# Interaction and Collaboration of SP1, HIF-1, and MYC

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Specificity protein 1 (SP1), hypoxia-inducible factor 1 (HIF-1), and MYC are important transcription factors (TFs). SP1, a constitutively expressed housekeeping gene, regulates diverse yet distinct biological activities; MYC is a master regulator of all key cellular activities including cell metabolism and proliferation; and HIF-1, whose protein level is rapidly increased when the local tissue oxygen concentration decreases, functions as a mediator of hypoxic signals. Systems analyses of the regulatory networks in cancer have shown that SP1, HIF-1, and MYC belong to a group of TFs that function as master regulators of cancer. Therefore, the contributions of these TFs are crucial to the development of cancer. SP1, HIF-1, and MYC are often overexpressed in tumors, which indicates the importance of their roles in the development of cancer. Thus, proper manipulation of SP1, HIF-1, and MYC by appropriate agents could have a strong negative impact on cancer development. Under these circumstances, these TFs have naturally become major targets for anticancer drug development. Accordingly, there are many SP1 or HIF-1 inhibitors available; however, designing efficient MYC inhibitors has been extremely difficult. Studies have shown that SP1, HIF-1, and MYC modulate the expression of each other and collaborate to regulate the expression of numerous genes.

hypoxia-inducible factor 1 SP1 MYC cancer

## 1. Introduction: Specificity Protein 1, Hypoxia-Inducible Factor-1, and MYC as Master Regulators of Cancer

Recent progress in systems biology has shown that several specific factors are participants of a network that function as master regulators of cancer [1][2][3]. Wilson and Volker Filipp investigated complementary omics in human cancer, and discovered a close teamwork of transcriptional and epigenomic machinery, which is tightly connected and comprises histone lysine demethylase 3A, basic helix-loop-helix factors, MYC, hypoxia-inducible factor 1 alpha (HIF1A), and sterol regulatory element-binding transcription factor 1, as well as differentiation factors such as activator protein 1, myogenic differentiation 1, specificity protein 1 (SP1), Meis homeobox 1, zinc finger E-box-binding homeobox 1, and ETS like-1 protein (ETS1) [1]. Cao et al. [2] showed that 10 long non-coding RNA (lncRNA)-transcription factor (TF) pairs including four glycolysis-related lncRNAs (FTX, long intergenic non-protein coding RNA 472, proteasome 20S subunit alpha 3 antisense RNA 1, and small nucleolar RNA host gene 14) and six TFs (forkhead box protein P1, SP1, MYC, FOX-M1, hypoxia-inducible factor 1 alpha [HIF1A], and FOS) are involved in the progression of human lung adenocarcinoma. Malik et al. [3] discovered, using a statistical method called CoMEx (Combined score of DNA Methylation and Expression) to assess differentially expressed and

methylated genes/microRNAs (miRNAs) between human seminoma and normal tissues, two hub miRNAs (miR-182-5p and miR-338-3p), five hub TFs (ETS1, HIF1A, hepatocyte nuclear factor-1 alpha, MYC, and SP1), and three hub genes (*cadherin 1*, *C-X-C chemokine receptor type 4*, and *Snail family transcriptional repressor 1*) in the seminoma-specific regulatory network. Interestingly, in all of these studies, three TFs, namely SP1, HIF1A, and MYC, were among the factors that participated in the cancer regulatory network. In addition, many studies have shown that SP1, HIF1A, and MYC are often upregulated in cancer [4][5][6][7][8][9]. Together, these data suggest that SP1, HIF1A, and MYC have crucial roles in cancer development, and that interfering with their activity could negatively impact cancer development and progressions. For this reason, enormous efforts have been undertaken to develop inhibitors for SP1, HIF1A, and MYC. Accordingly, numerous inhibitors of SP1 or HIF1A have been developed [10][11][12][13][14]; however, designing MYC inhibitors has been extremely difficult [15].

# 2. What Are SP1, HIF-1, and MYC, and How Do These TFs Benefit Cancer

## 2.1. SP1: Housekeeping Gene That Regulates Biological Activities

SP1 is a ubiquitous TF from the Sp/Krüppel-like family (KLF) of TFs, which are the major forms of zinc finger DNA-binding proteins [16]. The defining feature of SP1-like/KLF proteins is a highly conserved DNA-binding domain (>65% sequence identity among family members) at the C-terminus that has three tandem Cys2His2 (C2H2) zinc finger motifs [17]. Likewise, SP1 contains three highly homologous C2H2 regions [18][19], which exhibit direct binding to DNA at the C-terminal regions of the protein, thus enhancing gene transcription [20]. By contrast, the N-terminal regions of the proteins are more divergent [21]. SP1 has four unstructured domains A, B, C, and D, starting from the C-terminal region of the protein. The two main transactivating domains of SP1 are A and B, which are capable of direct interaction with the components of transcription machinery such as TATA-binding protein (TBP) and TBP-associated factor 4 [22]. The C domain is not indispensable but is highly charged and supports DNA binding and transactivation. The D domain, also known as the C-terminal region of SP1, has multimeric domains and is responsible for the binding of consensus sequences such as 5′-(G/T) GGGCGG(G/A)(G/A)(G/T)-3′ (the sequences are referred to as the GC box) [23]. The N-terminal region of SP1 is a small inhibitory domain, which mainly regulates the functions of domains A and B and is linked to the A domain with a serine/threonine-rich region [22]. The transcriptional activity and stability of SP1 are influenced by its post-translational modifications. SP1 undergoes acetylation, SUMOylation, ubiquitination, and glycosylation after its translation [24][25]. Acetylation of SP1 takes place in the DNA-binding domain [26]. Glycosylation occurs at the O-GlcNAc linkages at the serine and threonine residues in SP1, which can either induce or suppress DNA binding and transcription [27]. SUMOylation, occurring in the Lys16 region, controls the transcription of SP1 by instigating alterations in the chromatin structure, making the DNA inaccessible for transcription [28]. The proteasomal degradation of SP1 is carried out by ubiquitination, where the β-transducin repeat-containing protein (TCRP) ubiquitin ligase complex interacts with SP1 through the DSG (Asp-Ser-Gly) destruction box (β-TCRP binding motif) within the C-terminus of SP1 [29]. SP1 is critical for early embryonic development [30][31], but its expression decreases with age and there is evidence that the transformation of normal cells to cancer cells is associated with the upregulation of SP1, SP3, and SP4 [10][32].

Functional studies have demonstrated that the SP-like family of TFs regulates various genes responsible for cancer-related cellular mechanisms; SP1, SP3, and SP4 are also non-oncogene addiction (NOA) genes and thus are important drug targets [33]. NOA genes are essential for supporting the stress-burdened phenotype of tumors and thus are vital for their survival. The most important functional role of SP1 in normal cells is the regulation of cell cycle and cellular reprogramming [5]. Since cell proliferation and differentiation are the most active during the developmental stage of organisms, SP1 plays critical roles during early developmental stages perhaps for this reason [30][31]. This also indicates that SP1 is still an essential component of cellular mechanisms during adulthood although less so compared with during developmental stages.

## 2.2. HIF-1: Functions as a Mediator of Hypoxic Signals

HIF-1 is the most important factor involved in the cellular response to hypoxia [34][35]. The broad impact of HIF-1 on cell biology is reflected in the total number of hypoxic target genes, which is estimated to be approximately 1–2% of all human genes [36]. HIF-1 plays important roles in energy metabolism and angiogenesis, especially in cancer progression [34]. It is composed of two subunits, HIF1A and HIF1B (aryl hydrocarbon receptor nuclear translocator). Among these two subunits, only HIF1A is activated under hypoxia and HIF1B is not regulated by oxygen [35]. The dual functional protein apurinic/apyrimidinic endonuclease 1 is an enzyme in DNA base excision repair but also works as a redox factor to maintain HIF1A in the reduced state that is necessary for its transcriptional function [35]. In the presence of oxygen, prolyl hydroxylase hydroxylates HIF1A and hydroxylated HIF1A binds to the tumor suppressor von Hippel–Lindau protein (pVHL), a component of the E3 ubiquitin ligase complex. This interaction causes HIF1A to become ubiquitinated and targeted to the proteasome, where it is degraded. However, under hypoxia, HIF1A is not degraded by the proteasome since prolyl hydroxylase is not functional, so HIF1A dimerizes with HIF1B and binds to the hypoxia response element (HRE) in the promoters of target genes, initiating the expression of genes that promote adaptation to hypoxia [35]. HIF1A as well as the more cell-specific HIF2A are important regulators of the hypoxic response. Although both HIF1A and HIF2A are highly conserved at the protein level, share a similar domain structure, heterodimerize with HIF1B (HIF-2 is formed by the assembly of HIF2A and HIF1B), and bind to the same DNA sequence (the HRE), their effects on the expression of various genes differ [37].

## 2.3. SP1 and HIF-1

The importance of HIF-1 and SP1 in cancer development is beyond dispute. In fact, it has been shown that both HIF-1 and SP1 are involved in every aspect of cancer-related cellular mechanisms. For instance, both SP1 and HIF-1 play important roles in the regulation of cancer metabolism in carbohydrates [34][38][39][40][41] and lipids [42][43][44]. Both are involved in anticancer immunity via regulation of immune-related cells [45][46][47][48][49][50][51]; the tumor microenvironment (TME)/oncometabolites [52][53][54][55][56][57][58]; and transforming growth factor beta, which regulates the immune system [59][60][61][62][63][64]. SP1 promotes tumor angiogenesis via activation of vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), and VEGF receptor 3 (VEGFR3) [65][66][67], whereas HIF-1 is a master regulator of angiogenesis, participating in vasculature formation by synergistic correlations with other proangiogenic factors such as VEGF, placental growth factor, and angiopoietins [68]. In addition, SP1 plays an important role in each of the crucial events of metastasis, namely, adhesion, invasion,

migration, and angiogenesis [65][66][67][69][70][71]. Both SP1 and HIF-1 are also involved in the regulation of cellular stress mechanisms as mediators of the protection of cancer cells against various stresses [72][73][74].

### 2.4. MYC: A Master Regulator of Cellular Activity

MYC is a transcription factor that belongs to the basic helix-loop-helix-leucine zipper (bHLHZip) family and regulates cell growth, differentiation, metabolism, and cell death. Thus, MYC functions as a master regulator of major cellular functions [75][76][77][78]. Studies using knockout mice have shown that MYC is particularly important for cell growth (accumulation of the body mass) and is indispensable during the period of both embryogenesis and adulthood [79]. c-MYC is the prototype member of the MYC family, which also includes N-MYC and L-MYC proteins in mammalian cells. All three members of the MYC family are highly homologous but distributed differently. c-MYC is ubiquitous and highly abundant in proliferating cells, whereas N-MYC and L-MYC display more restricted expression at distinct stages of cell and tissue development. MYC proteins exist within the MYC/MAX/MXD network. To fold and become transcriptionally active, c-MYC must first heterodimerize with MAX, a process governed by the coiling of their bHLHZip domains. Once dimerized, the c-MYC/MAX complex acts as a master transcriptional regulator by binding via its basic region to the specific DNA consensus sequence 5′-CANNTG-3′. Due to the multifunctional activities of MYC in cellular functions, cancers with MYC activation elicit many of the important hallmarks essential for autonomous neoplastic growth. In fact, MYC aberrations or upregulation of MYC-related pathways occur in many cancers. In preclinical animal models, MYC inactivation can result in sustained tumor regression, a phenomenon that has been attributed to oncogene addiction [80].

## 3. Interactions among SP1, HIF-1, and MYC with One Another and Other TFs

### 3.1. Modulation of SP1, HIF-1, and MYC Activities

SP1, HIF-1, and MYC modulate the expression of numerous genes as major TFs. However, these TFs do not work independently and are in fact under the regulation of many other cellular components. For example, SP1, HIF-1, and MYC can interact and modulate the activities of each other. **Figure 1** shows the promoters of human *SP1*, *HIF1A*, and *MYC* genes [81][82][83][84][85][86][87][88]. ‘SP1′ and ‘HRE’ in the figure indicate the locations of SP1 and the HRE consensus sequences, respectively. The SP1 consensus sequences are usually the GC boxes, whereas the HIF-1 consensus sequences (of the HRE) usually contain the nucleotide residues ‘5′-RCGTG-3′. The *SP1* promoter contains numerous SP1 consensus sequences as well as NF-Y and E2F consensus sequences. SP1 binds to NF-Y and E2F consensus sequences as well as SP1 consensus sequences in the *SP1* promoter [82][83]. These data suggest that SP1 can autoregulate its transcriptional activity. In addition to these consensus sequences, there is an HRE in the *SP1* promoter (**Figure 1**) [81] to which HIF-1 binds and stimulates the transcriptional activity of the *SP1* promoter [81]. It has been shown that the mRNA and protein levels of SP1 are decreased by silencing HIF1A in human cultured esophageal squamous cell carcinoma cells, whereas overexpression of HIF1A significantly increases these levels [81]. These data indicate that HIF-1 upregulates SP1 through its binding to the HRE.

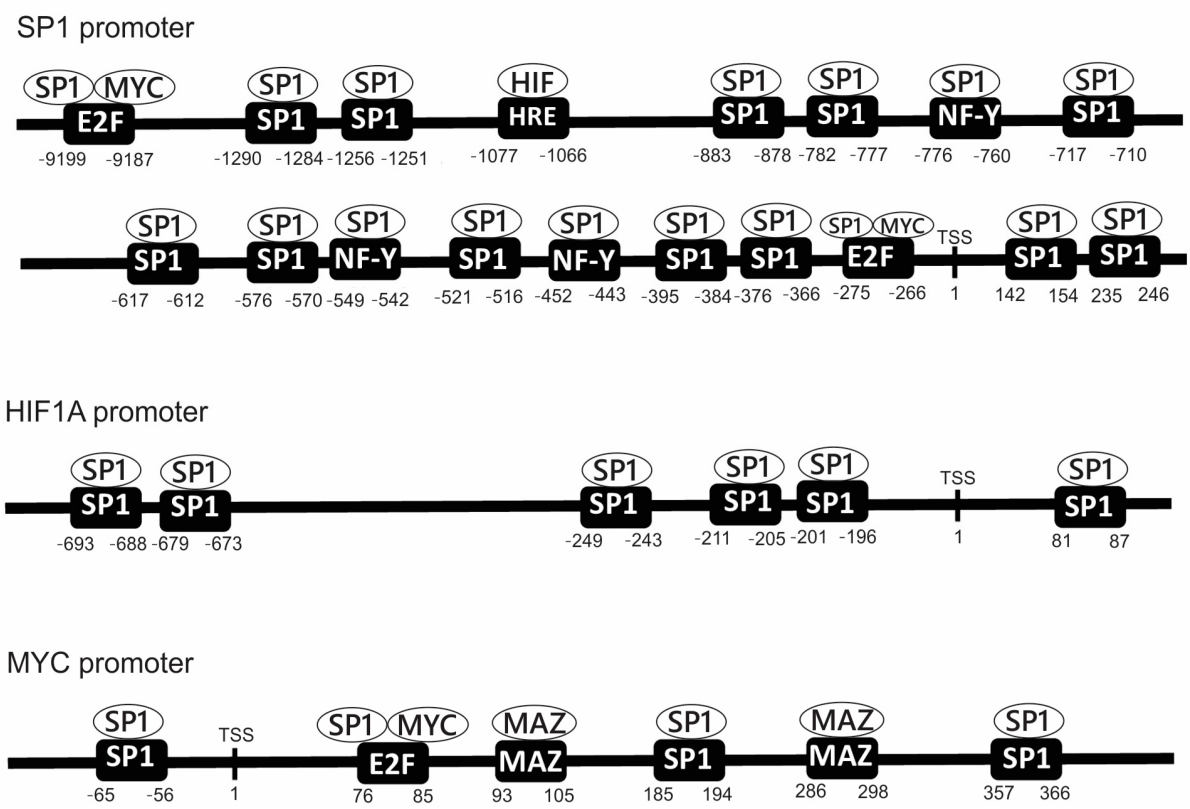


**Figure 1.** The promoter structures of human *SP1*, *HIF1A,* and *MYC* genes. The consensus sequences and their potential binding proteins are shown in each promoter. SP1 binds to SP1 consensus sequences (GC box) as well as NF-Y and E2F consensus sequences. HIF-1 binds to the HRE. MYC, similarly to SP1, binds to E2F. Myc-associated zinc finger protein (MAZ) is an important regulatory protein associated with *MYC* gene expression and binds to MAZ consensus sequences [86][88]. The nucleotide numbers are numbered from the transcription start site (TSS). The TSS for *MYC* gene promoter is for the P1 promoter [86][88].

## 3.2. Effect of HIF-1 on SP1 Gene Expression and Vice Versa

Expression of the *SP1* gene can be upregulated by HIF-1 transcriptionally by the binding of HIF-1 to its consensus sequences in the *SP1* gene promoter [81]. This is shown schematically in **Figure 2**A. Meanwhile, **Figure 2**B–D schematically shows how *HIF1A* expression is regulated by SP1, using several examples. Insulin increases *HIF1A* promoter activity by reactive oxygen species (ROS) via SP1 in murine 3T3-L1 preadipocytes [89]. *HIF1A* transcription is downregulated by protein arginine methyltransferase 1 (PRMT1), a protein whose transcription is regulated by SP1 in human Hela cervical carcinoma and human HEK293T embryonic kidney cells [90]. In the former example, SP1 is activated by phosphoinositide 3-kinase/protein kinase C via ROS, and then induces *HIF1A* transcription (**Figure 2**B). In the latter example, the suppression of PRMT1, which prevents the recruitment of SP1/SP3 to the *HIF1A* gene promoter, allows SP1/SP3 to activate the transcription of HIF1A (**Figure 2**C). In both cases, SP1 directly induces transcriptional activity of the *HIF1A* gene via its binding to SP1 consensus sequences in the *HIF1A* gene promoter (**Figure 1**) and upregulates expression of the *HIF1A* gene [77][78][79][80][81][82][83][84][85][91][92][93][94]. Meanwhile, SP1 can indirectly regulate HIF1A expression by modulating the gene expression of histone deacetylase 4 (*HDAC4*) in rat cardiomyocytes (**Figure 2**D) [95]. SP1 upregulates the activity of the *HDAC4*

gene promoter, thereby promoting deacetylation and impairing the secretion of high mobility group box 1 in mouse intestinal epithelial cells [96]. Likewise, HDAC4 can prevent the acetylation of HIF1A, thereby stabilizing the protein in human pVHL-null kidney cancer cell lines [97]. In this way, SP1 upregulates HIF1A expression either directly by activating *HIF1A* gene expression via binding to the *HIF1A* gene promoter (**Figure 2**B,C) or indirectly by stabilizing HIF1A protein via modulation of *HDAC4* gene expression (**Figure 2**D). Either way, SP1 increases the activity of HIF1A. Unlike the *HIF1A* gene, the *HIF1B* gene is constitutively expressed [98]. Therefore, the activity of HIF-1, which is composed of HIF1A and HIF1B, is regulated by adjusting the mRNA and protein levels of HIF1A in cells as well as by modulating the levels of co-activators for HIF-1 [37].

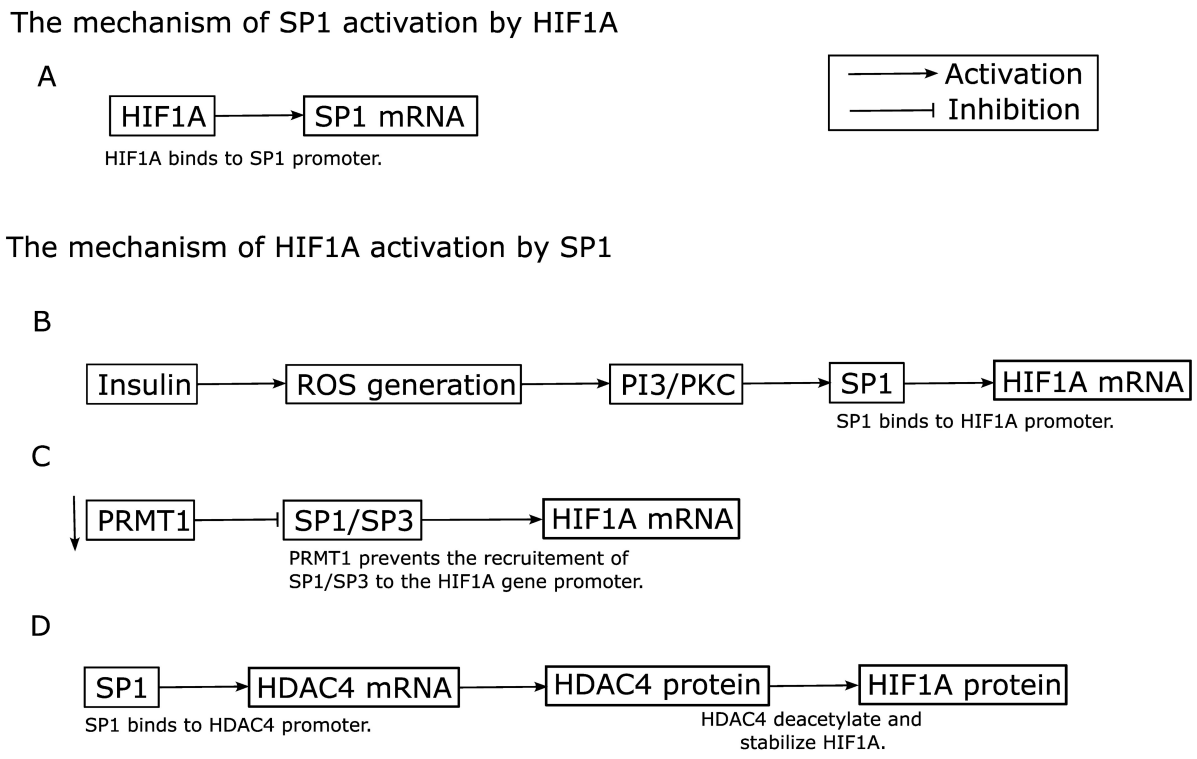


**Figure 2.** Schematic of the mechanism of activation of SP1 by HIF1A and that of HIF1A by SP1. (**A**) The mechanism of SP1 activation by HIF1A. (**B**–**D**) The mechanism of HIF1A activation by SP1. While HIF1A regulates SP1 expression via binding to the promoter of a *SP1* gene, SP1 can regulate HIF1A expression at both the mRNA level (**B**,**C**) and protein level (**D**). PKC: protein kinase C.

## 3.3. Effects of HIF-1 Compared to the Effects of SP1 on MYC Gene Activities

While HIF-1 induces *SP1* gene expression, it inhibits the activity of MYC (without affecting *MYC* gene expression) [81][99][100][101]. Since activation of MYC is usually associated with cell growth, MYC activities must be suppressed under hypoxia, which is a condition unsuitable for rapid cell growth due to a lack of oxygen, which is required for efficient biological energy production. Thus, under hypoxia, MYC activity is inhibited by HIF1A as an adaptive response that promotes cell survival under low oxygen conditions. Since there is no HRE in the *MYC* gene promoter (**Figure 1**), HIF1A is unlikely to inhibit transcription of the *MYC* gene by directly binding to the *MYC* promoter. However, there are several mechanisms by which HIF can inhibit MYC activity. First, HIF1A can

antagonize MYC transcriptional activity at MYC target genes by interfering with MYC binding to protein partners. For instance, HIF1A binds to MAX and disrupts MYC/MAX complexes, leading to reduced cyclin D2 expression, induction of p21 (CDKN1A), and G1 phase cell cycle arrest in human pVHL-null kidney cancer cell lines [102]. Meanwhile, under hypoxia, HIF-1 can induce MAX interactor 1, dimerization protein, which inhibits the transcriptional activity of MYC by competing for MAX and represses MYC target genes [103] such as peroxisome proliferator-activated receptor gamma coactivator 1-beta in human pVHL-null kidney cancer cell lines [104] or ornithine decarboxylase in multiple human cancer cell lines [105]. Second, HIF1A directly inhibits MYC transcriptional activity by DNA-binding site competition. For instance, HIF1A displaces MYC binding from the promoter of cyclin-dependent kinase inhibitor 1A (*CDKN1A*, *p21cip1*) and upregulates the expression of p21 (CDKN1A) in human HCT116 colorectal carcinoma cell line [106]. HIF1A also competes against MYC for binding to SP1, a coactivator of MYC, at the promoters of MYC target genes such as MutS homolog 2 (*MSH2*), *MSH6*, and nibirin, which encode DNA repair proteins, in human HCT116 colorectal carcinoma cell line [107][108] and the E-type prostanoid receptor in human HCA-7 colon cancer cell line [109]. Third, several studies have shown that HIF-1A promotes proteasomal degradation of MYC under chronic hypoxia conditions [104][110][111][112].

Recently, it was shown that MYC induces HIF2A expression as well. MYC has been shown to preferentially bind to the *HIF2A* gene promoter in mouse Sca1C+ cancer stem cells (CSCs) in a MYC-driven mouse T-cell leukemia model and the equivalent ATP-binding cassette superfamily G member 2+ CSC population in human acute lymphoblastic lymphoma, and activate HIF2A expression [113]. HIF2A regulates stem cell function by inducing the expression of octamer-binding transcription factor 4 [114] and AlkB homolog 5, an m6A demethylase that demethylates *Nanog* mRNA and increases Nanog expression [115]. In fact, the stem cell factors Nanog and SRY-box 2 facilitate MYC-mediated induction of HIF2A, playing a critical role in stem cell renewal and tumor stemness [116].

To date, there is limited literature on the effect of SP1 on *MYC* gene expression or the effect of MYC on *SP1* gene expression. However, Parisi et al. [117] identified a functionally distinct signature for strong dual MYC/SP1 sites in various gene promoters. This finding indicates that although SP1 and MYC do not greatly influence each other's expression transcriptionally or post-transcriptionally, there is a distinct mechanism by which they collaborate to regulate the transcription of specifically selected sets of target genes regulated by both SP1 and MYC.

Overall, these data suggest that there is a positive activation loop of HIF-1 (HIF1A) and SP1, which mostly occurs through induction of the transcriptional activity of the *HIF1A* gene via SP1 and that of the *SP1* gene via HIF-1 (**Figure 2**). HIF-1 negatively regulates MYC through post-transcriptional mechanisms, and MYC activates HIF-1 through post-transcriptional mechanism. Interestingly, unlike HIF-1 and MYC, there is a positive activation loop of HIF-2 and MYC, which occurs via the combination of both transcriptional and post-transcriptional mechanisms. By contrast, there does not seem to be a direct effect of SP1 on *MYC* transcription or of MYC on *SP1* transcription, although SP1 and MYC collaborate to transcriptionally regulate their target genes.

## 4. Collaboration of SP1, HIF-1, and MYC in Transcriptional Regulation of Their Target Genes

SP1, HIF-1, and MYC interact with each other either transcriptionally or post-transcriptionally and modulate the activity of each other, which demonstrates that there is some collaboration of these TFs in the execution of their activities. However, since SP1, HIF-1, and MYC are first and foremost TFs, their more important collaborations take place when these TFs modulate transcription of their target genes.

Many studies have investigated the mechanisms underlying how SP1 and HIF-1 collaborate in transcriptional regulation of their target genes. One example is the detailed study of the effect of SP1 and HIF-1 on the promoter activity of the human erythropoietin receptor gene [118]. That study showed that the binding of SP1 and HIF-1 to their binding sites in the promoter additively increases the transcriptional activity of the promoter. Another example is the detailed study on regulation of the human retinoic acid receptor-related orphan receptor alpha 4 (*RORalpha*) gene by the interaction between HIF-1 and SP1 [119]. In that case, it was shown that the binding sites for HIF-1 and SP1 in the promoter of this gene are situated closely to each other, and that HIF-1 functionally interacts with SP1 [119]. It was also shown that the HIF2A/SP1/HDAC4 network is involved in transcriptional activation of the human coagulation factor VII gene promoter [120]. Although HIF2A instead of HIF1A is involved in this case, these data suggest that the complex network of HIF1A/HIF2A/SP1/HDAC4 exists, as there is a link between SP1 and HIF1A via HDAC4 (**Figure 2**D) [95].

The collaboration of HIF-1 and MYC in transcriptional regulation of their target genes has already been described in the previous section. As aforementioned, since HIF-1 and MYC do not modify the expression of each other transcriptionally, the interaction between HIF-1 and MYC occurs either post-transcriptionally (HIF-1 usually suppresses MYC while MYC usually activates HIF-1) or through their collaboration to regulate the expression of their target genes. As an example of HIF-1 modulating the MYC-regulated transcription of genes, for instance, HIF-1 inhibits MYC-dependent induction of the transcriptional activity of the human *CDKN1A* gene promoter via a HIF1A–MYC mechanism [106]. This involves functional antagonism of the transcription repressor MYC via protein–protein interactions. This mechanism is independent of HIF1A DNA binding and transcriptional activity; instead, HIF1A displaces MYC from binding to the *CDKN1A* promoter. A similar mechanism also works for regulation of the human *MSH2* gene promoter [107]. In this case, neither HIF1A nor MYC binds directly to the *MSH2* promoter. Rather, both HIF1A and MYC discretely interact with the constitutively bound TF SP1 on the *MSH2* promoter, whereas HIF1A dominates SP1 binding in hypoxia by competing with MYC. As a result, SP1 acts as a molecular switch by recruiting HIF1A for the hypoxic repression of *MSH2*. This mechanism is a good example of how HIF-1 can suppress rather than induce gene expression under hypoxia. In addition, this mechanism also shows the diversity of how HIF-1, SP1, and MYC collaborate to control the transcriptional activity.

There is no evidence to suggest that SP1 and MYC directly affect the transcription of each other. However, the collaboration of SP1 and MYC in the regulation of their target genes has been well described in the literature [121][122][123][124][125][126]. Among the genes whose transcription is regulated by the collaboration of MYC and SP1, there are various genes involved in the regulation of CSCs such as telomerase reverse transcriptase (*TERT*), *BMI1*, cluster of differentiation 133 (*CD133*), and *CD147* [123][124][125][126]. These genes are often upregulated in cancer. In fact, most of the genes involved in the regulation of CSCs are regulated by HIF-1 as well [127][128][129][130]. Hence, these data indicate that the genes involved in the regulation of CSCs are in most cases regulated by SP1, HIF-1,

and MYC. Since CSCs possess ‘stemness’ properties, which are reflected in their capacity to self-renew and generate differentiated cells that contribute to tumor heterogeneity [131][132], the contribution of CSCs has fundamental importance in the development of cancer; therefore, the eradication of CSCs is crucial for the success of anticancer therapy. As aforementioned, SP1, HIF-1, and MYC are all participants of cancer regulatory networks. The fact that the genes involved in the regulation of CSCs are all controlled by SP1, HIF-1, and MYC indicates that the very reason why these TFs are important participants of cancer regulatory networks might be because they regulate CSCs.

Based on the current knowledge about the transcription factors SP1, HIF-1, and MYC, the following conclusions can be drawn. First, all HIF-1, SP1, and MYC are deeply involved in cancer-related cellular mechanisms including metabolism, angiogenesis, anticancer immunity, and regulation of TME. Importantly, HIF-1 and SP1 usually induce the expression of each other while HIF-1 suppresses the expression of MYC and MYC induces that of HIF-1. This indicates that HIF-1 and SP1 can cooperatively activate cancer-related cellular mechanisms while the relationship between HIF-1 and MYC regarding the regulation of cancer-related cellular mechanisms can be variable depending on the context. Second, the CSC-related genes, which have fundamental importance in oncogenesis, are all positively regulated by HIF-1, SP1, and MYC at the transcriptional level. Overall, these results suggest that inhibitors for HIF-1 and SP1 likely induce anticancer effects in cooperation by suppressing the activity of cancer-related cellular mechanisms (including the mechanisms underlying CSC regulation) while using MYC inhibitors as anticancer drugs requires some cautions.

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