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# Specificity protein 1: Its role in colorectal cancer progression and metastasis

Richa Bajpai, Ganji Purnachandra Nagaraju *

*Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA, 30322, USA*

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ABSTRACT

Specificity protein 1 (Sp1) is a widely expressed transcription factor that plays an important role in the promotion of oncogenes required for tumor survival, progression and metastasis. Sp1 is highly expressed in several cancers including colorectal cancer (CRC) and is related to poor prognosis. Therefore, targeting Sp1 is a rational for CRC therapy. In this review, we will recapitulate the current understanding of Sp1 signaling, its molecular mechanisms, and its potential involvement in CRC growth, progression and metastasis. We will also discuss the current therapeutic drugs for CRC and their mechanism of action via Sp1.



## 1. Introduction

An estimated 134,490 new colorectal cancer (CRC) cases worldwide and approximately 49,190 CRC related deaths are expected in 2016. CRC progression is initiated and controlled by altered gene expression activities. Transcription factors act as terminal modulators of gene expression and consequently represent rational targets for the development of anti-cancer drugs that induce CRC cell death and sensitize CRC cells to chemo and radio therapies. In the past few years, significant advances have been made in targeting CRC cells, retaining tumor suppressive molecules, and therapeutically modifying transcription factors. Clinical advances in our understanding of molecular signaling pathways have provided novel targets in cancer therapy, and many targeted agents have been evaluated in international randomized studies for CRC patients.

The mechanism of resistance to chemo- and radio therapy in CRC includes the triggering of Sp1, NF-κB and hypoxia inducible factor (HIF-1α). Sp1 is a transcriptional regulator that plays a significant role in CRC development and progression. It is highly expressed in human CRC tissues and CRC stem cells as compared to adjacent normal colon tissues (Guo et al., 2010; Song et al., 2001). These changes play a significant role in CRC metastasis. Recent studies have shown that the expression of other Sp members is also increased in CRC cell lines (Abdelrahim and Safe, 2005). Therefore, Sp1 is an important target for CRC therapy. In this timely review, the role of Sp1 in CRC is described in detail with respect to cell progression (proliferation and cell cycle), metastasis (invasion, migration and angiogenesis), and apoptosis.

* Corresponding author at: 1365 Clifton RD NE, Office 3025 Atlanta, GA 30322, USA.
*E-mail address:* pganji@emory.edu (G.P. Nagaraju).

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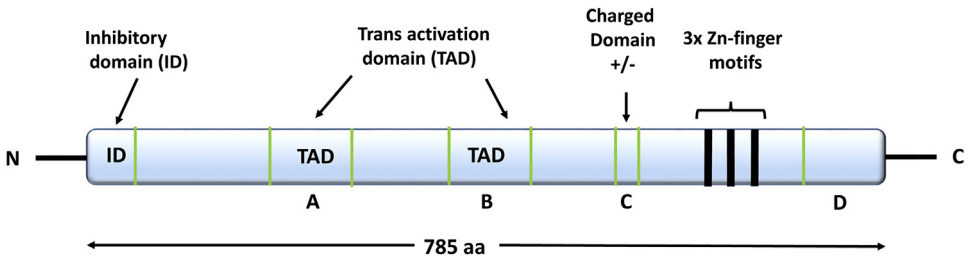


**Fig. 1.** Domain architecture and structural motifs of Sp1 protein. Sp1 comprises 785 amino acids organized into four distinct domains (A, B, C and D). Domains A and B are rich in glutamine amino acid and function as transactivating domains (TAD). The extreme N-terminus of Sp1 is a small inhibitory domain (IB) which regulates the function of domains A and B by directly interacting with corepressors. Domain C is a highly charged group of 69 residues comprising 12 negative and 6 positive charges. The C-terminal Domain D is only required for synergistic transactivation by Sp1. Sp1 consists of three Cys2-His2 type zinc finger motifs located between domains C and D, which function as its DNA binding domain (DBD).

## 2. Structure, binding site and biology of Sp1

Specificity protein 1 (Sp1) is a transactivation molecule, which belongs to the family of Sp or Krüppel-like factor (KLF) proteins (Briggs et al., 1986). The promoter regions of several genes which are involved in the regulation of diverse biological functions contain binding sites for Sp1 (Kadonaga et al., 1987). Sp1 protein is encoded by the *Sp1* gene located at the 12q13.1 locus in the human genome (Gaynor et al., 1993). Sp1 comprises 785 amino acids organized into four distinct domains (A, B, C and D) as shown in Fig. 1. Domains A and B are rich in glutamine amino acid and function as transactivating domains (TAD). They can interact directly with components of the transcription machinery i.e. TBP (TATA-binding protein) and TAF4 (TBP-associated factor 4). The extreme N-terminus of Sp1 is a small inhibitory domain (IB) which regulates the function of domains A and B by directly interacting with corepressors. Domain C is a highly charged group of 69 residues comprising 12 negative and 6 positive charges. The C-terminal Domain D is only required for synergistic transactivation by Sp1(Wierstra, 2008). Sp1 consists of three Cys2-His2 type zinc finger motifs located between domains C and D, which function as its DNA binding domain (DBD).

The binding site of Sp1 protein is termed as *Sp1 site* (Pugh and Tjian, 1990; Chu, 2012) and comprises a consensus GC-box 5′-(G/T) GGGCGG (G/A) (G/A) (C/T)-3′. Sp1 binds to GC boxes with the help of its zinc finger motifs (Briggs et al., 1986) and recruits other proteins and factors associated with transcriptional assembly. A promoter can have either single or multiple Sp1 sites. Sp1 can transactivate genes in three ways, by binding to a) a single Sp1 site as a monomer, b) a single Sp1 site as a homo-oligomer, or c) multiple Sp1 sites for synergistic transactivation (Deniaud et al., 2009). Usually Sp1 binds to GC boxes but it can also recognize and bind to GT rich regions with lower affinity (Wierstra, 2008).

Sp1 is the first described member of the Sp family. However, there are other members also and altogether they can be grouped broadly into the Sp1-4 group and the Sp5-9 group. Members of the Sp1-4 group have TADs, which are absent in the Sp5-9 group (Beishline, 2015). SP2 possesses only one TAD whereas Sp1, 3 and 4 have two TADs (Beishline, 2015). Sp1 and 3 are ubiquitously expressed (Yang et al., 2004) whereas Sp4 is found in brain tissues (Supp et al., 1996). Due to the presence of homologous sequences among different Sp molecules, the activity and expression of Sp1 is compensated for by its own family members. For example, the DNA binding regions of Sp1 and Sp3 share over 90% DNA sequence homology (Suske, 1999). Therefore, they bind to similar DNA sequences with a similar affinity, competing against each other (Hagen et al., 1994). The ratio of Sp1:Sp3 dictates the outcome of gene regulation (Li et al., 2004; Davie et al., 2008). Sp3 suppresses Sp1-mediated transactivation of genes whose promoters have two or more *Sp1* binding sites but does not affect the transactivation of genes with only one *Sp1* site (Yu et al., 2003; Li and Davie, 2010).

There are 12,000 *Sp1* binding sites in the human genome, which are linked with genes regulating several aspects of human biology. The impact of Sp1 expression has been implicated in diverse cellular processes including those in embryonic and early postnatal development (Marin et al., 1997) and with increasing age (Ammendola et al., 1992). The presence of a high number of *Sp1* binding sites explains the function of Sp1 as an activator or a repressor in cell growth, differentiation, chromatin remodeling, immunity, apoptosis, and DNA damage (Cawley et al., 2004). Sp1 activity is regulated by post-translational changes including acetylation, phosphorylation, glycosylation, and proteolytic processing (Chang and Hung, 2012). Given the multidimensional impact of Sp1 on various cellular processes, it plays opposing roles in cancer cells as an oncogene or a tumor suppressor in the establishment of six well known hallmarks of malignancy: independence, sensitivity to growth signals, evasion of apoptosis, limitless replicative potential, vascularization, and tissue invasion and metastasis. Consistent with this, the expression levels of Sp1 were found to be elevated in a variety of cancers including breast, colon, pancreas, bladder and prostate (Davie et al., 2008; Kong et al., 2010; Chuang et al., 2009).

## 3. Role of Sp1 in cell proliferation

Cancer cells exhibit uncontrolled growth and cell division, collectively termed as cell proliferation. Sp1 induces the expression of many genes involved in cell survival and proliferation pathways (Black et al., 2001). Suppression of Sp1 expression by Sp1 siRNAs reduced the growth of colon cancer stem cells (CCSCs) and induced apoptosis (Zhao et al., 2013a). Further, the proportion of CCSC markers CD44+/CD166+ was potentially decreased following Sp1 knock-down (Zhao et al., 2013a). These results showed that, Sp1 knock-down decreased the characteristics of CCSCs. As a result, Sp1 suppression may be significantly useful therapeutic approach to cure colon cancer. Dividing cells need a continuous supply of fatty acids for the biosynthesis of membrane phospholipids (Natter and Kohlwein, 2013). This is also an efficient source of energy. To cope with growing demands, many cancer cells express high levels of fatty acid synthase (FAS) enzyme, inhibition of which reduces cell proliferation and tumor growth (Flavin et al., 2010). The FAS gene promoter is regulated by Sp1 and SREBP (sterol regulatory element-binding protein-1) transcription factors. Sp1 maintains the expression of FAS directly and also by regulating SREBP-1c in colon cancer (Lu and Archer, 2010). Cancer cells also control the signaling and reprogramming of cellular metabolism by modifying histones in chromosomes. Class I histone deacetylases, such as HDAC1 and HDAC2, which are overexpressed in many cancer types including colon cancer, regulate epidermal growth factor receptor (EGFR) signaling in cancer cell lines. EGFR is a