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Mini Review

Sp1: Emerging roles—Beyond constitutive activation of TATA-less housekeeping genes

Inken Wierstra *

Wißmannstr. 17, D-30173 Hannover, Germany

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The transcription factor Sp1

The transcription factor Sp1 (specificity protein 1) is ubiquitously expressed and possesses three C_2H_2-type zinc fingers as DBD (DNA-binding domain) [1–5]. Sp1 binds to GC-boxes with the consensus sequence 5′-G/T-**GGGCGG**-G/A-G/A-C/T-3′ or 5′-G/T-G/A-**GGCG**-G/T-G/A-G/A-C/T-3′ [6,7]. It binds also to CT-boxes and GT-boxes, but with significantly lower affinities. For example, the CT-box 5′-GGGG**A**GGGGC-3′ and the GT-box 5′-GGGG**T**GGGGC-3′ are bound threefold or sixfold more weakly, respectively, than the GC-box (5′-GGGG**C**GGGGC-3′ [8].

The transactivator Sp1 has two glutamine-rich TADs (transactivation domains), namely the domains A and B [3,9,10], which each interact directly with both TBP (TATA-binding protein) [11,12] and TAF4 (TBP-associated factor 4) (Fig. 1) [13–20].

The transcriptional activity of Sp1 is regulated by post-translational modifications as well as by interactions with other proteins, among them many tumor suppressors and oncogenes (Fig. 2, see below) [21–28].

The Sp/KLF transcription factor family

The expression level of the ubiquitous Sp1 has been found to be regulated in several biological settings [21,22,24,25,28]. However, often different studies reported contradictory results. Moreover, Sp1 is a member of the Sp/KLF (Krüppel-like factor) transcription factor family, whose members share a highly conserved DBD (sequence identity more than 65%) with three adjacent Cys_2His_2-type zinc fingers so that they bind to GC- and/or GT-boxes with overlapping specificities and affinities [21,29–34]. Consequently, it is insufficient to know only the Sp1 expression because the final outcome will be determined by the current ratio of the expression and activity of Sp1 to the expression and activity of other family members.

The Sp/KLF family is subdivided into the Sp family, which favors GC-boxes, and the KLF family, which prefers GT-boxes and comprises activators as well as repressors [21,30,32]. Nevertheless, at least the three KLF family members KLF9, KLF10 and KLF11 have a DNA-binding specificity very similar, if not identical, to Sp1 so that they recognize classical GC-boxes, too [29,30,35].

The Sp transcription factor family

The Sp family is subdivided into Sp1–4 and Sp5–9, which either contain or lack N-terminal glutamine-rich TADs, respectively

* Fax: +49 511 883536.
E-mail address: iwiwiwi@web.de.

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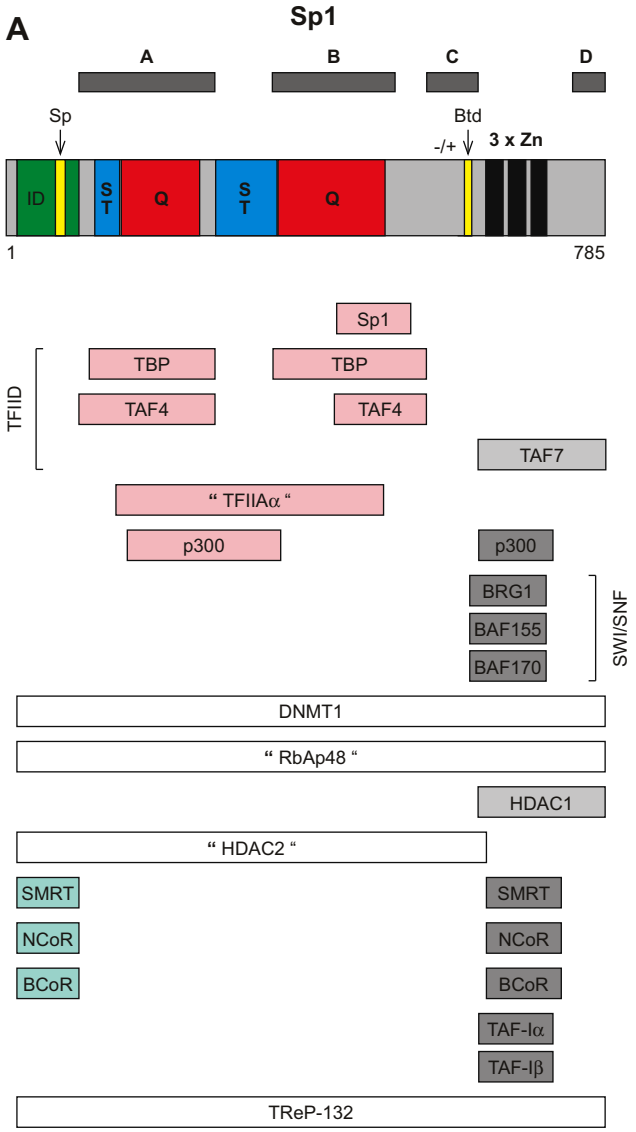
[21,22,24,25,28,35,36]. In the first group, Sp1, Sp3 and Sp4, which possess two glutamine-rich TADs, bind to GC- and GT-boxes with identical high or low affinities, respectively [37]. In contrast, Sp2, which has only one such TAD, exhibits a different DNA-binding specificity and does not bind to GC-boxes [38]. Both Sp1 and Sp3 are ubiquitously expressed whereas Sp4 displays a very tissue-restricted expression pattern and is abundant predominantly in the brain [37].



B

domain	own trans-activation potential	trans-activation via a single binding site	synergistic trans-activation via multiple binding sites	superactivation	
				DNA-bound molecule	super-activator
A	strong	required	required	either A or B required	both A plus B required
B	strong	required	required		
C	weak	not required	not required	not required	not required
D	none	not required	required		

Sp1 and Sp3

The ubiquitous transcription factors Sp1 and Sp3 exhibit very similar, if not identical, DNA-binding specificities and affinities so that they compete for binding to the same GC-, CT- and GT-boxes [37–44]. Therefore, the Sp1:Sp3 ratio plays an important role in gene regulation [21,22,24,25,28,35,36]: the outcome depends on cellular context and promoter architecture, which can determine distinct behavior of Sp3. On some promoters, Sp3 cooperates with Sp1 whereas Sp3 suppresses the Sp1-mediated transactivation of other promoters. Similarly, promoters differ with respect to the ability of Sp3 to substitute for Sp1 or not. Additionally, several different isoforms of Sp3 exist [45].

In general, Sp3 represses the Sp1-mediated transactivation of promoters with two or more Sp1 sites (e.g. *c-myc*, *c-src*, *dhfr* (*dihydrofolate reductase*), *odc* (*ornithine decarboxylase*)) (Fig. 4), but does not affect the Sp1-mediated transactivation of promoters with only one Sp1 site (e.g. *tk* (*hymidine kinase*), *histone H4*) [39–42,44,46,47,49]. Sp3 possesses an ID (inhibitory domain) that can repress its two TADs so that Sp3 transactivates reporter constructs with a single Sp1 site, but not those with at least two Sp1 sites [39,48,49]. Moreover, Sp3 lacks the ability of Sp1 to transactivate synergistically via two or more Sp1 sites [39,44,49]. Consequently, if Sp3 displaces Sp1 from promoters with at least two Sp1 sites the stronger transactivator Sp1 is replaced by the weaker transactivator Sp3 resulting in a net repression of the initial Sp1-mediated transactivation.

Sp1 and the basal transcription machinery

Sp1 is a transactivator [2,3]. It binds directly to other Sp1 molecules and forms homooligomers [9,10,17,44,50–52]. First, Sp1 transactivates simply via a single Sp1-binding site [3,9,10]. Second, it transactivates synergistically with itself via two or more Sp1-binding sites without cooperative DNA-binding [3,9,10,44]. Third, it superactivates the Sp1-mediated transcription [9,10]. For superactivation one Sp1 molecule binds to DNA whereas the superactivator does not bind to DNA, but interacts with the DNA-bound Sp1 molecule [9,10].

Four domains of Sp1 are involved in transcriptional activation (Fig. 1) [3]: the domains A and B represent the two strong glutamine-rich TADs [3,9,10], which each interact directly with both TBP [11,12] and TAF4 [13–20]. They are required for transactivation via one Sp1-binding site, for synergistic transactivation via at least two Sp1-binding sites and for superactivation [3,9,10]. Domain D lacks any own transactivation potential and is dispensable

Fig. 1. Functional domains of Sp1 and interactions of Sp1 with general transcription factors, co-regulators and chromatin remodeling factors. (A) Sp1 has 785 amino acids. ID, inhibitory domain, green [54,55]; ST, serine/threonine-rich domain, blue; Q, glutamine-rich domain, red; 3 × Zn, 3 C_2H_2-type zinc fingers, DBD, black [1–5]; Sp, Sp box, yellow; Btd, Buttonhead box, yellow. The Sp box contains an endoproteolytic cleavage site [22]. The Buttonhead box is conserved in all Sp family members [22]. The domains A, B, C, and D (dark gray boxes) are involved in transcriptional activation (summarized in B) [3,9,10]. Domain C is highly charged (−/+) with 12 negative and six positive charges in a 69 residue stretch [3]. The coloring indicates to which domain of Sp1 the interaction partners bind: green, ID; red, glutamine-rich TADs A or/and B; dark gray, DBD; light gray, DBD and/or domain D. All the protein–protein interactions are direct with the exception of the binding to TFIIAα, RbAp48 and HDAC2, which has not been demonstrated to be direct (quotation marks). For references see Supplementary data. (B) The domains A and B represent the TADs of Sp1 [3,9,10]. Domain D is dispensable for transactivation via a single Sp1-binding site, but is essential for synergistic transactivation via two or multiple Sp1-binding sites [3,9,10,53].

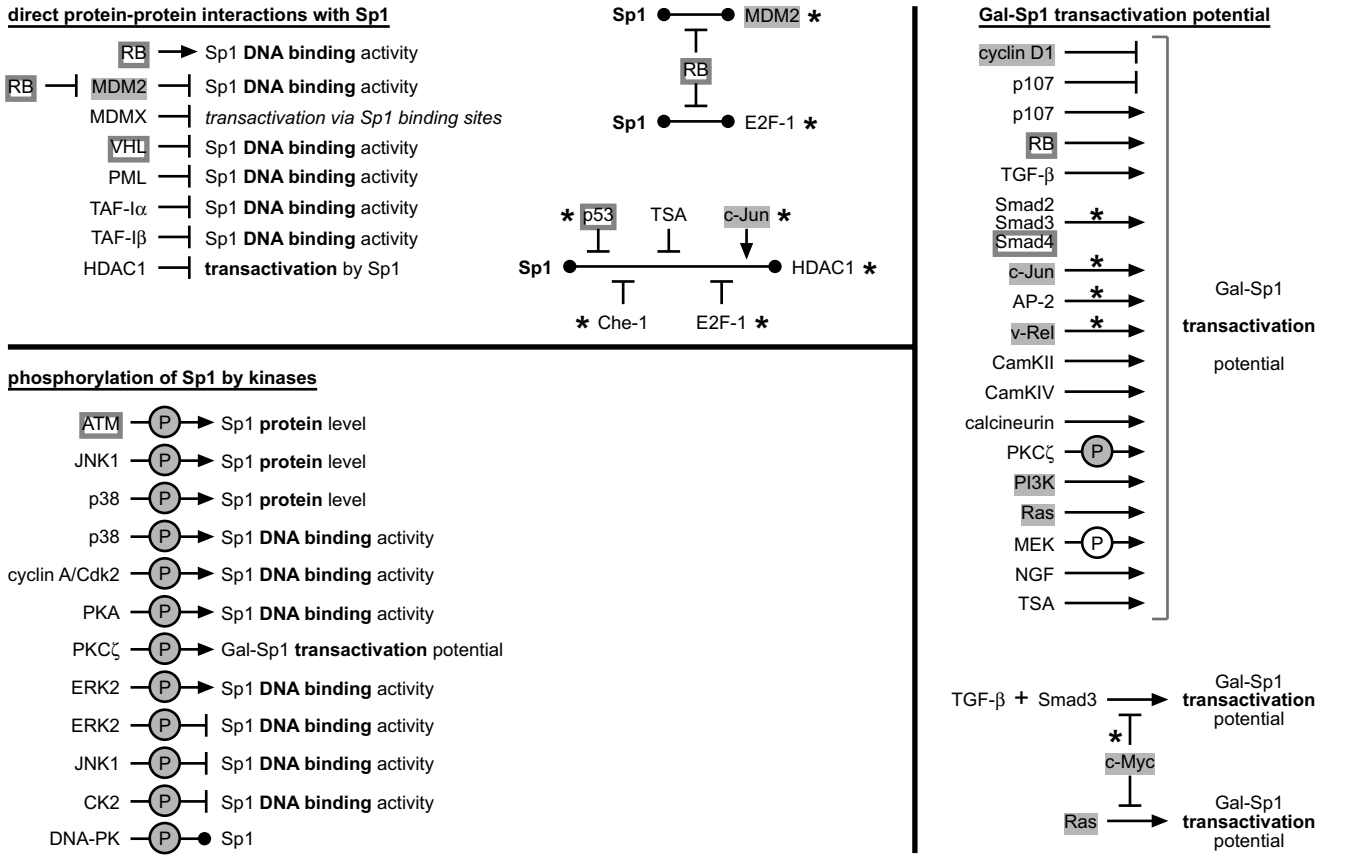


Fig. 2. Regulation of Sp1. Arrows and —| signs depict positive or negative effects, respectively. Tumor suppressors (dark gray frame) and oncogenes (light gray boxes) are marked. For references see Supplementary data. Direct protein–protein interactions of Sp1: Left part: Listed are proteins that bind to Sp1 directly (see Supplementary Table 1) and their effects on Sp1. HDAC1 is unlikely to interfere with the DNA-binding by Sp1 because Sp1 recruits HDAC1 to its target genes. MDMX (MDM4), which is similar to MDM2, may also inhibit the DNA-binding by Sp1. Right part: Direct protein–protein interactions with Sp1 are shown as lines with needle heads. The disruption of these interactions by competing proteins is depicted by —| signs. c-Jun strengthens the interaction between Sp1 and HDAC1 (arrow) [87]. Asterisks indicate proteins that bind to Sp1 directly. RB binds directly to E2F-1 [239,240] and MDM2 [162,241], but not to Sp1 [242,243]. TSA (trichostatin A) is a HDAC inhibitor. Phosphorylation of Sp1 by kinases: Listed are kinases that phosphorylate (P) Sp1 and their effects on Sp1. The outcome of the phosphorylation by DNA-PK is unclear. PKCζ, protein kinase C ζ; JNK1, c-Jun N-terminal kinase 1; CK2, casein kinase 2; DNA-PK, DNA-dependent protein kinase. Gal-Sp1 transactivation potential: The transcriptional activity of Sp1 (via Sp1-binding sites) depends on both the DNA-binding activity and the transactivation potential of Sp1. In contrast, the transactivation by Gal-Sp1-fusion proteins depends only on the transactivation potential of Sp1, but is independent of the DNA-binding by Sp1, because Gal-Sp1-fusion proteins bind to DNA via their heterologous DBD of yeast GAL4. Asterisks depict direct protein-protein interactions. The white circle indicates the phosphorylation (P) of Sp1 by ERK2, which is activated by MEK (MAPK (mitogen-activated protein kinase)/ERK kinase). CamK, Ca^{2+}/calmodulin-dependent kinase; PI3K, phosphatidylinositol-3 kinase; NGF, nerve growth factor.

for transactivation via a single Sp1 site and for superactivation [9,10]. However, domain D is essential for synergistic transactivation via two or multiple Sp1 sites [3,9,10,53]. In contrast, domain C possesses a low transactivation potential but is required neither for transactivation via one Sp1 site nor for synergistic transactivation via at least two Sp1 sites nor for superactivation [3,9,10].

The extreme N-terminus of Sp1 represents an ID and suppresses the transactivation by the TADs A and B [54,55]. Consistently, this ID interacts directly with the corepressors SMRT (silencing mediator of retinoid and thyroid receptor), NCoR (nuclear hormone receptor corepressor) and BCoR (BCL-6 interacting corepressor) (Fig. 1A) [56].

The directly contacted TAF4 is essential for Sp1-driven *in vitro* transcription [14,57,58]. In addition, Sp1 binds directly to TAF7 [59], but not to TAF1, TAF2 [14], TFIIB (transcription factor IIB) [60–62] or TFIIF [63] (Fig. 1A). Accordingly, Sp1 recruits TBP/TFIID and stimulates transcription initiation, but not transcriptional elongation [63–70]. This efficient recruitment of TFIID explains the well-known ability of Sp1 to induce the transcription of TATA-less genes.

Sp1 increases also the stable assembly of TFIIB and TFIIE into the preinitiation complex [61]. In a yeast two-hybrid assay, Sp1 interacted with TFIIAα (Fig. 1A) [71]. This interaction could be indirect because Sp1 directly binds TBP and TAF4, which in turn both directly bind TFIIA. Anyway, TFIIA was found to enhance the Sp1-driven *in vitro* transcription [72].

The Sp1-driven *in vitro* transcription from both naked and chromatin templates requires the Mediator (CRSP, cofactor required for Sp1) [73–79]. However, a direct interaction between Sp1 and subunits of the Mediator was not found [74,75,80]. The Mediator subunit MED23 (DRIP-130) is required for transactivation of the *KiSS-1* (*metastin*, *kisspeptin*) promoter by Sp1 [81] although at least domain A of Sp1 does not bind to MED23 (CRSP130) [75].

The Mediator (CRSP) is required for synergistic activation of *in vitro* transcription from chromatin templates by Sp1 + NF-κB (nuclear factor-κB) [75] and by Sp1 + SREBP-1a (sterol regulatory element-binding protein-1a) [74,75,78–80,82–84] (Table 1). This synergism of Sp1 + SREBP-1a requires also CBP (CREB (cAMP response element-binding protein)-binding protein) [74,80].

In one study, PC4 (positive cofactor 4) stimulated the Sp1-driven *in vitro* transcription from a naked template and PC4 and the Mediator (PC2) together exerted an additive or synergistic effect [73]. In contrast, in another study, low and high concentrations of PC4 did not affect or even inhibited, respectively, the Sp1-driven *in vitro* transcription from a naked template [76].

Table 1
Sp1 transactivates synergistically with other transcription factors

Synergistic transactivation by Sp1 +	Target gene		Direct interaction of Sp1 with		References
FOXM1c	c-Myc		FOXM1c	Forkhead box M1c	[214,244]
E2F-1	N-Myc		E2F-1		[245–248]
	TK	thymidine kinase			
	DHFR	dihydrofolate reductase			
E2F-1/DP-1	c-Myc		E2F-1		[41,249]
	$p18^{INK4c}$				
p53	p21		p53		[106,195–197]
	PUMA	p53-upregulated mediator of apoptosis			
p73α	p21		p73α		[197]
p73β	p21		p73β		[197]
c-Jun/c-Fos	CD11c	α-subunit of the leukocyte integrin p150,95	c-Jun		[149]
Smad3 + Smad4	COL1A2	α2(I) collagen	Smad3, Smad4		[145]
Smad2 + Smad3 + Smad4	p15		Smad2, Smad3, Smad4		[143]
GATA-1	α-globin		GATA-1		[250,251]
	γ-globin				
	EpoR	erythropoietin receptor			
NF-YA + NF-YB + NF-YC	CBS-1b	cystathionine-β-synthase-1b	NF-YA, NF-YC	nuclear factor-Y	[252–258]
	PKM	pyruvate kinase M			
	ChREBP	carbohydrate response element-binding protein			
	NPR-A	natriuretic peptide receptor-A guanylyl cyclase A			
RelA (p65)	HIV-1 LTR	human immunodeficiency virus type-1 long terminal repeat	RelA	NF-κB, nuclear factor-κB	[74,75,80,138–140]
HNF-4	apoCIII	apolipoprotein CIII	HNF-4	hepatocyte nuclear factor-4	[259]
SREBP-1a	ChREBP		[a]	sterol regulatory element-binding protein-1a	[258,260–263]
	FAS	fatty acid synthase			
	AceCS1	acetyl-CoA synthetase 1			
	ACC	acetyl coenzyme A carboxylase			
SREBP-1a	LDLR	low density lipoprotein receptor	[a]		[74,75,78–80,82–84,262,264–267]
NeuroD1	secretin		NeuroD1		[268]
HTLF	PAI-1	plasminogen activator inhibitor-1	HTLF	helicase-like transcription factor	[269]
HMGI-Y	IR	insulin receptor	HMGI-Y	high mobility group I-Y	[270]
AP-2	AM	adrenomedullin	AP-2	activator protein-2	[148]
Oct-1	U2 snRNA	U2 small nuclear RNA	Oct-1	octamer-binding protein-1	[141,271,272]
Sp1	p21		Sp1	specificity protein 1	[3,9,10,53]
	SV40 early	simian virus 40 early transcription unit			

[a] A direct interaction of SREBP-1a with Sp1 in solution could not be demonstrated, but Sp1 and SREBP-1a are thought to interact directly if they are bound to DNA [265].

Sp1 and chromatin remodeling

Sp1 binds directly to p300 (Fig. 1A) [85–88], which functions as a coactivator for each of the two Sp1 TADs A and B [85,89] and which is required for transactivation of the *p21* and *12(S)-lipoxygenase* promoters by Sp1 [87,90]. The coactivator CBP/p300 is a HAT (histone acetyltransferase) and Sp1 stimulates the HAT activity of CBP [91] although at least domain A of Sp1 does not bind to CBP [74,80]. Sp1 binds also directly to TReP-132 (132-kDa transcriptional regulating protein), which functions as a coactivator for Sp1 in transactivation of the *p21* and *p27* promoters [92].

Moreover, Sp1 recruits the ATP-dependent chromatin remodeling complex SWI/SNF (switching defective/sucrose nonfermenting) [93,94]. Sp1 binds directly to the SWI/SNF subunits BAF155, BAF170 and BRG1 (Brahma-related gene 1) (Fig. 1A) [93–96]. BRG1 is one of the two alternative SWI/SNF ATPases In contrast, at least the DBD of Sp1 does not bind to the other SWI/SNF ATPase BRM (Brahma) [94]. BRG1, BAF155 and BAF170 are part of both SWI/SNF complexes, i.e. BAF (BRG1-associated factor, SWI/SNF-A) and PBAF (polybromo- and BAF-containing complex, SWI/SNF-B). However, Sp1-driven *in vitro* transcription from a chromatin template requires specifically PBAF whereas neither BAF nor the ISWI (imitation switch) complex ACF (ATP-utilizing chromatin assembly and remodeling factor) can substitute [78]. The synergistic activation of *in vitro* transcription by Sp1 + SREBP-1a from a chromatin template displays the same specific requirement of PBAF [78]. At the BRG1-activated *MMP-2* (*matrix metalloproteinase* 2) promoter, BRG1 enhances the binding of Sp1, but decreases the association of Sp3 [96].

Furthermore, Sp1 binds directly to the histone chaperones TAF-Iα (template-activating factor-Iα) and TAF-Iβ (Fig. 1A), which both inhibit the binding of Sp1 to DNA (Fig. 2) [97].

Sp1 is capable of binding nucleosomal DNA [98] and exhibits a robust genuine boundary activity, i.e. it can block the spreading of heterochromatin and establish a localized nonsilenced chromatin domain (“euchromatin”) within a heterochromatic region [99]. In consistence, Sp1-binding sites protect CpG islands from methylation [100,101].

Sp1 is not only involved in the positive regulation of genes, but also in their negative regulation. Accordingly, Sp1 binds directly to HDAC1 (histone deacetylase 1) [87,102–106] and DNMT1 (DNA methyltransferase 1) (Fig. 1A) [107,108]. Sp1 is implicated in the HDAC-dependent repression of the *p21* [106,109–112], *SSeCKS* (*Src-suppressed C kinase substrate*) [113], *TK* [102] and *hTERT* (*human telomerase reverse transcriptase*) [104,114–121] promoters (Figs. 2 and 4) whereas Sp1 represses the *MAZ* (*Myc-associated zinc finger protein*) promoter HDAC-independently, but instead methylation-dependently through recruitment of DNMT1 [107]. HDAC1, HDAC2, RbAp46 (retinoblastoma protein-associated protein 46)

and RbAp48 form the core module of the two HDAC complexes Sin3 and NuRD (nucleosome remodeling histone deacetylase, Mi-2). Sp1 interacts with HDAC1, HDAC2 [105,119] and RbAp48 [105] as well as with the corepressors SMRT, NCoR and BCoR [56] (Fig. 1A), which recruit the Sin3 complex, suggesting that Sp1 may recruit the Sin3 HDAC complex.

Regulation of Sp1

The ubiquitous transcription factor Sp1 [30,35,36] was initially considered a constitutive activator of housekeeping genes and other TATA-less genes, which are usually not highly regulated. However, it is now clear that Sp1 represents also an important player in inducible gene expression and in cell growth control. First, the transcriptional activity of Sp1 is regulated by post-translational modifications as well as by interaction partners, among them prominent tumor suppressors and oncogenes (Figs. 2 and 4) [22–27]. Second, the protein products of many Sp1 target genes are key factors in normal cell growth control and oncogenesis (Fig. 3). Third, Sp1 is implicated in cell proliferation and tumorigenesis [21,28]. In general, Sp1 appears to be a very versatile partner of other transcription factors, oncogenes and tumor suppressors and the outcome of this complex interplay seems to be highly context-dependent. Often the decisive signal is perceived and transmitted by these partners, but they are unable to exert the respective biological response without Sp1.

Post-translational modifications of Sp1

Sp1 is subject to several post-translational modifications, which modulate the Sp1 protein level, the DNA-binding activity of Sp1 or the transactivation potential of Sp1, namely phosphorylation by at least nine kinases (Fig. 2) [23,27], acetylation by p300 [86,87,122], glycosylation (O-linkage of *N*-acetylglucosamine, O-GlcNAc) [17,123–125], ubiquitylation [126], sumoylation [55,126] and poly(ADP-ribosyl)ation by PARP-I (poly(ADP-ribose) polymerase-I) [127].

Interestingly, most of the kinases affect the DNA-binding by Sp1 (Fig. 2). Phosphorylation of Sp1 by ERK2 (extracellular signal-regulated kinase 2) mediates the activation of *vegf* transcription by the Ras-Raf signaling pathway (Fig. 4) [128,129]. Cyclin A/Cdk2 (cyclin-dependent kinase 2) enhances the transactivation of the *dhfr* promoter by Sp1 (Fig. 4) [130]. Phosphorylation of Sp1 by p38 is involved in the stimulation of *filamin A* transcription in response to mechanical force (Fig. 4) [131,132]. ATM (ataxia telangiectasia mutated) stimulates the Sp1-mediated transactivation of the *igf-Ir* promoter (Fig. 4) [133]. Phosphorylation of Sp1 by PKA (protein kinase A) mediates the activation of *cyp11a* (*cholesterol side chain cleavage enzyme*, $P450_{SCC}$) transcription by cAMP (cyclic adenosine monophosphate) (Fig. 4) [134].

PARP-I reduces the DNA-binding activity of Sp1 [127]. Sumoylation of Sp1 inhibits the endoproteolytic cleavage of its N-terminal ID and thus represses Sp1-dependent transcription [55].

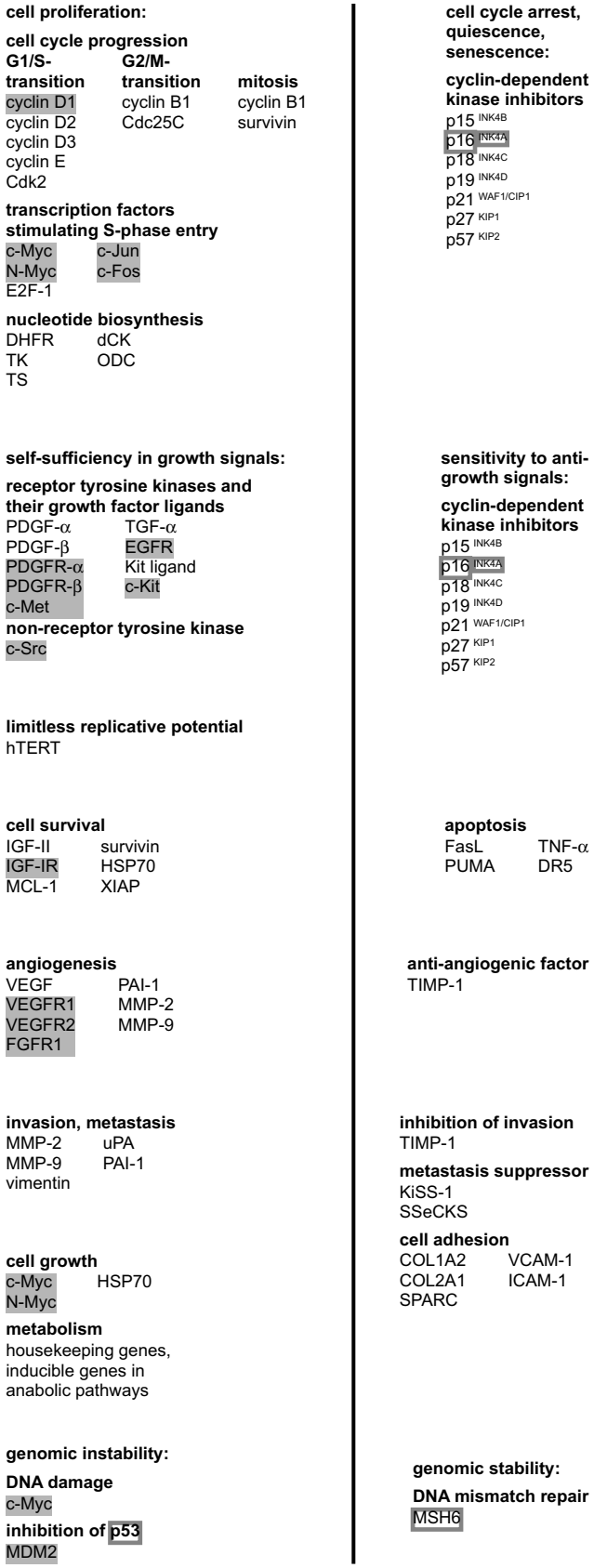


Fig. 3. Functions of Sp1 target genes. Sp1 target genes, which promote cell proliferation and oncogenesis, are shown to the left. Sp1 target genes, which suppress proliferation and tumorigenesis, are shown to the right. Many of these genes play more than one role, which is not shown. Tumor suppressors (dark gray frame) and oncogenes (light gray boxes) are marked. For references see Supplementary data. Cdc25C, cell division cycle 25C; dCK, deoxycytidine kinase; PDGF, platelet-derived growth factor; PDGFR, PDGF receptor; c-Met, HGFR, hepatocyte growth factor receptor; EGFR, epidermal growth factor receptor; c-Kit, SCFR, stem-cell factor receptor; IGF, insulin-like growth factor; IGF-IR, IGF-I receptor; MCL-1, myeloid cell leukemia-1; XIAP, X-linked inhibitor of apoptosis protein, BIRC4, baculoviral IAP repeat-containing 4; VEGF, vascular endothelial growth factor; VEGFR1, VEGF receptor-1; FGFR1, fibroblast growth factor receptor-1; uPA, urokinase-type plasminogen activator; PAI-1, plasminogen activator inhibitor-1; FasL, Fas ligand; PUMA, p53-upregulated mediator of apoptosis; DR5, death receptor 5, KILLER, TRAIL-R2, TNF-related apoptosis-inducing ligand receptor 2; TIMP-1, tissue inhibitor of metalloproteinases-1; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1.

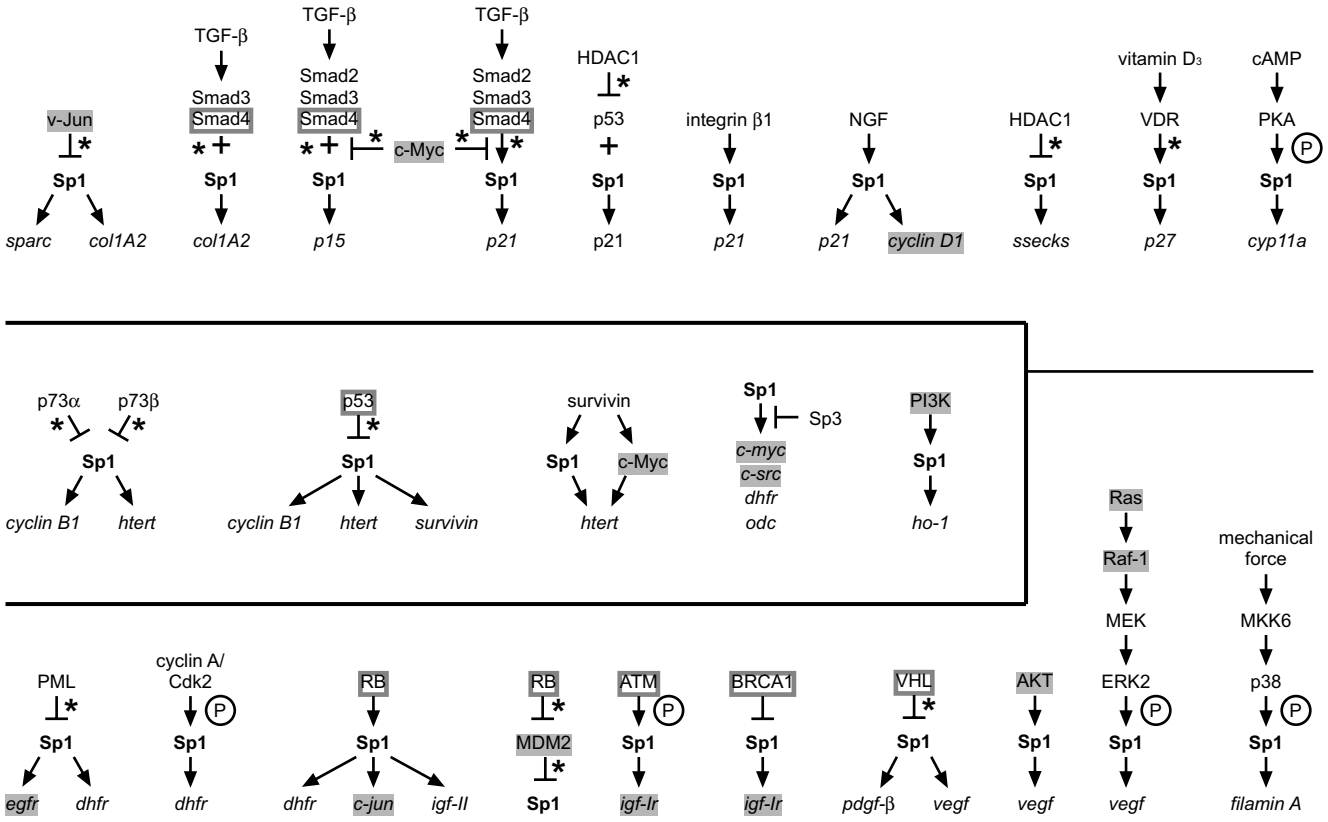


Fig. 4. Regulation of Sp1 target genes by signals and proteins that regulate Sp1. Arrows and —| signs depict positive or negative effects, respectively. Tumor suppressors (dark gray frame) and oncogenes (light gray boxes) are marked. Asterisks indicate direct protein–protein interactions (see Supplementary Table 1). Circles indicate the phosphorylation (P) of Sp1. The positive effects of the tumor suppressors RB and ATM on the Sp1-mediated transcription of the E2F-target gene *dhfr*, the growth factor *igf-II* and the oncogenes *c-jun* or *igf-Ir*, respectively, may represent artefacts caused by the overexpression of RB and ATM. For references see Supplementary data. VDR, vitamin D_3 receptor; ho-1, heme oxygenase-1; AKT, PKB, protein kinase B; MKK6, MAPK kinase kinase 6.

O-linked glycosylation (O-GlcNAc) of domain B prevents the binding of this TAD to TAF4 and to other Sp1 molecules and thus impairs the transactivation potential of Sp1 [17,124]. In contrast, the O-GlcNAc state of Sp1 has no effect on its degradation by the proteasome [125,135–137]. Instead, O-GlcNAc modification of the Rpt2 ATPase in the 19S cap inactivates the 26S proteasome, inhibits the proteasome-dependent proteolysis of Sp1 and consequently rises the Sp1 protein level [125].

Sp1 is acetylated in response to oxidative stress [122] and deacetylated upon exposure of human epidermoid carcinoma A431 cells to PMA (phorbol-12-myristate-13-acetate) [87]. The effects of the coactivator and HAT p300 on Sp1 are quite complicated: acetylation of Sp1 at K703 by p300 reduces their interaction and thus the transcriptional activity of Sp1 [87] because p300 functions as a coactivator for Sp1 [85,87,89,90]. p300, but not Tip60, another coactivator and HAT, binds directly to the DBD of Sp1, acetylates its DBD and stimulates the DNA-binding activity of its DBD, the latter remarkably independently of acetylation of the DBD [86]. Binding of the Sp1 DBD to DNA inhibits both its interaction with and its acetylation by p300 [86].

Sp1 and synergism

Sp1 transactivates synergistically with a large variety of transcription factors (Table 1; Supplementary Table 2). Transcription factors can synergize either by binding DNA cooperatively or by recruiting the basal transcription machinery synergistically, even if their binding sites are saturated. Examples for cooperative DNA-binding are Sp1 and RelA [138–140] as well as Sp1 and Oct-1 (octamer-binding protein-1) [141], which each interact directly. Table 1 lists transcription factors, which transactivate synergistically with Sp1 and bind to Sp1 directly. Nevertheless, a direct interaction is not a prerequisite for synergism of transcription factors. Many transcription factors interact and synergize with Sp1, but it is unclear whether this interaction is direct. Some of them are listed in Supplementary Table 2. Moreover, a lot of transcription factors superactivate the Sp1-mediated transactivation by binding to DNA-bound Sp1, but not to DNA. Table 2 lists examples for superactivation of Sp1 by transcription factors, which bind to Sp1 directly. The Smads [53,142–145], AP-2 (activator protein-2) [146–148] and c-Jun [149–151] exemplify that the same transcription factor can superactivate the Sp1-mediated transactivation of some target genes without binding to DNA itself and transactivate synergistically with Sp1 other target genes, which implies the binding of both to DNA (Tables 1 and 2, Figs. 2 and 4). Often synergism and superactivation can be found at the same promoter (and its mutants) dependently on the presence or absence of the respective DNA-binding sites. The property of Sp1 to interact directly with a large variety of transcription factors (Supplementary Table 1) provides countless possibilities for synergism and superactivation.

A recurring theme is the synergism of the ubiquitous factor Sp1 with tissue-specific (e.g. GATA-1 in erythroid cells) and signal-induced (e.g. SREBP-1 in response to sterol depletion) factors in the regulation of tissue-specific (e.g. globins, EpoR (erythropoietin receptor)) or signal-inducible (e.g. proteins for cholesterol uptake, cholesterol and fatty acid biosynthesis) groups of target genes, respectively (Table 1; Supplementary Table 2).

Enhanceosomes are prominent examples for synergism of multiple transcription factors. Diverse extracellular stimuli induce the

Table 2
Sp1-mediated transactivation is superactivated by other transcription factors

Superactivation of Sp1-mediated transactivation by	Target gene		Direct interaction of Sp1 with	References
c-Jun	p21 vimentin		c-Jun	[150,151]
Smad2 + Smad3 + Smad4	p21		Smad3, Smad4	[53,142,144]
AP-2	KiSS-1 CYP11A1	metastin, kisspeptin cholesterol side chain clea-vage cytochrome $P450_{SCC}$	AP-2	[146,147]
VDR[a]	p27		VDR	[273–275]
Sp1	SV40 early	simian virus 40 early transcription unit	Sp1	[9,10]
c-Jun	reporter construct with GAL4-binding sites	superactivation of GAL4-Sp1	c-Jun	[150]
Smad2 + Smad3 + Smad4	reporter construct with GAL4-binding sites	superactivation of GAL4-Sp1	Smad2, Smad3, Smad4	[142,144]
AP-2	reporter construct with GAL4-binding sites	superactivation of GAL4-Sp1	AP-2	[146]
E2F-1	DHFR promoter with point-mutated E2F-binding sites	superactivation of Sp1	E2F-1	[246]
GATA-1	GATA-1-binding site immediately upstream of a TATA-box	superactivation of Sp1	GATA-1	[251]

[a] vitamin D_3 receptor.

expression of the proinflammatory cytokine TNF-α (tumor necrosis factor-α). Sp1 is part of the TNF-α enhanceosomes, which are assembled on the TNF-α promoter in response to virus infection (ATF-2/c-Jun, NFAT, Sp1), infection by *Mycobacterium tuberculosis* and LPS (lipopolysaccharide) stimulation (ATF-2/c-Jun, Ets-1/2, Elk-1, Egr-1, Sp1, CBP/p300), but Sp1 is not part of the TNF-α enhanceosome, which is formed after exposure to calcium ionophore (ATF-2/c-Jun, NFAT) [152–154].

Sp1 interacts with the oncogene c-Myc (Supplementary Table 1) [155] and cooperates with c-Myc in transactivation of the *htert* promoter [156]. Survivin, which upregulates the hTERT mRNA and protein expression, increases the binding of both Sp1 and c-Myc to the *htert* promoter (Fig. 4) [157]. Promoters that are co-occupied by Sp1 and c-Myc tend to be active, i.e. they are above-average TFIID-bound, and to have a permissive chromatin state [158].

Sp1 binds directly the ERα (estrogen receptor α) and ERβ (Supplementary Table 1) [159,160] and cooperates with them in transactivation of several estrogen-inducible genes, for example those encoding DNA polymerase α, TS (thymidylate synthase), ADA (adenosine deaminase), CAD (carbamoyl-phosphate synthetase/aspartate carbamoyl transferase/dihydroorotase) and Bcl-2 (B-cell lymphoma 2) [26,161].

Protein–protein interactions of Sp1

Synergism and superactivation offer oncogenes (e.g. c-Jun, v-Rel) and tumor suppressors (e.g. p53, Smad4) the possibility to utilize Sp1 for their purposes (Figs. 2 and 4, Tables 1 and 2). In addition, tumor suppressors and oncogenes, which bind directly to Sp1, affect Sp1 also through other mechanisms (Figs. 2 and 4).

Binding of the oncogene MDM2 (mouse double minute 2) to Sp1 prevents Sp1 from DNA-binding (Fig. 2) [162]. In turn, interaction of the tumor suppressor RB (retinoblastoma protein) with the same domain of MDM2 as Sp1 releases Sp1 from MDM2 and thus restores the DNA-binding by Sp1 (Figs. 2 and 4) [162]. Similarly, binding of Sp1-I to Sp1 inhibits the DNA-binding by Sp1 and the interaction of RB with Sp1-I frees Sp1 enabling Sp1 to bind to the *c-jun* promoter (Fig. 4) [163]. Sp1-I is an unknown protein (approx. 20 kDa) [163], but not MDM2 (491 amino acids). RB increases also the transactivation potential of Sp1 dependently on TAF1 whereas, vice versa, cyclin D1 decreases the transactivation potential of Sp1 dependently on TAF1 (Fig. 2) [164–166].

The tumor suppressors p53 (*htert* promoter) [167], VHL (von Hippel-Lindau tumor suppressor) [168] and BRCA1 (breast cancer-associated gene 1) [169] as well as the p53-related p73β (*htert* promoter) [170,171] and the putative tumor suppressor PML (promyelocytic leukemia) [172] interfere with DNA-binding by Sp1 (Figs. 2 and 4). In contrast, p53, p73α and p73β suppress the *cyclin B1* (and *survivin*) promoter through Sp1 without interfering with the binding of Sp1 to this promoter (Fig. 4) [108,173,174]. Similarly, the viral oncogene v-Jun represses the *sparc* (*secreted protein, acidic and rich in cysteine*, *osteonectin*) and *col1a2* (*a2*(*I*) *collagen*) promoters through Sp1 without affecting the binding of Sp1 to them (Fig. 4) [175,176].

An additional mode for gene activation through Sp1 is the disruption of the direct interaction between Sp1 and HDAC1 (Fig. 2) [87,102–106], which Sp1 recruits to its target genes. For example, Sp1 is implicated in the HDAC-dependent repression of the *p21* [106,109–112], *SSeCKS* [113], *TK* [102] and *hTERT* [104,114–121] promoters (Fig. 4). E2F-1 binds to the same domain of Sp1 as HDAC1 so that they compete for binding to Sp1 (Fig. 2) [102]. Consequently, E2F-1 displaces HDAC1 from Sp1 and releases Sp1 target genes from their repression by HDAC1 [102]. Similarly, Che-1 [177] and p53 [106] bind to Sp1 and disrupt the interaction between Sp1 and HDAC1 (Fig. 2). In contrast, the oncogene c-Jun binds to Sp1 and strengthens the binding of HDAC1 to Sp1 (Fig. 2) [87].

Sp1 is involved in the TGF (transforming growth factor)-β-induced activation of the *p15* [143] and *p21* [53,142,144] promoters by Smad2, Smad3 and the tumor suppressor Smad4 (Fig. 4, Tables 1 and 2). The TGF-β-activated Smad2/3/4 serve as coactivators for Sp1, probably through their recruitment of the coactivator p300 (Fig. 2, Table 2) [142–144]. The expression of *p15* and *p21* is central to the TGF-β-induced cell cycle arrest in G1-phase [178]. In contrast, the TGF-β antagonist c-Myc induces S-phase entry and represses the *p15* and *p21* promoters [110,111,155,178,179]. c-Myc prevents also the induction of *p15* [179] and *p21* [155] transcription by TGF-β, Smad2/3/4 and Sp1 (Fig. 4) [110,111]. For this purpose, c-Myc, which binds directly to Smad2 and Smad3 [179] and interacts also with Sp1 [155], interferes with the coactivation of Sp1-mediated transcription by TGF-β-activated Smad2/3/4 (Fig. 2) [179]. Additionally, c-Myc targets the *p15* and *p21* promoters through Miz-1, which binds to the initiator elements of these genes [110,111,180].

The tumor suppressor p53 and the oncogene c-Myc demonstrate the versatility of Sp1 because they both use Sp1 for positive as well as negative regulation of genes (Figs. 2 and 4, Table 1).

Implication of Sp1 in cell growth control and tumorigenesis

Mapping of Sp1-binding sites on chromosomes 21 and 22 led to the minimal estimation of 12,000 Sp1-binding sites in the full human genome [181]. Initially, the ubiquitous transcription factor

Sp1 was considered a constitutive activator of housekeeping genes and other TATA-less genes. Indeed, countless Sp1 target genes encode proteins for intermediary metabolism. In recent years it became clear that Sp1 is also intimately involved in cell growth control and tumorigenesis [21,28]. Among Sp1 target genes (Fig. 3) are many key players in cell proliferation and oncogenesis including prominent oncogenes and tumor suppressors. Sp1 target genes belong to each of the six hallmarks of cancer [182,183]: self-sufficiency in growth signals, insensitivity to anti-growth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis and tissue invasion and metastasis. Representatives for the enabling characteristics genomic instability and cell growth/metabolism (mobilization of resources) [182,183] are also found among Sp1 target genes.

With respect to cell cycle progression Sp1 activates the transcription of the genes encoding D-type cyclins, cyclin E, Cdk2, E2F-1 and c-Myc (Fig. 3), which are key factors for progression through G1-phase and entry into S-phase. Thus, Sp1 should have the potential to promote G1/S-transition because cyclin D/Cdk4 and cyclin E/Cdk2 together induce the entry into S-phase [184,185] and because E2F-1 and c-Myc are the two only transcription factors, which can induce S-phase entry of quiescent cells [186–188]. Accordingly, Sp1 overexpression increased the percentage of cells in S-phase whereas siRNA-mediated knockdown of Sp1 decreased the S-phase cell population [28,189–191]. The finding that a dominant-negative Sp1 mutant protein arrested HeLa cervix carcinoma cells in G1-phase and inhibited their proliferation indicates a requirement of Sp1 for cell cycle progression through G1-into S-phase [192]. Interestingly, Sp1 was found to be phosphorylated specifically in mid-late G1-phase [193]. Moreover, another dominant-negative form of Sp1 prolonged the S-phase and reduced the growth rate [194].

However, Sp1 is versatile and activates also the transcription of the genes encoding all seven cyclin-dependent inhibitors, i.e. $p15^{INK4B}$, $p16^{INK4A}$, $p18^{INK4C}$, $p19^{INK4D}$, $p21^{WAF1/CIP1}$, $p27^{KIP1}$ and $p57^{KIP2}$ (Fig. 3). Therefore Sp1 should have the potential to contribute to cell cycle arrest, i.e. transient quiescence or permanent senescence. Consistently, p53 synergizes with Sp1 in transactivation of the *p21* promoter (Table 1) [106,195–197] and Smad2/3/4 synergize with Sp1 in transactivation of the *p15* promoter in response to the growth-inhibitory cytokine TGF-β (Fig. 4, Table 1) [143].

Sp1 target genes include both pro- and anti-angiogenic factors as well as both proteins promoting and inhibiting invasion and metastasis (Fig. 3). Consistently, depletion of Sp1 by siRNA impaired the angiogenic potential of PANC-1 pancreatic adenocarcinoma cells [198]. The Mediator subunit MED23 is essential for transactivation of the *KiSS-1* promoter by Sp1 [81]. In accordance, exogenous Sp1 and MED23 together reduced the invasive and migratory behavior of WM2664 and A375SM metastatic melanoma cells comparable to overexpression of the metastasis suppressor KiSS-1 itself [81]. In contrast, a Sp1 U1snRNA/ribozyme inhibited the anchorage-independent growth on soft agar of malignantly transformed PH2MT and γ2-3A/SB1 fibrosarcoma cells [199].

Sp1 target genes comprise both pro- and anti-apoptotic factors as well as both proteins ensuring and perturbing genomic stability (Fig. 3). In consistence, Sp1 overexpression induced apoptosis whereas a dominant-negative form of Sp1 suppressed apoptosis [200–202]. In contrast, siRNA-mediated knockdown of Sp1 enhanced the H_2O_2-induced apoptosis of U2OS osteosarcoma cells, but had no effect in untreated cells [203]. With respect to genomic stability, depletion of Sp1 by siRNA increased the number of DNA double-strand breaks after exposure to ionizing radiation, but had no effect in untreated cells [203].

The Sp1 target gene c-Myc [41,43,46,49,204–215] is a very potent oncogene, which stimulates every aspect of cell proliferation, cell growth and oncogenesis [188,216], so that Sp1 should have the potential to support tumorigenesis. In accordance, a Sp1 U1snRNA/ribozyme inhibited the tumor formation of malignantly transformed PH2MT and γ2-3A/SB1 fibrosarcoma cells in athymic mice [199]. Moreover, depletion of Sp1 by siRNA decreased the tumor growth and metastasis of N67 gastric cancer cells in nude mice [217]. Similarly, Sp1 knockdown by siRNA diminished the tumor growth of PANC-1 and FG pancreatic adenocarcinoma cells in athymic nude mice [198]. Finally, Sp1 was found to be overexpressed in several human cancers and the Sp1 level correlated with tumor grade/stage and poor prognosis [28,217–223].

In summary, these often contradictory results demonstrate that the outcome of Sp1 action is highly context-dependent underscoring the versatility of Sp1.

Sp1 in human disease

Huntington's disease (HD), an inherited autosomal dominant neurodegenerative disorder, is caused by mutant huntington (htt) proteins, which are charaterized by expanded N-terminal polyQ (polyglutamine) tracts encoded by corresponding expansions of the CAG trinucleotid repeats in the *htt* gene. Both wild-type and mutant huntington directly interact with Sp1 and TAF4, but mutant huntington binds Sp1 with a significantly higher affinity [20,224–226]. Mutant huntington, but not wild-type huntington, disrupts the interaction between Sp1 and TAF4, blocks the binding of Sp1 to DNA, inhibits Sp1-driven *in vitro* transcription from naked as well as chromatin templates and impairs the transcription of the *dopamin D2 receptor* gene, a Sp1 target gene [20,224,225]. The molecular chaperone HSP (heat shock protein) 40 reduces the interaction of mutant huntington with Sp1 [226]. Thus, Sp1 represents one of the targets of mutant huntington affected in HD [227].

Human Burkitts' lymphoma, especially aggressive B-cell lymphoma, are characterized by a reciproke chromosome translocation between the *c-myc* locus and one of the immunglobulin loci IgH, Igκ or Igλ, which results in severe deregulation of *c-myc* transcription by the positive-regulatory elements of these immunglobulin genes so that the very potent oncogene c-Myc is permanently highly expressed [215]. Sp1 and the Sp1-binding sites upstream of the *c-myc*-P1 promoter are important for activation and deregulation of the translocated *c-myc* promoter by the κEi + κE3' enhancers of the Igκ locus [43,211] and by the HS1234 enhancer of the IgH locus [228]. Thus, Sp1 is implicated in the pathology of some human Burkitt's lymphoma with translocations to the Igκ or IgH loci [215].

The tumor suppressor p53, also known as "the guardian of the genome", is essential to preserve genomic stability and to prevent oncogenesis [229,230]. In response to DNA damage, p53 induces either cell cycle arrest and DNA repair to eliminate the sustained damage or apoptosis to eliminate the irreversibly damaged cell [231,232]. The p53 gene is the most frequently mutated gene in human cancer. It is mutated in approx. 50% of all human cancers. Since the p53 pathway (ARF-MDM2-p53) is inactivated in virtually every tumor the remainder is thought to contain alterations in other components of the p53 pathway, e.g. the oncogene MDM2 or the tumor suppressor ARF (alternative reading frame) [233]. The E3 ubiquitin ligase MDM2 interacts directly with p53 and inhibits p53 by blocking its TAD, promoting its export into the cytoplasm and triggering its degradation by the 26S proteasome through ubiquitination of p53 [234]. The naturally occuring SNP (single nucleotide polymorphism) 309 in the intronic *mdm2* promoter results in increased MDM2 expression, consequently in attenuation of p53 function and finally in acceleration of tumor formation [235–238]. MDM2 is a Sp1 target gene (Fig. 3) [235]. SNP309 increases the binding of Sp1 to the intronic *mdm2* pro-

moter and the transactivation of the *mdm2* promoter by Sp1 [235]. Accordingly, SNP309 causes higher MDM2 mRNA and protein levels, the latter of which were demonstrated to depend on the presence of Sp1 [235,236]. Thus, Sp1 contributes to the inactivation of the p53 tumor suppressor pathway in human cancer.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bbrc.2008.03.074.

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