathway and the p53 pathway suppress tumor formation by the induction of cell cycle arrest or apoptosis. The forced inactivation of both pathways in normal cells renders cells tumorigenic and both pathways are disabled in most cancers, indicating that these two pathways play pivotal roles in tumor suppression in normal cells.

The transcription factor E2F, the principal target of the RB pathway, plays central roles in cell proliferation by activating a repertoire of growth-related genes. Consistent with this, overexpression of E2F1, an activator type of E2F family members, in quiescent cells induces progression into S phase [4]. Since E2F plays central roles in cell proliferation, it has generally been thought that defects in the RB pathway upregulate E2F and promote hyperplasia, contributing to tumorigenesis. However, it has also been reported that E2F plays a pivotal role in tumor suppression. E2F1 knockout mice showed increased incidence of tumor formation [5], suggesting a role of E2F1 in tumor suppression. Overexpression of E2F1 also activates p53, the main effector of the p53 pathway, and promotes apoptosis [6], rather than cell proliferation. Knocking out p53 attenuates E2F1-induced apoptosis [7], supporting that the induction of apoptosis is mediated through activation of p53. Of note, the overexpression of E2F1 activates the tumor suppressor gene ARF, an upstream activator of p53 [3]. These observations suggest that E2F plays a pivotal role in tumor suppression by activating ARF, and consequently p53. Interestingly, E2F selectively induces the ARF gene upon forced inactivation of pRB, which mimics dysfunction of the RB pathway, but not in response to physiological inactivation of pRB by growth stimulation [8, 9]. This observation implies that E2F activates the ARF gene specifically in response to oncogenic changes, contributing to tumor suppression. Consistent with this notion, the E2F activation of the ARF gene is detected only in cancer cells and is not observed in normal growing cells [8, 9]. Thus, E2F stimulation of ARF gene expression can serve as a tool to discriminate cancer cells and normal growing cells. In this chapter, we describe the roles of E2F in cell proliferation and tumor suppression, focusing on the mechanism of E2F dependent, selective regulation of tumor suppressor genes, specifically in response to oncogenic changes.

2. E2F plays central roles in cell proliferation

The proliferation of mammalian cells is dependent on growth stimulation, which promotes cell cycle progression. Once a cell passes through the restriction (R) point, located in late G1 phase, it is programmed to automatically proceed to the end of M phase. Thus, the regulation of the R point is a critical determinant of cell cycle progression and cell proliferation. Key regulators of the R point are the transcription factor E2F, which activates a repertoire of growth-related genes, and the tumor suppressor pRB, which inhibits E2F.

E2F consists of eight family members (E2F1-8), which, based on their function, are divided into transcriptional activators (E2F1–E2F3a) and transcriptional repressors (E2F3b–E2F8). E2F regulates thousands of genes important for cell cycle progression, DNA replication, DNA damage checkpoint, and DNA repair, and plays central roles in cell proliferation [10]. E2F-modulated cell cycle regulatory genes include Cyclin E [11], Cyclin A [12], and CDC2 [13, 14].
Cyclin E/CDK2 promotes G1 to S phase transition by inactivating pRB through phosphorylation. Cyclin A/CDK2 promotes progression through S phase. Cyclin A/CDC2 and Cyclin B/CDC2 promote progression through G2 and progression into and through M phase, respectively. E2F-modulated DNA replication genes include *Cdc6* [15], *Cdt1* [16], *Cyclin E* [11], *ASK* [17], and *Cdc45* [18]. Origin recognition complex (ORC) binds to replication origins and marks where DNA replication takes place. Cdc6 and Cdt1 bind to ORC and promote initiation of DNA replication by recruiting the DNA helicase MCM complex to replication origins (Figure 1). Cyclin E/CDK2 phosphorylates MCM complex and promotes loading of it onto chromatin. ASK/Cdc7 activates MCM complex by phosphorylation and Cdc45 recruits DNA polymerase α onto chromatin. These E2F targets are essential for DNA replication and G1-S phase transition [19–23]. Accordingly, knocking out all members of activator-type E2Fs (*E2F1–E2F3*) abolishes cell proliferation [24]. Precise replication of genomic DNA is important to avoid mutation. E2F also activates genes involved in DNA damage checkpoint, such as *ATM* [25] and *Chk1* [26], and DNA repair, including *Claspin* [27], *BRCA1* [28], and *Rad51* [27]. Thus, E2F plays a pivotal role in cell proliferation by activating a number of genes critical for cell cycle progression and precise DNA replication.

Figure 1. Role of E2F targets in DNA replication. E2F plays central roles in DNA replication by activating genes coding for factors involved in initiation of DNA replication, DNA synthesis, DNA damage checkpoint, and DNA repair.
3. The RB pathway in the control of cell proliferation

pRB is the product of the first identified tumor suppressor gene retinoblastoma (RB1) [29]. pRB is the principal regulator of G1 to S phase transition by restraining E2F and plays a crucial role in tumor suppression. Based on considerable structural homology, p107 and p130, together with pRB, comprise the RB family. During transition from G1 to S phase upon growth stimulation, RB is inactivated through phosphorylation by CDKs, thereby unleashing E2F and allowing cell cycle progression.

In quiescence, RB family members (pRB and p130) bind to E2F3b-E2F5 on its target promoters and repress their expression (Figure 2). The interaction of RB with the transactivation domain of E2F inhibits E2F’s transcriptional activity. Furthermore, RB actively represses the expression of E2F target genes by changing chromatin structure through recruitment of histone deacetylase (HDAC) [30], histone methyltransferase (Suv39H1) [31], components of the chromatin remodeling complex (hBrm and BRG1) [32], and DNA methyltransferase (DNMT1) [33] onto their promoters. Upon growth stimulation, D-type cyclin-dependent kinases (CDK4 and 6) are activated, and inactivate p130 and pRB through phosphorylation inhibit binding of RB to E2F3b-5

![Figure 2. Regulatory mechanism of E2F target genes by E2F and RB. In quiescence, RB family members bind to E2Fs on its target promoters and repress their expression. In response to growth stimulation, Cyclin/CDK inactivates RB family through phosphorylation, activating E2F and its target gene expression.](image-url)
and its target promoters. This leads to the release of E2F from suppression by RB and induces its target genes including E2F1-3a and Cyclin E [11, 34]. Cyclin E activates CDK2, which further inactivates RB through phosphorylation. This constitutes a positive feedback loop inactivating RB and activating E2F, resulting in the further induction of E2F targets and initiation of S phase [35]. Thus, regulated functional interactions of E2F and RB play pivotal roles in promoting and restraining cell proliferation, respectively. Given its importance in restraining cell proliferation, RB is often referred to as a “gatekeeper” in the control of cell proliferation.

Consistent with the critical role of RB in restraining cell proliferation, mutation or deletion of the RB1 gene is responsible for retinoblastoma and various types of cancers including breast cancer [36], osteosarcoma [37], and small cell lung cancer (SCLC) [38]. Since mutation of p107 and p130 are uncommon and considering their function and frequency of inactivation, pRB is thought to be the pivotal tumor suppressor regulating G1-S phase transition [2, 39]. However, although increased tumorigenesis is not detected in p107−/− or p130−/− mice, RB1−/+p107−/− or RB1−/+p130−/− compound mice are more prone to tumor formation than RB1−/− mice [40]. This suggests that, upon loss of pRB function, p107 and p130 can, to some extent, compensate for the tumor suppressor function of pRB [41].

In cancer cells, regulation of G1-S phase transition is lost by the disruption of the RB pathway, which is regarded as a hallmark of cancer [2, 42] (Figure 3). Defects in the RB pathway such as deletion or mutation of RB1 or silencing of its promoter by hypermethylation have been found in breast cancer [36], osteosarcoma [37], and SCLC [38]. Mutation or deletion of the CDK inhibitor
or silencing of its promoter by hypermethylation was detected at high frequency in a variety of cancers including prostate, renal, and colon cancer [43, 44]. Gene amplification and consequent overexpression of cyclin D1 or CDK4 are also detected in various cancers [45, 46]. Upstream activators of the Cyclin D1 gene such as c-Myc and Ras are overexpressed or constitutively activated in cancers [47, 48], suggesting that these mutations also contribute to the overexpression of Cyclin D1. Taken together, the RB pathway is, at least at some point, disabled or compromised in almost all cancers. Consequently, pRB is functionally inactivated and E2F activity and its target gene expression are upregulated, leading to the aberrant cell proliferation. This underscores the importance of the RB pathway in tumor suppression.

4. The p53 pathway in the control of cell cycle arrest and apoptosis

p53 plays crucial roles in tumor suppression through the induction of cell cycle arrest or apoptosis (programmed cell death). TP53, which codes for p53, is the most frequently mutated gene in a variety of cancers including skin cancer [49], nonsmall cell lung cancer (NSCLC) [50], and breast cancer [51]. TP53 knockout mice are prone to tumor formation [52, 53] and enhanced expression of p53 induces cell cycle arrest or apoptosis [54]. The target genes involved in cell cycle arrest include CDK inhibitor p21<sup>Cip1</sup>, 14–3-3σ, and GADD45 [55] (Figure 4). CDK inhibitor p21<sup>Cip1</sup>, which binds to and inhibits Cyclin D/CDK4, 6, Cyclin E/CDK2, Cyclin A/CDK2, and Cyclin B/CDK1, induces G1 and G2/M arrest [56]. 14–3-3σ binds to the phosphatase Cdc25C, which activates Cyclin B/CDK1, and inhibits its activity by the translocation of the complex from the nucleus into the cytoplasm [57]. GADD45 binds to and inactivates Cdc25C, consequently inhibiting CDK1 to induce G2/M arrest [58]. Activation of these genes by p53 is thought to contribute to tumor suppression through the induction of cell cycle arrest. The target genes involved in apoptosis include Bax [59], Bak [60], Noxa [61], and Puma [62] (Figure 4). Bax and Bak are Bax family members, whose insertion into mitochondrial membrane induces release of cytochrome c and apoptosis. Apoptosis induced by various stimulations is disabled in Bax/Bak-knocked out cells, indicating that Bax and Bak are central players in the induction of programmed cell death [63]. Noxa and Puma directly and indirectly activate Bax and Bak [64]. These observations suggest that p53 contributes to tumor suppression by the induction of apoptosis through activation of Bax and Bak.

The transcriptional activity of p53 is strictly regulated by its binding factors. The oncogene product HDM2, an E3 ubiquitin ligase, induces proteolysis of p53 through ubiquitination and inhibits its activity (Figure 5). Under nonstressed conditions, expression of p53 is kept at low levels by binding of HDM2. In response to DNA damage, Chk2 and ATM phosphorylate and activate p53 by inhibiting binding of HDM2 [65]. The tumor suppressor ARF stabilizes p53 by inhibiting HDM2 activity though its sequestration into the nucleolus [66]. Importantly, the expression of ARF is induced by oncogenic changes such as defects in the RB pathway including overexpression of c-myc and Ras [67], and expression of ARF is upregulated in various cancer cells [68]. Based on these observations, ARF is described as a “sensor of oncogenic stresses” and is thought to play crucial roles in tumor suppression, through up-regulation of p53, in response to oncogenic changes. Supporting the importance of its function, mutation, and deletion of ARF is detected in various cancers [69] and ARF<sup>−/−</sup> mice are prone to tumor formation [70]. The
5. Pivotal roles of E2F in tumor suppression

E2F plays crucial roles not only in cell proliferation but also in tumor suppression. E2F1−/− mice are prone to tumor formation [5] and overexpression of E2F1 induces apoptosis, suggesting that E2F contributes to tumor suppression through the induction of apoptosis.
The target genes involved in apoptosis include ARF and TAp73 [7, 67] (Figure 6). ARF is an upstream activator of p53 and plays an important role in transmitting oncogenic signals to p53. The transcription factor TAp73 is a homolog of p53 and induces apoptosis through upregulation of p53 target genes in a p53-independent manner [73]. Apoptosis induced by the overexpression of E2F1 is attenuated in TP53−/− cells and TAp73−/− cells, and is disabled in TP53−/+TAp73−/− cells [7]. Moreover, PPP1R13B and JMY, whose products function as coactivators of p53 and TAp73, are also E2F targets (Figure 6) [74], indicating that E2F1 induces apoptosis primarily via p53 and TAp73. Other tumor suppressor genes that are E2F targets include MOAP1, RASSF1, and BIM (Figure 6). MOAP1 forms a complex with RASSF1 and activates the proapoptotic protein Bax. BIM is a member of the BH3-only family, which induces apoptosis through direct or indirect activation of Bax [75]. In addition, Bax is also a target of p53 and TAp73 [60]. These observations indicate that E2F suppresses tumor formation by the induction of apoptosis through upregulation of p53, TAp73, and their downstream effectors. Importantly, we demonstrated that E2F activates ARF and TAp73 genes upon forced inactivation of pRB, which mimics dysfunction of the RB pathway, but not in response to the physiological inactivation of pRB through growth stimulation [8, 9]. Moreover, a search for genes regulated by E2F in a similar manner to ARF and TAp73 identified PPP1R13B, JMY, MOAP1, RASSF1, and BIM [76]. These results suggest that E2F contributes to tumor suppression by inducing these genes specifically upon dysfunction of the RB pathway. Consistent with this

**Figure 6.** The pathway of E2F-induced apoptosis. In response to oncogenic changes, E2F induces apoptosis through upregulation of p53, TAp73, and their downstream effectors.
notion, E2F activity that activates the ARF and TAp73 genes is detected only in cancer cells and is not present in normal cells [8, 9], underscoring the importance of E2F in tumor suppression. Since E2F selectively activates these tumor suppressor genes in the context of dysfunctional pRB, such E2F activity is referred to as “deregulated E2F activity.” This E2F-dependent tumor suppression mechanism implies that disruption of both the p53 and RB pathways is necessary for tumor formation.

6. Regulation of E2F activity to induce apoptosis

Among E2F family members, activator-type E2Fs (E2F1-3) induce tumor suppressor genes such as ARF and TAp73, with E2F1 exhibiting the highest such activity [9, 76]. Therefore, to understand the regulation of tumor suppression by E2F, elucidation of the mechanism, by which E2F1 activates tumor suppressor genes, is important. Several factors that bind E2F1 and affect its activity are summarized in Table 1. TopBP1 is phosphorylated by Akt/PKB upon growth stimulation. The phosphorylated TopBP1 associates with E2F1 [77] and recruits Brg1, a component of chromatin remodeling complex, to E2F1, resulting in the inhibition of E2F1 induction of the ARF gene [78]. Jab1, a coactivator of c-Jun [79], binds to E2F1 through the marked box domain and promotes the induction of apoptosis by E2F1 [80, 81]. RIP140 and VHL repress the activation of the ARF promoter by E2F1 [82, 83]. ARF also functions as a transcription cofactor that binds to the transactivation domain of E2F1 to repress E2F1 activation of the ARF promoter [84]. PRMT5 methylates E2F1 on arginine residues 111 and 113, and destabilizes E2F1 [85]. SENP8 deNEDDylates (removes NEDD8) and stabilizes E2F1, resulting in enhancing activation of TAp73 promoter [86]. Sirt1, a histone deacetylase, represses E2F stimulation of the TAp73 promoter [87]. These studies revealed that E2F’s ability to activate tumor suppressor genes is regulated by various factors such as transcription cofactors, post-translational modifiers, and histone modifiers. The mechanism of the regulation of E2F activity by these factors is not known in detail and its elucidation is imperative.

<table>
<thead>
<tr>
<th>Gene name</th>
<th>Function</th>
<th>Monitoring promoter</th>
<th>Effect on E2F activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jab1</td>
<td>Transcription cofactor of c-Jun</td>
<td>ARF, TAp73</td>
<td>Upregulation</td>
</tr>
<tr>
<td>SENP8</td>
<td>Sentrin-specific protease</td>
<td>TAp73</td>
<td>Upregulation</td>
</tr>
<tr>
<td>ARF</td>
<td>Inhibitor of HDAC2, transcription cofactor of c-myc</td>
<td>ARF</td>
<td>Repression</td>
</tr>
<tr>
<td>PRMT5</td>
<td>Methylase</td>
<td>TAp73</td>
<td>Repression</td>
</tr>
<tr>
<td>RIP140</td>
<td>Transcription cofactor of estrogen receptor</td>
<td>ARF</td>
<td>Repression</td>
</tr>
<tr>
<td>Sirt1</td>
<td>Histone deacetylase</td>
<td>TAp73</td>
<td>Repression</td>
</tr>
<tr>
<td>TopBP1</td>
<td>Transcription cofactor of Miz</td>
<td>ARF</td>
<td>Repression</td>
</tr>
<tr>
<td>VHL</td>
<td>E3 ubiquitin ligase, transcription cofactor of p53</td>
<td>ARF</td>
<td>Repression</td>
</tr>
</tbody>
</table>

Table 1. E2F-binding factors and their effects on its activity to activate tumor suppressor genes.

In cancer treatment, specifically targeting cancer cells is important for optimal therapeutic efficacy. One strategy is to utilize a cancer-specific promoter to express a cytotoxic gene or a viral gene required for the replication. By regulating a suicide gene such as HSV-TK or a proapoptotic gene under the control of cancer-specific promoters, the gene is expressed specifically in cancer cells and causes cell death [88–90]. Alternatively, by regulating a viral gene required for viral replication under the control of these promoters, the gene is expressed specifically in cancer cells, allowing viral replication and cell lysis in a cancer cell-specific manner [91–93]. In this approach, therapeutic effects and side effects are dependent on the promoter activity in cancer cells and normal cells, respectively. Therefore, a promoter with optimal cancer cell-specificity should be used.

For a promoter to be cancer specific, it should have two important characteristics. First, the promoter should have low activity in normal cells to avoid side effects. Second, it should exhibit high activity in a wide variety of cancer cells for maximum therapeutic effects. As promoters thought to exemplify these parameters, hTERT and E2F1 promoters have been utilized. hTERT is a catalytic component of telomerase, which is not expressed in most somatic cells but is present in many types of cancers [94]. Thus, the hTERT promoter exhibits strong promoter activity in many types of cancer cells. However, given that normal stem cells also express hTERT, the hTERT promoter may exhibit strong promoter activity in these cells [95]. The E2F1 promoter is activated by E2F, whose activity is upregulated in cancer cells due to defects in the RB pathway. Thus, E2F1 promoter also exhibits strong promoter activity in many types of cancer cells. However, the E2F1 promoter is also stimulated by physiological E2F activity induced by growth stimulation and thus has a strong promoter activity in normal growing cells [34].

In contrast to the hTERT and E2F1 promoters, which may exhibit strong promoter activity in normal cells, the tumor suppressor ARF promoter, which specifically responds to deregulated E2F activity, is thought to be a better candidate. E2F activity stimulating the ARF promoter, is detected only in cancer cells and not in normal cells [8]. ARF is expressed at high levels in various cancer cells, but not in normally growing cells [68]. Furthermore, the activity of the ARF promoter is detected specifically in tumor tissues and not in normal tissues in vivo as revealed using ARF<sup>GFP/GFP</sup> mice [96]. These observations indicate that the ARF promoter shows optimal cancer cell specificity in a wide variety of cell types and has excellent therapeutic potential.

We showed that the ARF promoter exhibited greater cancer cell specificity than the E2F1 promoter [97]. Adenovirus expressing HSV-TK, a suicide gene, under the control of the ARF promoter (Ad-ARF-TK) had more selective cytotoxicity in cancer cells than the analogous E2F1 promoter construct [97]. Moreover, overexpression of the CDK inhibitor p21<sup>Cip</sup> upregulated deregulated E2F activity specifically in cancer cells and augmented cancer cell-specific cytotoxicity of Ad-ARF-TK [98]. These observations underscore the utility of the ARF promoter and deregulated E2F activity in mediating cancer-specific gene expression (Figure 7, upper panel). Furthermore, overexpression p21<sup>Cip</sup> alone could induce E2F dependent apoptosis specifically in cancer cells [98], suggesting that induction or enhancement of deregulated E2F activity could be a drug target to induce cancer cell-specific apoptosis (Figure 7, lower panel). It must be worth testing whether drug-based CDK inhibitors also exhibit similar effects to
p21\textsuperscript{Cip}. Since p21\textsuperscript{Cip} inhibits most of CDKs, identification of responsible CDK, which inhibits deregulated E2F activity, is also important. By using specific inhibitor to the responsible CDK, deregulated E2F activity could be more efficiently enhanced. The combination of deregulated E2F-mediated suicide gene therapy and enhancement of deregulated E2F activity using appropriate CDK inhibitor should also improve deregulated E2F-mediated cancer therapy.


8. Conclusion

E2F is the principal target of the tumor suppressor pRB and defects in the RB pathway are observed in almost all cancers. Upon oncogenic changes, E2F activates ARF, an upstream activator of p53 and TAp73, resulting in the induction of apoptosis. Importantly, the E2F activity to stimulate ARF and TAp73 expression is not induced by the physiological activation of E2F, such as growth stimulation. Therefore, E2F suppresses tumor formation by inducing apoptosis specifically in response to oncogenic changes through the activation of ARF and TAp73. Moreover, deregulated E2F-dependent activation of the ARF gene is observed only in cancer cells, and not in normal cells, suggesting that deregulated E2F activity represents a beneficial tool to specifically target cancer cells in cancer treatment.
Evidence supporting the potential availability of deregulated E2F activity in cancer therapy is accumulating. The regulation of suicide genes by the ARF promoter has more selective cytotoxicity in cancer cells than the analogous E2F1 promoter construct. Moreover, overexpression of p21<sup>Cip1</sup> upregulates deregulated E2F activity and augments cancer-specific cytotoxicity of the ARF promoter construct. Furthermore, overexpression of p21<sup>Cip1</sup> alone can induce E2F-dependent apoptosis specifically in cancer cells. Therefore, deregulated E2F activity can drive selective gene expression and induce apoptosis specifically in cancer cells, supporting its therapeutic potential in a variety of cancers. The development of cancer therapies based upon deregulated E2F activity will require detailed characterization of the components and molecular mechanisms underlying its functional role in oncogenesis and tumor suppression and merits further investigation.

Acknowledgements

This work is supported in part by JSPS KAKENHI Grant number 15K06957.

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARF</td>
<td>Alternative reading frame</td>
</tr>
<tr>
<td>ASK</td>
<td>Activator of S-phase kinase</td>
</tr>
<tr>
<td>ATM</td>
<td>Ataxia telangiectasia mutated</td>
</tr>
<tr>
<td>Bax</td>
<td>Bcl-2-associated X protein</td>
</tr>
<tr>
<td>Bak</td>
<td>Bcl-2 homologs antagonist/killer</td>
</tr>
<tr>
<td>BIM</td>
<td>BCL-2 interacting mediator of cell death</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Breast cancer susceptibility genes 1</td>
</tr>
<tr>
<td>BRG1</td>
<td>Brahma-related gene-1</td>
</tr>
<tr>
<td>Cdc</td>
<td>Cell division cycle</td>
</tr>
<tr>
<td>CDK</td>
<td>Cyclin-dependent kinase</td>
</tr>
<tr>
<td>Cdt1</td>
<td>Chromatin licensing and DNA replication factor 1</td>
</tr>
<tr>
<td>Chk1</td>
<td>Checkpoint kinase 1</td>
</tr>
<tr>
<td>Chk2</td>
<td>Checkpoint kinase 2</td>
</tr>
<tr>
<td>DNMT1</td>
<td>DNA methyltransferase 1</td>
</tr>
<tr>
<td>E2F</td>
<td>E2 transcription factor</td>
</tr>
<tr>
<td>GADD45</td>
<td>Growth arrest and DNA-damage-inducible gene 45</td>
</tr>
<tr>
<td>GFP</td>
<td>Green fluorescent protein</td>
</tr>
<tr>
<td>hBrm</td>
<td>human Brahma</td>
</tr>
<tr>
<td>HDAC</td>
<td>histone deacetylase</td>
</tr>
<tr>
<td>HDM2</td>
<td>Human double minute 2</td>
</tr>
</tbody>
</table>
HSV-TK    Herpes simplex virus-1 thymidine kinase
hTERT    Human telomerase reverse transcriptase
Jab1    Jun activation domain-binding protein 1
JMY    Junction-mediating and regulatory protein
MCM    Minichromosome maintenance
MOAP1    Modulator of apoptosis 1
NSCLC    nonsmall cell lung cancer
ORC    Origin recognition complex
PKB    protein kinase B
PPP1R13B    Protein phosphatase 1 regulatory subunit 13B
PRMT5    Protein arginine methyltransferase 5
Puma    p53 upregulated modulator of apoptosis
RASSF1    Ras association domain family member 1
RB    Retinoblastoma
RIP140    Receptor-interacting protein 140
SCLC    Small cell lung cancer
SENP8    Sentrin specific protease family member
Suv39H1    suppressor of variegation 3–9 homolog 1
TopBP1    DNA topoisomerase II-binding protein 1
VHL    Von Hippel–Lindau

Author details

Kenta Kurayoshi, Eiko Ozono, Ritsuko Iwanaga, Andrew P. Bradford, Hideyuki Komori, Keigo Araki and Kiyoshi Ohtani*

*Address all correspondence to: btm88939@kwansei.ac.jp

1 Department of Biomedical Chemistry, School of Science and Technology, Kwansei Gakuin University, Sanda, Hyogo, Japan
2 Chromosome Replication Lab, The Francis Crick Institute, UK
3 Department of Craniofacial Biology, University of Colorado School of Dental Medicine, Anschutz Medical Campus, Aurora, CO, USA
4 Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, CO, USA
5 Center for Stem Cell Biology, Life Sciences Institute, University of Michigan, Ann Arbor, MI, USA
References


Johnson DG, Ohtani K, Nevins JR. Autoregulatory control of E2F1 expression in response to positive and negative regulators of cell cycle progression. Genes & Development. 1994;8:1514-1525

Henley SA, Dick FA. The retinoblastoma family of proteins and their regulatory functions in the mammalian cell division cycle. Cell Division. 2012;7:10


[67] Lowe SW, Sherr CJ. Tumor suppression by Ink4a-Arf: Progress and puzzles. Current Opinion in Genetics & Development. 2003;13:77-83


[81] Hallstrom TC, Nevins JR. Jab1 is a specificity factor for E2F1-induced apoptosis. Genes & Development. 2006;20:613-623


