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Insights into the Regulation of Survivin Expression in Tumors

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Abstract

Survivin, an anti-apoptotic protein was found to be expressed in tumors, whereas in normal tissues the expression of this protein was shown to be absent or extremely low. Survivin exhibits multifunctional activity in tumor cells. Survivin is the smallest member of the inhibitor of apoptosis protein family and was demonstrated to have key roles in regulating cell division and inhibiting apoptosis. The cancer protein survivin was shown to be associated with tumor cell progression, invasiveness, resistance to therapeutics and poor prognosis. Its level in tumors is associated with deregulation of several oncogenic pathways. In this review, a delineation of survivin expression and progress in understanding the survivin transcriptional regulation with the emphasis of augmented apoptosis in cancer and its link to the Hedgehog pathway and cancer stem cells is discussed.

Keywords: Survivin; GLI2; Hedgehog; Survivin promoter; Sp1

Introduction

Survivin is a member of the IAP (inhibitor of apoptosis) gene family and is markedly overexpressed exclusively in cancers but not in normal adult tissues [1-7] implying that it could be an ideal target for cancer directed therapy. Strong expression of survivin in tumors correlates with a poor cancer treatment response and poor outcomes. Notably, survivin is also present in some nonmalignant cells such as myeloid stem cells and peripheral blood mononuclear cells, T lymphocytes [6], melanocytes [8] and in hyperplastic polyps and sessile serrated adenomas [9]. Furthermore, survivin is widely expressed during embryogenesis in many tissues like human fetal lungs, liver, heart, kidney and gastrointestinal tract [5]. Apart from its role in anti-apoptosis, survivin also plays a critical role in regulating the cell cycle at mitosis. To prevent apoptosis, survivin interacts with many regulatory factors [10]. Survivin is a small protein (displaying approximately 16.5-kDa band on SDS electrophoresis) and contains a single baculovirus IAP repeat but no RING finger motif, found in other IAP protein members. It is generally thought that transcriptional deregulation is a major mechanism involved in the aberrant expression of survivin in cancers. Transcription of the survivin gene proceeds from a single promoter but 5 splicing isoforms arise from the primary transcript [3]. The common survivin isoform contains 4 exons and isoform ΔEx3 (lacking exon 3) interacts with 4-exon survivin in the mitochondria where they inhibit mitochondrial-dependent apoptosis. Other survivin splice variants also colocalize with survivin in the mitochondria [3].

Despite the fact that almost 20 years elapsed from the discovery of survivin [11] and the mechanisms of its anti-apoptotic activities were widely studied [4], only little is known about its transcriptional regulation and maintenance of the high survivin levels is tumors. Here we briefly review the mechanisms of survivin transcriptional upregulation in the tumor tissue.

Positive Regulation of Survivin Expresssion

The survivin promoter harbors binding sites for several pro-oncogenic transcription factors (Sp1, STAT3, NF-kB, KLF5, E2F1, GATA1, DEC1 or TCF4) [6] that may be important in the elevation of survivin levels specifically in individual tumors. It is not known whether these sites could render sufficient survivin promoter activity required for the high survivin expression observed in all malignant cells. The most important transcription factors which maintain the survivin basal expression are Sp1 and Sp3. Several putative G/C-rich Sp-binding sites are present in the TATA-less survivin proximal promoter, two of which have been recognized as essential in regulating basal promoter activity [12]. Sp1-4 factors may play a role in activating some signaling pathways and receptors and contribute to oncogenic properties of cancer cells [13]. Attenuation of Wnt/β-catenin signaling resulted in inhibition of survivin expression in several cell types, suggesting a positive regulation of survivin expression by this pathway in the tested cell lines [14,15]. Herceptin inhibited survivin expression through the ErbB2-β-catenin/TCF4 pathway in breast cancer cells, completely dependent on TCF-4 binding sites in the promoter [16]. CBP (CREB-binding protein) seems to be a crucial cofactor for β-catenin/TCF-mediated upregulation of survivin, whereas CBP paralog p300 protein has an inhibitory effect [17].

Another upregulated signaling in cancer is the PI3K/Akt/mTOR pathway, which has been demonstrated to activate survivin expression in small cell lung cancer (SCLC) [18]. IGF-I (insulin-like growth factor-I) activated survivin expression in prostate cancer cells [19,20]. KLF5 transcription factor displayed positive effect on survivin expression in leukemia cells [21], and in ovarian CSC (cancer stem cells) [22]. In chondrocytes, DEC1-mediated apoptosis protection was achieved through the activation of survivin expression. DEC1 was demonstrated to activate survivin promoter, supported by two Sp1 sites [23]. Further, E2F1 protein positively correlated with survivin expression [24] and E2F1-3 transcription factors increased survivin expression in embryonic fibroblasts [25]. SOX2, a stem cell factor, directly upregulated survivin expression [26]. Hypoxia has also been

reported to upregulate survivin and its promoter activity [27]. Pokemon is a pro-oncogenic transcription factor that was shown to bind the survivin promoter through the GT boxes and promoted survivin expression in MCF-7 breast cancer cells [28]. Interestingly, among various subtypes of non-small cell lung cancer (NSCLC), the survivin expression was higher in squamous cell carcinomas than in adenocarcinomas [29]. CK2 (casein kinase 2) promotes the survivin expression through the upregulation of β-catenin-dependent transcription [30,31]. Since the survivin promoter is also regulated negatively, mainly through the p53 protein, the positive transactivation effect of the HPV protein E6 on survivin is mediated via the p53 degradation [32]. Survivin expression was completely abolished by the knockdown of BRG1, a critical ATPase of the SWI/SNF-chromatin remodeling complex, indicating a direct regulation of survivin by an epigenetic mechanism [33]. Interestingly, Xu et al. [2] identified several polymorphisms in the survivin gene promoter, one of which is located at the repressor CDE/CHR element. This mutation was common among cancer cell lines, resulting in increased survivin transcription. Is has also been reported that the treatment of cancer cells with Hoechst33342, an AT-rich DNA-binding agent, upregulated survivin expression and promoter activity through the AT-rich DNA element in the survivin promoter [34].

Survivin expression, Hedgehog/GLI signaling pathway, and cancer stem cells

Recent studies have identified that the Hedgehog/GLI signaling cascade activates survivin transcription. We have identified many potential GLI-binding sites in the survivin promoter [35]. All sites contained 1-3 mismatched bases. However, it has been shown that these non-consensus GLI motifs are bound by GLI with similar affinity as consensus sites and lead to a strong transcriptional activation [36]. Across a wide panel of tumor cell lines, we found by using GANT61, a low molecular weight inhibitor of GLI factors, that survivin expression depends on GLI2 in at least one-half of tumor cell lines tested [35]. GLI2 associated with survivin promoter in chromatin immunoprecipitation assays and the expression of endogenous survivin could be easily evoked by ectopic GLI2 in human fibroblasts IMR90, where both survivin and GLI2 were normally silent. These findings have been supported by immunohistochemical staining, revealing correlation of GLI2 and survivin reactivity in tumor areas with a strong expression of both proteins [35]. Thus, survivin is a transcriptional target of GLI2 in a high proportion of various cancer cell lines including melanoma, NSCLC, SCLC, pancreas, and colorectal cancer and these findings may constitute a more general mechanism of survivin upregulation in tumors.

Many other target genes of Hedgehog/GLI pathway have been declared [37] but these might represent targets only in limited specific cell contexts. Survivin was described as a therapeutic target in Sonic Hedgehog-driven medulloblastoma [38], a tumor with invariant aberration of Hedgehog/GLI signaling, supporting our study. GANT61 was shown to induce caspase-independent apoptosis of SK-N-LO cells accompanied with a decrease of survivin [39]. The Hedgehog/GLI effector GLI1 is activated in malignant pleural mesothelioma and can be inhibited by SMO (Smoothened) inhibitors. SMO is a critical Hedgehog pathway membrane component. This SMO inhibition or GLI1 silencing resulted in reduced tumor growth and decreased survivin levels [40]. Overwhelming evidence points towards additional, noncanonical mechanisms of GLI1/2 factors activation, thus bypassing the necessity of upstream ligand signaling. Many cancer-deregulated pathways can directly activate GLI factors in tumor cells [41,42]. Therefore, GLI activity is not strictly dependent on the upstream SMO activation in tumor cells. Upregulated GLI proteins are associated with the invasive potential, epithelial-mesenchymal transition (EMT) and stemness of tumors [43,44]. Moreover, GLI2 is a direct activator of SOX2 transcription in telencephalic neuroepithelial cells and SOX2 expression decreases in the developing neuroepithelium of Gli2-deficient mice [4,45]. Additionally, it has been shown that SOX2 regulates self-renewal and tumorigenicity of human melanoma-initiating cells [46]. Of note, Notch1 cooperates with survivin to maintain stemness and stimulates proliferation of human keratinocytes [47]. Taken together, survivin, in a large part through the Hedgehog/GLI pathway, substantially contribute to the pro-oncogenic activities including stemness in human cancer.

Negative Regulation of Survivin Expression

It has long been known that a low or null survivin expression in normal tissues is maintained predominantly by the p53 protein [48-50]. This is mediated by the p53 target protein p21 [51]. If p21/CDKN1A gene is deleted, p53-mediated repression is abolished [51]. Unlike Notch1, Notch2 inhibited survivin transcription [52]. Further, Egr-1 (early growth response 1 transcription factor) is also a negative regulator of survivin transcription. Its repression is direct, as Egr-1 binds to the promoter *in vitro* and in cells [53]. Similarly, KLF4 transcription factor is capable of binding the survivin promoter and repressing the expression of the survivin gene [54]. Caveolin-1 inhibits expression of survivin via a transcriptional mechanism involving the beta-catenin-TCF pathway, dependent on E-cadherin [55]. Tumor suppressor PTEN, a dual specificity phosphatase which represses the AKT/mTOR pathway, also silences the expression of survivin, independently of p53. The repression involves direct occupancy of the survivin promoter by factors FOXO1 and FOXO3a [56]. Peculiar regulation of survivin expression was observed in normal melanocytes which express survivin. While E2F transcription factors normally upregulate survivin transcription (above), E2F2 is a negative regulator of survivin expression in melanocytes. This repression requires active Rb protein. On the other hand, in the absence of activating stimuli, p53 and Rb proteins repress survivin transcription in normal melanocytes [7]. Yang et al. have demonstrated that TGF-β rapidly downregulates survivin expression in prostate epithelial cells. This repression involves Rb/E2F4 repressive complex and the CDE/CHR motif in the survivin promoter which acts as repressor element [57].

Inhibitors of Survivin Expression

Because the inhibition of survivin expression reduces the tumor cell phenotype and because survivin may be a valid cancer therapeutic target, experiments were made to inhibit the survivin promoter by various agents. Hedamycin, a GC-rich DNA binding drug, downregulated survivin expression. Hedamycin-DNA interaction abrogated the binding of Sp1 to the survivin promoter and decreased its activity [58]. Further, selenium, a chemopreventive agent for many cancers, downregulated survivin expression similarly as hedamycin, i.e. via binding to the specific DNA site and preventing the association of Sp1 with DNA in the survivin promoter [59]. Anti-cancer antibiotics mithramycin A and doxorubicin also downregulated the endogenous survivin gene expression [60]. Since ras oncogenes augment the survivin levels, ras inhibitor farnesyl thiosalicylic acid has been tested in glioblastoma multiforme U87 cells. It substantially decreased the survivin protein level and induced caspase-dependent cell death [61].

Notably, natural flavonoid compound wogonin induced apoptosis accompanied by a significant decrease of survivin and increase of Bax and p53. LY294002, a specific PI3K inhibitor, significantly accelerated wogonin-induced cell apoptosis [62]. Importantly, a specific survivin suppressant YM155 (sepantronium bromide), already tested in clinical trials, robustly inhibits survivin activity at low concentrations and is a promising drug for the targeted therapy of tumors. YM155 inhibits survivin activity via disruption of Sp1-DNA interaction in the survivin core promoter [63].

Tumor-specific survivin promoter can be used in gene therapy

As survivin expression is strictly confined to the tumor tissue, attempts have been made to utilize the survivin promoter in vectors carrying tumor-deleterious agents such as oncolytic viruses in both *in vitro* and *in vivo* studies. The survivin promoter specificity has been verified by expressing SEAP (secreted alkaline phosphatase), showing no expression in normal cells and tissues and high expression in tumors in cell culture and in mice [1]. The tumor specificity of survivin expression was also tested in lung cancer cells with the vector expressing a luciferase gene driven by the survivin promoter and evaluated *in vitro* and *in vivo* [64]. High specificity for tumor tissue was observed, indicating that survivin promoter is a cancer-specific promoter and may be useful in cancer gene therapy. Lu at al. [65] tested four promoters for tumor cell specificity in melanoma cell lines and found survivin promoter as the best among others. Conditionally replicating survivin promoter-responsive adenovirus (CRA) exhibited cancer-selective replication and induction of cell death. Survivin-CRA efficiently replicated and potently induced cell death in most types of cancer whereas the minimal viral replication in normal cells did not induce any detectable cytotoxicity [66]. Similarly, recombinant adenoviral vector in which survivin promoter and a luciferase reporter gene were inserted into the E1-deleted region of the adenovirus vector exerted results positive only for the tumor tissue [67]. A specific adenoviral vector, in which E1A and E4 protein expression was dependent on survivin promoter activity, was replicated more than 100-fold better in bladder tumor cells than in normal cells [68]. It implies that the survivin promoter may be utilized for the construction of a replication-competent adenovirus to treat bladder cancers. The last three studies [66-68] were performed both *in vitro* and *in vivo*. Taken together, survivin promoter may prove to be a good candidate for transcriptional targeting in cancer gene therapy of a variety of tumors.

Concluding Remarks and Future Perspectives

The data showing that survivin expression and Hedgehog signaling pathway are linked through the transcription factor GLI2, which activate endogenous survivin expression and can ectopically evoke survivin in normal, survivin non-expressing cells [35], could open new ways of tumor therapy. Chemical inhibitors of GLI2 and survivin are available and may act in synergy during treatment. In some tumor cells transcription factors other than GLI2 may keep the high survivin expression, dependent on the cell context. This might be highly individual for each tumor. Furthermore, survivin promoter has been shown to be highly specific for tumor cells and tissue *in vitro* and *in vivo* in several studies [1,64-68], having a therapeutic potential in gene therapy. So, we ought to continue exploring survivin protein as a target of treatment and survivin promoter as a carrier of deleterious agents to tumor cells.

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References

1. Bao R, Connolly DC, Murphy M, Green J, Weinstein JK, et al. (2002) Activation of cancer-specific gene expression by the survivin promoter. J Natl Cancer Inst 94: 522-528.
2. Xu Y, Fang F, Ludewig G, Jones G, Jones D (2004) A mutation found in the promoter region of the human survivin gene is correlated to overexpression of survivin in cancer cells. DNA Cell Biol 23: 419-429.
3. Caldas H, Jiang Y, Holloway MP, Fangusaro J, Mahotka C, et al. (2005) Survivin splice variants regulate the balance between proliferation and cell death. Oncogene 24: 1994-2007.
4. Altieri DC (2008) New wirings in the survivin networks. Oncogene 27: 6276-6284.
5. Adida C, Crotty PL, McGrath J, Berrebi D, Diebold J, et al. (1998) Developmentally regulated expression of the novel cancer anti-apoptosis gene survivin in human and mouse differentiation. Am J Pathol 152: 43-49.
6. Boidot R, Végran F, Lizard-Nacol S (2014) Transcriptional regulation of the survivin gene. Mol Biol Rep 41: 233-240.
7. Chen X, Duan N, Zhang C, Zhang W (2016) Survivin and Tumorigenesis: Molecular Mechanisms and Therapeutic Strategies. J Cancer 7: 314-323.
8. Raj D, Liu T, Samadashwily G, Li F, Grossman D (2008) Survivin repression by p, Rb and E2F2 in normal human melanocytes. Carcinogenesis 29: 194-201.
9. Parfitt JR, Driman DK (2007) Survivin and hedgehog protein expression in serrated colorectal polyps: an immunohistochemical study. Hum Pathol 38: 710-717.
10. Altieri DC (2010) Survivin and IAP proteins in cell-death mechanisms. Biochem J 430: 199-205.
11. Ambrosini G, Adida C, Altieri DC (1997) A novel anti-apoptosis gene, survivin, expressed in cancer and lymphoma. Nat Med 3: 917-921.
12. Xu R, Zhang P, Huang J, Ge S, Lu J, et al. (2007) Sp1 and Sp3 regulate basal transcription of the survivin gene. Biochem Biophys Res Commun 356: 286-292.
13. Safe S, Abdelrahim M (2005) Sp transcription factor family and its role in cancer. Eur J Cancer 41: 2438-2448.
14. Lee SC, Kim OH, Lee SK, Kim SJ (2015) IWR-1 inhibits epithelial-mesenchymal transition of colorectal cancer cells through suppressing Wnt/Î²-catenin signaling as well as survivin expression. Oncotarget 6: 27146-27159.
15. Hseu YC, Thiyagarajan V, Tsou HT, Lin KY, et al. (2016) *In vitro* and *in vivo* anti-tumor activity of CoQ0 against melanoma cells: inhibition of metastasis and induction of cell-cycle arrest and apoptosis through modulation of Wnt/β-catenin signaling pathways. Oncotarget.
16. Zhu H, Zhang G, Wang Y, Xu N, He S, et al. (2010) Inhibition of ErbB2 by Herceptin reduces survivin expression via the ErbB2-beta-catenin/TCF4-survivin pathway in ErbB2-overexpressed breast cancer cells. Cancer Sci 101: 1156-1162.
17. Ma H, Nguyen C, Lee KS, Kahn M (2005) Differential roles for the coactivators CBP and p300 on TCF/beta-catenin-mediated survivin gene expression. Oncogene 24: 3619-3631.
18. Belyanskaya LL, Hopkins-Donaldson S, Kurtz S, Simões-Wüst AP, Yousefi S, et al. (2005) Cisplatin activates Akt in small cell lung cancer cells and attenuates apoptosis by survivin upregulation. Int J Cancer 117: 755-763.

19. Vaira V, Lee CW, Goel HL, Bosari S, Languino LR, et al. (2007) Regulation of survivin expression by IGF-1/mTOR signaling. Oncogene 26: 2678-2684.
20. Song K, Shankar E, Yang J, Bane KL, Wahdan-Alaswad R, et al. (2013) Critical role of a survivin/TGF-Î²/mTORC1 axis in IGF-I-mediated growth of prostate epithelial cells. PLoS One 8: e61896.
21. Zhu N, Gu L, Findley HW, Chen C, Dong JT, et al. (2006) KLF5 Interacts with p53 in regulating survivin expression in acute lymphoblastic leukemia. J Biol Chem 281: 14711-14718.
22. Dong Z, Yang L, Lai D (2013) KLF5 strengthens drug resistance of ovarian cancer stem-like cells by regulating survivin expression. Cell Prolif 46: 425-435.
23. Li Y, Xie M, Yang J, Yang D, Deng R, et al. (2006) The expression of antiapoptotic protein survivin is transcriptionally upregulated by DEC1 primarily through multiple sp1 binding sites in the proximal promoter. Oncogene 25: 3296-3306.
24. Huang CL, Liu D, Nakano J, Yokomise H, Ueno M, et al. (2007) E2F1 overexpression correlates with thymidylate synthase and survivin gene expressions and tumor proliferation in non-small-cell lung cancer. Clin Cancer Res 13: 6938-6946.
25. Jiang Y, Saavedra HI, Holloway MP, Leone G, Altura RA (2004) Aberrant regulation of survivin by the RB/E2F family of proteins. J Biol Chem 279: 40511-40520.
26. Feng R, Zhou S, Liu Y, Song D, Luan Z, et al. (2013) Sox2 protects neural stem cells from apoptosis via up-regulating survivin expression. Biochem J 450: 459-468.
27. Yang L, Cao Z, Li F, Post DE, Van Meir EG, et al. (2004) Tumor-specific gene expression using the survivin promoter is further increased by hypoxia. Gene Ther 11: 1215-1223.
28. Zu X, Ma J, Liu H, Liu F, Tan C, et al. (2011) Pro-oncogene Pokemon promotes breast cancer progression by upregulating survivin expression. Breast Cancer Res 13: R26.
29. Nakano J, Huang CL, Liu D, Ueno M, Sumitomo S, et al. (2005) Survivin gene expression is negatively regulated by the p53 tumor suppressor gene in non-small cell lung cancer. Int J Oncol 27: 1215-1221.
30. Tapia JC, Torres VA, Rodriguez DA, Leyton L, Quest AF (2006) Casein kinase 2 (CK2) increases survivin expression via enhanced beta-catenin-T cell factor/lymphoid enhancer binding factor-dependent transcription. Proc Natl Acad Sci U S A 103: 15079-15084.
31. Ponce DP, Yefi R, Cabello P, Maturana JL, Niechi I, et al. (2011) CK2 functionally interacts with AKT/PKB to promote the Î²-catenin-dependent expression of survivin and enhance cell survival. Mol Cell Biochem 356: 127-132.
32. Borbély AA, Murvai M, Kónya J, Beck Z, Gergely L, et al. (2006) Effects of human papillomavirus type 16 oncoproteins on survivin gene expression. J Gen Virol 87: 287-294.
33. Ondrusova L, Vachtenheim J, Reda J, Zakova P, Benkova K (2013) MITF-independent pro-survival role of BRG1-containing SWI/SNF complex in melanoma cells. PLoS One 8: e54110.
34. Wu J, Apontes P, Song L, Liang P, Yang L, et al. (2007) Molecular mechanism of upregulation of survivin transcription by the AT-rich DNA-binding ligand, Hoechst33342: evidence for survivin involvement in drug resistance. Nucleic Acids Res 35: 2390-2402.
35. Vlckova K, Ondrusova L, Vachtenheim J, Reda J, Dundr P, et al. (2016) Survivin, a novel target of the Hedgehog/GLI signaling pathway in human tumor cells. Cell Death Dis 7: e2048.
36. Winklmayr M, Schmid C, Laner-Plamberger S, Kaser A, Aberger F, et al. (2010) Non-consensus GLI binding sites in Hedgehog target gene regulation. BMC Mol Biol 11: 2.
37. Katoh Y, Katoh M (2009) Hedgehog target genes: mechanisms of carcinogenesis induced by aberrant hedgehog signaling activation. Curr Mol Med 9: 873-886.
38. Brun SN, Markant SL, Esparza LA, Garcia G, Terry D, et al. (2015) Survivin as a therapeutic target in Sonic hedgehog-driven medulloblastoma. Oncogene 34: 3770-3779.
39. Matsumoto T, Tabata K, Suzuki T (2014) The GANT, a GLI inhibitor, induces caspase-independent apoptosis of SK-N-LO cells. Biol Pharm Bull 37: 633-641.
40. Shi Y, Moura U, Opitz I, Soltermann A, Rehrauer H, et al. (2012) Role of hedgehog signaling in malignant pleural mesothelioma. Clin Cancer Res 18: 4646-4656.
41. Lauth M, Toftgård R (2007) Non-canonical activation of GLI transcription factors: implications for targeted anti-cancer therapy. Cell Cycle 6: 2458-2463.
42. Robbins DJ, Fei DL, Riobo NA (2012) The Hedgehog signal transduction network. Sci Signal 5: re6.
43. Nanta R, Kumar D, Meeker D, Rodova M, Van Veldhuizen PJ, et al. (2013) NVP-LDE-225 (Erismodegib) inhibits epithelial-mesenchymal transition and human prostate cancer stem cell growth in NOD/SCID IL2RÎ³ null mice by regulating Bmi-1 and microRNA-128. Oncogenesis 2: e42.
44. Lotti R, Palazzo E, Petrachi T, Dallaglio K, Saltari A, et al. (2016) Survivin Modulates Squamous Cell Carcinoma-Derived Stem-Like Cell Proliferation, Viability and Tumor Formation *in Vivo*. Int J Mol Sci 17.
45. Takanaga H, Tsuchida-Straeten N, Nishide K, Watanabe A, Aburatani H, et al. (2009) Gli2 is a novel regulator of sox2 expression in telencephalic neuroepithelial cells. Stem Cells 27: 165-174.
46. Santini R, Pietrobono S, Pandolfi S, Montagnani V, D'Amico M, et al. (2014) SOX2 regulates self-renewal and tumorigenicity of human melanoma-initiating cells. Oncogene 33: 4697-4708.
47. Palazzo E, Morandi P, Lotti R, Saltari A, Truzzi F, et al. (2015) Notch Cooperates with Survivin to Maintain Stemness and to Stimulate Proliferation in Human Keratinocytes during Ageing. Int J Mol Sci 16: 26291-26302.
48. Mirza A, McGuirk M, Hockenberry TN, Wu Q, Ashar H, et al. (2002) Human survivin is negatively regulated by wild-type p53 and participates in p53-dependent apoptotic pathway. Oncogene 21: 2613-2622.
49. Hoffman WH, Biade S, Zilfou JT, Chen J, Murphy M (2002) Transcriptional repression of the anti-apoptotic survivin gene by wild type p53. J Biol Chem 277: 3247-3257.
50. Fischer M, Quaas M, Nickel A, Engeland K (2015) Indirect p53-dependent transcriptional repression of Survivin, CDC25C, and PLK1 genes requires the cyclin-dependent kinase inhibitor p21/CDKN1A and CDE/CHR promoter sites binding the DREAM complex. Oncotarget 6: 41402-41417.
51. Löhr K, Möritz C, Contente A, Dobbelstein M (2003) p21/CDKN1A mediates negative regulation of transcription by p53. J Biol Chem 278: 32507-32516.
52. Quillard T, Devalliere J, Chatelais M, Coulon F, Séveno C, et al. (2009) Notch2 signaling sensitizes endothelial cells to apoptosis by negatively regulating the key protective molecule survivin. PLoS One 4: e8244.
53. Wagner M, Schmelz K, Dörken B, Tamm I (2008) Transcriptional regulation of human survivin by early growth response (Egr)-1 transcription factor. Int J Cancer 122: 1278-1287.
54. Zhang G, Zhu H, Wang Y, Yang S, Liu M, et al. (2009) Krüppel-like factor 4 represses transcription of the survivin gene in esophageal cancer cell lines. Biol Chem 390: 463-469.
55. Torres VA, Tapia JC, Rodriguez DA, Lladser A, Arredondo C, et al. (2007) E-cadherin is required for caveolin-1-mediated down-regulation of the inhibitor of apoptosis protein survivin via reduced beta-catenin-Tcf/Lef-dependent transcription. Mol Cell Biol 27: 7703-7717.
56. Guha M, Plescia J, Leav I, Li J, Languino LR, et al. (2009) Endogenous tumor suppression mediated by PTEN involves survivin gene silencing. Cancer Res 69: 4954-4958.
57. Yang J, Song K, Krebs TL, Jackson MW, Danielpour D (2008) Rb/E2F4 and Smad2/3 link survivin to TGF-beta-induced apoptosis and tumor progression. Oncogene 27: 5326-5338.
58. Wu J, Ling X, Pan D, Apontes P, Song L, et al. (2005) Molecular mechanism of inhibition of survivin transcription by the GC-rich sequence-selective DNA binding antitumor agent, hedamycin: evidence

of survivin down-regulation associated with drug sensitivity. J Biol Chem 280: 9745-9751.

59. Chun JY, Hu Y, Pinder E, Wu J, Li F, et al. (2007) Selenium inhibition of survivin expression by preventing Sp1 binding to its promoter. Mol Cancer Ther 6: 2572-2580.
60. Estève PO, Chin HG, Pradhan S (2007) Molecular mechanisms of transactivation and doxorubicin-mediated repression of survivin gene in cancer cells. J Biol Chem 282: 2615-2625.
61. Blum R, Jacob-Hirsch J, Rechavi G, Kloog Y (2006) Suppression of survivin expression in glioblastoma cells by the Ras inhibitor farnesylthiosalicylic acid promotes caspase-dependent apoptosis. Mol Cancer Ther 5: 2337-2347.
62. Huang KF, Zhang GD, Huang YQ, Diao Y (2012) Wogonin induces apoptosis and down-regulates survivin in human breast cancer MCF-7 cells by modulating PI3K-AKT pathway. Int Immunopharmacol 12: 334-341.
63. Cheng Q, Ling X, Haller A, Nakahara T, Yamanaka K, et al. (2012) Suppression of survivin promoter activity by YM155 involves disruption of Sp1-DNA interaction in the survivin core promoter. Int J Biochem Mol Biol 3: 179-197.
64. Chen JS, Liu JC, Shen L, Rau KM, Kuo HP, et al. (2004) Cancer-specific activation of the survivin promoter and its potential use in gene therapy. Cancer Gene Ther 11: 740-747.
65. Lu B, Makhija SK, Nettelbeck DM, Rivera AA, Wang M, et al. (2005) Evaluation of tumor-specific promoter activities in melanoma. Gene Ther 12: 330-338.
66. Kamizono J, Nagano S, Murofushi Y, Komiya S, Fujiwara H, et al. (2005) Survivin-responsive conditionally replicating adenovirus exhibits cancer-specific and efficient viral replication. Cancer Res 65: 5284-5291.
67. Zhu ZB, Makhija SK, Lu B, Wang M, Kaliberova L, et al. (2004) Transcriptional targeting of tumors with a novel tumor-specific survivin promoter. Cancer Gene Ther 11: 256-262.
68. Seo HK, Seo JB, Nam JK, Jeong KC, Shin SP, et al. (2014) Development of replication-competent adenovirus for bladder cancer by controlling adenovirus E1a and E4 gene expression with the survivin promoter. Oncotarget 5: 5615-5623.