HHS Public Access

Author manuscript

Sci China Life Sci. Author manuscript; available in PMC 2018 July 17.

Published in final edited form as:

Sci China Life Sci. 2018 July ; 61(7): 808–814. doi:10.1007/s11427-017-9230-2.

Epigenetic mechanism of Survivin dysregulation in human cancer

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Abstract

Survivin (coding gene *BIRC5*) is a dual functional protein acting as a critical inhibitor of apoptosis (IAP) and key regulator of cell cycle progression. It is usually produced in embryonic tissues during development and undetectable in most adult tissues. Overexpression of Survivin frequently occurs in various human cancers and increased Survivin correlates with poor clinic outcome, tumor recurrence, and therapeutic resistance. Because of its selective expression in tumor, but not normal tissues, Survivin has been recognized as an attractive target for cancer treatment. Although several therapeutic approaches targeting Survivin are actively under clinical trials in human cancers, to date no Survivin-targeted therapy has been approved for cancer treatment. Numerous studies have devoted to uncover the underlying mechanism resulting in Survivin dysregulation at multiple levels, such as transcriptional and post-transcriptional regulation. The current article provides a literature review on the transcriptional and epigenetic regulation of Survivin expression in human cancers. We focus on the impact of DNA methylation and histone modifications, including specific lysine methylation, demethylation, and acetylation on the expression of Survivin. The latest development of epigenetic approaches targeting Survivin for cancer treatment are also discussed.

Keywords

Survivin; epigenetics; DNA methylation; histone modification; cancer therapy

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Conflict of interests

The authors declare that they have no conflict of interests.

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Introduction

Survivin (encoded by the gene *BRIC5*) is a member of the inhibitor of apoptosis (IAP) family (Sah et al., 2006). It is distinguished from other IAPs because of its bi-functionality as a regulator of both apoptosis and cell mitosis. Survivin is frequently overexpressed in a wide variety of human malignancies, but is scarce in the majority of adult normal tissues (Altieri, 2003; Ambrosini et al., 1997). Aberrant Survivin expression is associated with tumor cell proliferation, progression, angiogenesis, therapeutic resistance, and poor prognosis (Hirano et al., 2015; Li et al., 2015; Liu et al., 2008; Sokolowska et al., 2015). Thus, Survivin has been considered as a diagnostic and prognostic marker. It has also been identified as an excellent molecular target for cancer therapy (Pennati et al., 2008; Ryan et al., 2009; Sato et al., 2009; Weiss et al., 2008). Regulatory mechanisms of *BIRC5* gene expression are not fully understood. It is well known that expression of a gene can be regulated at the transcriptional and post-translational levels, whereas the expression of Survivin is thought to be regulated primarily at the transcriptional level. Thus, how to develop a potent therapeutic method targeting Survivin poses a challenge. One strategy is to elucidate the precise mechanisms controlling *BIRC5* gene expression and identify prevalent control factors. The aim of the current article is to provide a literature review on the transcriptional and epigenetic regulation of Survivin expression in human cancers. The latest advance of epigenetic targeting of Survivin for cancer treatment are also discussed.

1. Transcriptional factors binding to the promoter region of *BRIC5* gene

The gene coding Survivin is *BIRC5*, which locates at chromosome 17q25 in humans and consists of three introns and four exons. Expression of *BIRC5* is high during fetal development and in most tumors, yet low in adult tissues. Alternatively spliced transcript variants encoding distinct Survivin isoforms are described (Altieri, 1994a, b). Numerous transcription factors have been predicted binding to specific sequences in the promoter region of *BIRC5* and are involved in its transcriptional regulation. The majority of binding sites for transcription factors are clustered in a proximal area of the promoter (–250…+70 from the transcription initiation point). The 10 most studied transcription factors and their relevant binding sites are shown in figure 1. The functional binding sites for Sp1 (Chen et al., 2011; Cheng et al., 2012; Zhang et al., 2015), NF-κB (Angileri et al., 2008; Papanikolaou et al., 2011; Wang et al., 2010), Stat3 (Huang et al., 2014; Kim et al., 2016), Rb (Raj et al., 2008; Yang et al., 2008), p53 (Vaziri et al., 2005; Zhou et al., 2002), and Egr1 (Wagner et al., 2008b) have been found in *BIRC5* gene promoter, suggesting a possible involvement of these factors in direct control of *BIRC5* gene expression. Among them, Sp1, Stat3 and NF-κB activate expression of *BIRC5* gene. For example, eight possible Sp1 binding sites with canonical or close to canonical sequence (G/T)(G/A)GGCG- (G/T)(G/A)(G/A)(C/T) were found in the promoter region of *BIRC5* (Li and Altieri, 1999; Mityaev et al., 2008). The binding site called "Sp1-complex" relative to the transcription initiation point is actually a cluster composed of two overlapping putative Sp1 binding sites. Simultaneous introduction of several mutations into the sequence of the Sp1-complex cluster leads to a sharp decrease in *BIRC5* gene promoter activity (Xu et al., 2007). Some transcriptional factors inhibit *BIRC5* expression. The tumor suppressor p53, as well as the transcription factor Egr1 are involved in repression of *BIRC5* gene promotor (Nakano et al., 2005). P53-

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mediated inhibition of *BIRC5* gene expression has been verified in a number of studies (Chang et al., 2013). It has also been shown that *BIRC5* is transcriptionally repressed upon DNA damage by wild type p53. Pradhan et al have published a serial of articles to elucidate the molecular basis of doxorubicin-induced down-regulation of *BIRC5* transcription (Esteve et al., 2005, 2007; Smallwood et al., 2007). Expectedly, these different transcriptional factors can work together to regulate *BIRC5* gene expression. For example, in colorectal cancer HCT116 cells treated with doxorubicin, the transcriptional factor Sp1 retains on *BIRC5* promoter, acting as an anchor to recruit p53. Furthermore, coordination among the transcriptional factors is necessary because of overlaps of their binding sites. For instance, p53 may inhibit activation of *BIRC5* expression by preventing the *BIRC5* promoter from HIF (hypoxia inducing factor) binding. This can be achieved via competition for binding with overlapping sites. Moreover, p53 may counteract the binding of Sp1 factor, thereby suppressing *BIRC5* promoter activity (Esteve et al., 2007; Smallwood et al., 2007).

2. Methylation status of BRIC5 promoter in human cancers

Abnormal DNA methylation status is frequently observed in a variety of human cancers. Hypermethylation of CpG islands in the promoter regions of tumor suppressive genes generally mediates loss of the gene expression. In contrast, DNA hypomethylation is widely spread over chromosomes, hence loosening the intrinsic heterochromatin regions, activating the latent retrotransponson's, causing genomic instability, and subsequently resulting in activation of gene transcription (Baylin and Jones, 2011; Das and Singal, 2004). This section summarizes the current knowledge of *BIRC5* promoter methylation in human cancers.

Sequence analysis of the 5′ flanking region of *BIRC5* gene reveals a GC-rich region ranges from -254nt (from starting codon ATG) to +110nt in exon 1. The percentage of GC di-nucleotides in this region ranges between 65% to 80%, with a CG:GC ratio of 0.98, hence reaching the length and base composition criteria of a canonical CpG island (Ambrosini et al., 1997; Li and Altieri, 1999). However, the relationship between *BIRC5* promoter methylation and its expression is complicated. Higher expression levels of Survivin may not always correlate with less methylated promoter. Several studies show no difference between normal and neoplastic tissues regarding the methylation status in the CpG island of *BIRC5* promoter. DNAs extracted from fetal liver, normal breast, colon and uterus, as well as breast and lung cancer tissues are all unmethylated at the CpG island (Li and Altieri, 1999). The methylation status of *BIRC5* promoter in various tumors can be divided into the following three scenarios.

2.1 Promoter methylation irrelevant to BIRC5 expression

In cervical carcinomas (Chaopatchayakul et al., 2010), esophageal cancers (Yang et al., 2009), and acute myeloid leukemia (AML) (Wagner et al., 2008a), the methylation patterns of *BIRC5* promoter have been shown to have no relationship to Survivin expression and tumor progression. Analyses of the CpG island in *BIRC5* promoter reveal no methylation in normal tissues and cervical carcinoma (Chaopatchayakul et al., 2010). In esophageal cancers, *BIRC5* mRNA is overexpressed. However, this overexpression is not due to its promoter hypomethylation, as it is unmethylated in both cancer and non-cancerous tissues,

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regardless of Survivin expression profile (Yang et al., 2009). Overexpression of Survivin is common in AML and the potential involvement of *BIRC5* promoter methylation has been studied. Results show that *BIRC5* promoter is unmethylated in both peripheral blood mononuclear cells and AML blasts, suggesting that the methylation status is not a major contributor of Survivin re-expression during leukemogenesis (Wagner et al., 2008a).

No *BIRC5* promoter methylation has been found in astrocytoma and non-astrocytoma tissues (Yu et al., 2004), whereas a study with 27 glioblastoma multiforme samples shows *BIRC5* promoter methylation in 8 samples (Hervouet et al., 2010). Although statistical analysis suggests a positive correlation between methylation and the expression levels of DNMT1 (DNA methyltransferase 1) in glioblastoma, clinical outcome analyses indicate that the methylation profile of *BIRC5* has no association with patient survival (Hervouet et al., 2010). Despite there is no relevance of *BIRC5* promoter methylation with its expression in glioma, folate supplementation induces downregulation of *BIRC5* mRNA via increasing its DNA methylation (Hervouet et al., 2009). Folate treatment enhances temozolomide-induced apoptosis and inhibits proliferation of glioma cells through methylation of apoptosis-related genes, among them, *BIRC5*-encoded Survivin is considered as a molecular determinant in the reduction of cell proliferation and gain of sensitivity in apoptosis (Hervouet et al., 2009). Similar results are also reported in rodent models of glioma showing that folate supplementation is able to limit tumorigenesis (Cartron et al., 2012).

2.2 Hypomethylation correlated with high expression of BIRC5

Unmethylated promoter (hypomethylation) may contribute to the elevated expression of Survivin in oral squamous cell carcinomas (OSCCs). Tanaka et al (Tanaka et al., 2003) compared the expression of Survivin in OSCCs and oral pre-malignant lesions. While 41 of 71 (58%) OSCC cases were positive immunohistochemical staining for Survivin and 14 of 38 (37%) oral pre-malignant lesion cases were positive for Survivin staining. There was no positive staining for Survivin in the corresponding normal tissues. Methylation of *BIRC5* promoter was studied in 9 OSCCs and their matched normal tissues. Among them, 4 normal tissues had methylated *BIRC5* promoter and all tumor tissues had no evidence of *BIRC5* promoter methylation. Despite of the low sample number, the data provided an insight of Survivin expression possibly regulated by DNA hypomethylation in OSCCs (Tanaka et al., 2003).

2.3 Hypermethylation correlated with high expression of BIRC5

Different from aforementioned, the expression levels of Survivin are positively correlated with its promoter methylation in endometrial cancers. In normal endometrial tissues, *BIRC5* promoter is completely unmethylated, however, the methylation levels increase from low grade to high grade endometrial cancers correlated with elevated expression of Survivin protein (Nabilsi et al., 2009). The hypermethylation of *BIRC5* promoter in endometrial cancers is found to block the binding of p53, a repressor of *BIRC5* gene transcription, to its promoter region, hence increase Survivin expression (Nabilsi et al., 2009). Similar phenomenon of the high grade tumors companying with higher levels of methylated *BIRC5* promoter often occurs in patients with bladder cancer (Berrada et al., 2012). Although hypermethylation of *BIRC5* promoter is more frequently observed in high grade tumors and

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increases from low to high stages, there is no significant correlation between stages/grades and the methylation status of *BIRC5* promoter (Berrada et al., 2012). Additional studies are warranted to determine whether the underlying mechanism is the same as that in endometrial cancers.

3. Histone modifications contributing to Survivin dysregulation

A histone modification is a covalent post-translational modification of histone proteins, which mainly includes specific residue methylation/demethylation, phosphorylation, acetylation, ubiquitylation, sumoylation, etc. These modifications can influence gene expression by altering chromatin structure or recruiting different histone modifiers. In this section, we discuss the effect of histone H3 methylation and acetylation on Survivin expression in human cancers.

3.1 Histone H3 methylation and demethylation in regulating BIRC5 expression

During cellular differentiation, the ratio between permissive and repressive epigenetic modifications is either maintained or swiftly changed to create cell-type-specific patterns of gene expression. In general, methylation on both histone H3 lysine 9 (H3K9) and histone H3 lysine 27 (H3K27) mediates heterochromatin formation and participates in silencing gene expression at euchromatic sites. On the other hand, methylation on histone H3 lysine 4 (H3K4) and lysine 79 (H3K79) usually leads to activation of gene transcription. During this regulatory process, both histone methylases and demethylases play important roles to control gene expression. These epigenetic modulators are also involved in regulation of Survivin expression. Some transcriptional factors cooperated with the epigenetic modulators to regulate *BIRC5* gene expression. It has been shown that p53 and DNA methyltransferase I (DNMT1) play a pivotal role in the epigenetic suppression of *BIRC5* (Esteve et al., 2007). P53 recruits DNMT1, which may facilitate the promoter hypermethylation, and p53 may also recruit other epigenetic modulators, including the histone lysine methyltransferase G9a. G9a is able to catalyze methylation reactions on H3K9 to generate dimethylation of H3K9 (H3K9me2), which provides a binding platform for heterochromatin protein 1 (HP1). Coordination of the epigenetic regulatory proteins creates a suppressive chromatin complex in the proximal promoter region of *BIRC5*, and thereby results in *BIRC5* gene repression upon doxorubicin treatment (Esteve et al., 2007; Smallwood et al., 2007). A recent study suggests that Bmi1 represses Survivin expression in a cell type specific manner via increasing trimethylation of H3K27 (H3K27me3) and direct binding of Bmi1 to the promoter region of *BIRC5* (Acquati et al., 2013).

3.2 Histone H3 acetylation and deacetylation in regulating BIRC5 expression

Histone acetylation and deacetylation are essential parts of gene regulation. Histone hyper-acetylation is generally associated with chromatin decondensation, allowing DNA to be accessible to binding proteins, and thereby increases transcriptional activity. In contrast, histone hypo-acetylation contributes to chromatin condensation and transcriptional repression. These reactions are typically catalyzed by enzymes with “histone acetyltransferase” (HAT) or “histone deacetylase” (HDAC) activities. Tsai et al (Tsai et al., 2015) have shown that increased histone acetyltransferase p300 (p300HAT) activity in

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human melanoma A375 cell line and murine colon adenocarcinoma C26 cell line may enhance Survivin expression. Others report that liver cancer initiation is controlled by the transcription factor AP-1 through SIRT6-dependent inhibition of Survivin, because SIRT6 represses Survivin expression by reducing histone H3K9 acetylation and inhibiting NF-κB activity (Min et al., 2012).

4. Epigenetic strategies targeting Survivin for cancer treatment

Different types of cancer may have slight or significant differences in the way how the *BIRC5* gene expression is regulated. Distinct methylation status of *BIRC5* promoter is observed in different tissues and cancers. Thus, further investigations assessing the detailed epigenetic regulation of *BIRC5* gene transcription in certain cancer types are necessary before we may apply novel epigenetic strategies targeting of Survivin for cancer treatment. If elevated expression of Survivin is positively related to the unmethylated *BIRC5* promoter, then inducing methylation of *BIRC5* promoter seems to be a reasonable approach to downregulate Survivin. Following this thought, Li and colleagues (Li and Ma, 2010) have tested a novel method to induce hypermethylation of *BIRC5* promoter in non-small cell lung cancer (NSCLC) NCI-H460 cell line. They develop a short methylated oligonucloetide called SurKex, which is complementary to the *BIRC5* promoter. After treatment with SurKex, the *BIRC5* mRNA and its encoded protein (Survivin) were dramatically decreased in NCI-H460 cells. The growth of tumor xenografts derived from NCI-H460 cells in mice was also significantly inhibited. Detailed analyses confirmed that downregulation of Survivin was attributed to the following three mechanisms: 1) SurKex induced site-specific de novo methylation on CpG islands in the complementary region of *BIRC5* promoter, which involved activation and participation of DNMT1. 2) SurKex induced histone hypermethylation at its target region, which increased levels of H3K9me2 and H3K27me3. 3) SurKex also triggered histone H4 lysine 16 (H4K16) deacetylation at its target region. This histone deacetylation was demonstrated to guide DNA methylation in *BIRC5* silencing upon SurKex treatment (Li and Ma, 2010; Ma et al., 2010; Ma et al., 2011). Thus, the novel technology using methylated oligonucloetide to induce site-specific methylation at hypomethylated “site-of-interest” seems to be a promising approach for cancer therapy.

Similarly, detailed analyses of histone modifications not only improve our understanding of epigenetic regulation of *BIRC5* gene transcription during cancer progression, they may also facilitate the development of histone modifying enzyme-targeted therapeutic agents. To this end, a number of recent studies suggest that HDAC inhibitors (HDACis) may be added into cancer treatment regimens because of their inhibitory effects on Survivin expression in a wide variety of human cancer cells. The class I HDACi, MS-275 (also known as SNDX-275 or entinostat) suppressed proliferation and induced apoptosis in human myeloma U266 cells, which might be associated with the downregulation of Survivin expression (Ma et al., 2009). We have shown that entinostat is able to effectively inhibit Survivin expression via induction of the *Survivin*-targeting miRNAs in NSCLC cells, and thereby significantly enhance the antitumor activity of paclitaxel against NSCLC (Wang et al., 2016). Feng et al examined the cytotoxic effects of a pan-HDACi, TSA in combination with silibinin on two pancreatic cancer cell lines (Panc1 and Capan2), and investigated the possible mechanisms (Feng et al., 2015). Their studies found that combinatorial treatment of TSA and silibinin exerted an

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additive growth inhibitory effect on the pancreatic cancer cells by inducing cell cycle G2/M arrest and apoptosis. Moreover, treatment with TSA and silibinin resulted in a profound reduction in the expression of cyclin A2, cyclin B1, Cdk1, and Survivin. Sakai T et al. reported that the combinations of a novel HDACi OBP-801 (also known as YM753) and the phosphatidylinositol 3-kinase (PI3K) inhibitor LY294002 synergistically inhibited cell growth and induced apoptosis in renal cell carcinoma, which was resistant to traditional cancer therapies. It was partly due to markedly decreased Survivin protein levels (Yamada et al., 2013).

Perspectives

Survivin is selectively overexpressed in tumors, but undetectable in normal tissues (Altieri, 2008; Kanwar et al., 2013), and increased Survivin correlates with poor prognosis, tumor recurrence, and drug resistance in various human cancers (Coumar et al., 2013; Zaffaroni and Daidone, 2002). Thus, inhibition of Survivin is likely an efficacious therapy in reducing relapse risk and improving the survival of cancer patients. Yet, there is currently no FDA-approved Survivin-targeted therapy for cancer treatment. Recent studies on the epigenetic mechanisms of Survivin dysregulation in human cancers provides us a new avenue to identify novel epigenetic strategy to downregulate Survivin. In addition, it has been suggested that epigenetic alteration is one of the major mechanisms influencing expression of miRNAs, and the miRNAs binding to 3′-UTR of *BIRC5* mRNA play an important role in controlling Survivin expression. Thus, the specific changes of miRNA expression profiles in cancer cells present unique opportunities to manipulate Survivin expression epigenetically (Lu et al., 2005). Our recent studies show that the “sister” miRNAs work cooperatively to inhibit their common targets (Wahdan-Alaswad and Liu, 2013; Wang et al., 2013), inspiring us to believe that those miRNAs with multiple binding sites on 3′-UTR of *BIRC5* mRNA should be more specific and effective than the miRNAs with single binding sites to downregulate Survivin. Therefore, in addition to the epigenetic approaches targeting *BIRC5* transcription discussed above, specific miRNAs may represent exciting tools to inhibit Survivin for cancer therapy (Huang et al., 2015). We are currently testing whether miR-542-3p, which has three binding sites on the 3′-UTR of *BIRC5* mRNA, may be potentially developed as a unique anti-Survivin agent to enhance chemotherapy for cancer treatment. Nonetheless, the molecular basis of Survivin dysregulation in human cancers is far from well understood. Further investigations on the underlying mechanisms will certainly facilitate the development of novel Survivin-targeted therapy for cancer treatment.

Acknowledgments

This work was supported in part by the NIH/NCI (R01CA201011) and the National Natural Science Foundation of China (81472763) (to BL).

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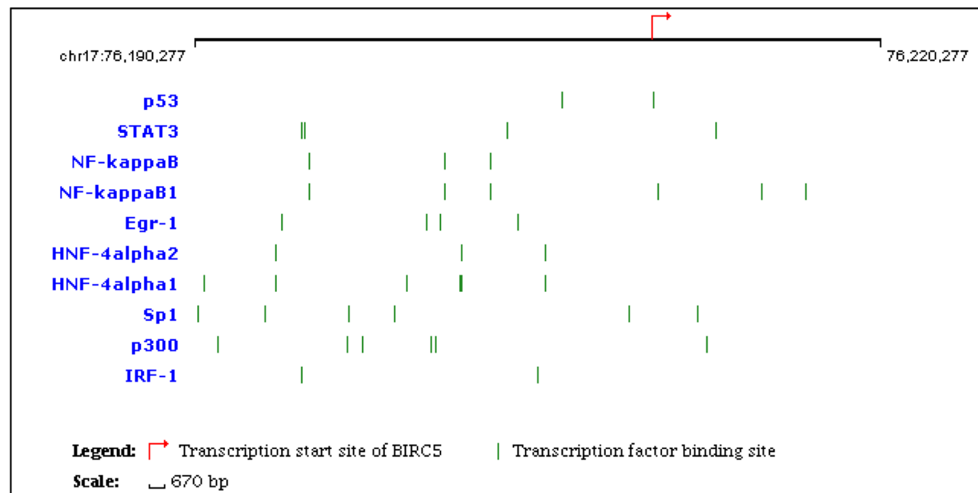

Fig 1.

Diagram depicting the 10 most relevant transcription factors and their predicted binding sites in 20kb upstream and 10kb downstream of the transcription start site of BIRC5 (Adapted from http://www.sabiosciences.com/chipqpcrsearch.php).