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Sp transcription factor family and its role in cancer

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Abstract

Specificity protein 1 (Sp1) and other Sp and Krüppel-like factor (KLF) proteins are members of a family of transcription factors which bind GC/GT-rich promoter elements through three C_2H_2-type zinc fingers that are present at their C-terminal domains. Sp1–Sp4 proteins regulate expression of multiple genes in normal tissues and tumours. There is growing evidence that some Sp proteins play a critical role in the growth and metastasis of many tumour types by regulating expression of cell cycle genes and vascular endothelial growth factor. Sp/KLF proteins are also potential targets for cancer chemotherapy.

Keywords: Sp1; Sp2; Sp3; Sp4; Transcription factors; Cancer; VEGF

1. Introduction

Specificity protein 1 (Sp1) was the first transcription factor identified and cloned, and shown to be a sequence-specific DNA-binding protein that activated a broad and diverse spectrum of mammalian and viral genes [1–5]. Sp1 protein recognises GC/GT boxes and interacts with DNA through three C_2H_2-type zinc fingers located at the C-terminal domain [6–8]. Based on results of crystal structure and NMR studies, each of the three zinc fingers in Sp1 recognises three bases in one strand, and a single base in the complementary strand of the GC-rich elements where the consensus Sp1 binding site is 5′-(G/T)GGGCGG(G/A)(G/A)(C/T)-3′ [9,10]. A recent NMR study now shows that the more C-terminal zinc finger 1 has reduced specificity and can also bind only two bases in the recognition sequence [11]. This may account for the interactions of Sp1 with diverse GC-rich promoter sequences and for Sp1-dependent regulation of a large number of mammalian genes in normal and transformed cells [12–14]. Although Sp1 binding affinities to non-consensus GC-rich motifs may be lower than for consensus sequences, their functional interactions in regulating gene expression may be highly significant.

2. Sp family of transcription factors and their expression in tumours

Sp1 is a member of a growing family of nuclear proteins that modulate gene transcription and the Sp/Krüppel-like factors (KLFs) are categorised by their similar modular structures [reviewed in [15–20]]. Sp1–Sp4 form a subgroup (Fig. 1) which contain several distinct overlapping features/regions which include activation domains (AD), the C-terminal zinc finger DNA-binding region, and an inhibitory domain (ID) in Sp3 that is involved in the suppressive activity of Sp3. Sp5–Sp8 are structurally similar and appear to be truncated forms of Sp1–Sp4 in which portions of the N-terminal regions have been deleted. The chromosomal locations of Sp1–Sp8 are adjacent to a HOX gene cluster. At least 15 KLFs have been characterised, and these proteins also

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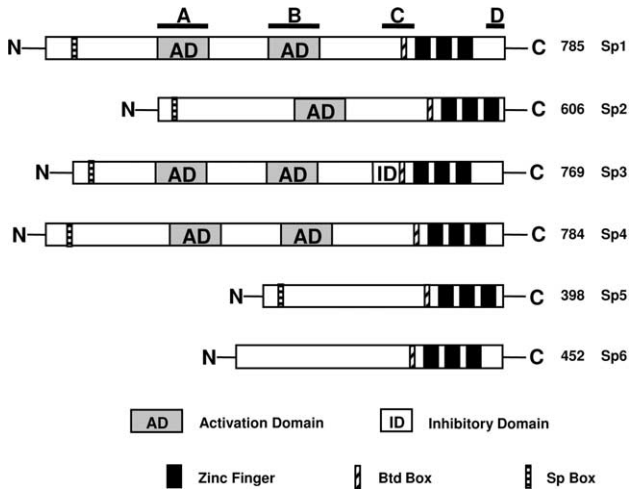

Fig. 1. Structural features of Sp proteins. Sp1–Sp6 proteins contain several common domains in their C-terminal region, whereas Sp5 and Sp6 exhibit a truncated N-terminal structure [15–20]. Buttonhead (Btd) and Sp boxes are conserved regions in all Sp proteins [17].

contain the three zinc finger motifs but exhibit considerable structural variability. KLF subfamilies include the basal transcription element binding (BTEB) proteins and transforming growth factor β (TGFβ)-inducible early gene (TIEG) proteins. The function of individual Sp/KLF proteins is continually being defined and depends, in part, on the temporal and tissue-specific patterns of individual gene expression. Sp1 is widely expressed in many tissues/cells; however, the relative quantitative expression is not well defined and may be highly variable. For example, studies on the developmental expression of Sp1 in the mouse showed that Sp1 mRNA levels in different tissues varied by at least 100-fold [21]. Sp1 directly interacts with TATA-binding protein associated factors (TAFs) and other nuclear cofactors which comprise the basal transcription factors [22–26]. Sp1-mediated transcription also involves a cofactor required for Sp1 (CRSP) complex which has been identified in HeLa cervical adenocarcinoma cells [27–29]. The CRSP complex contains multiple proteins and resembles, in part, protein complexes associated with other transcription factors similar to the yeast/mediator protein complex [30]. Interactions of mediator-like complexes with other Sp proteins have not been reported; however, it is likely that these occur and may play a role in the differential regulation of Sp-dependent gene expression.

Although the specific physiological functions of Sp proteins have not been determined, results of gene knockout studies in mice have provided valuable insights on some critical functions of these genes. For example, $Sp1^{-/-}$ embryos exhibit multiple abnormalities and retarded development and embryolethality on day 11 of gestation [31]. $Sp2^{-/-}$ mice have not been reported; however $Sp3^{-/-}$ mice exhibit growth retardation, defects in late tooth formation, and the animals die at birth [32,33]. $Sp4^{-/-}$ mice either die shortly after birth or survive with significant growth retardation. In addition, male (but not female) $Sp4^{-/-}$ mice do not reproduce and have abnormal reproductive behaviour [34]. It is clear from these and other Sp/KLF gene knockout studies that this family of transcription factors plays critical roles in normal development of tissues/organs.

There is also emerging evidence that Sp protein expression may be a critical factor in tumour development, growth and metastasis; however, most of these studies are limited and have focused primarily on Sp1 protein/mRNA expression. Wang and coworkers investigated Sp1 and vascular endothelial growth factor (VEGF) expression in gastric tumours [35]. Sp1 protein was highly expressed in nuclei of gastric tumour cells, whereas minimal to non-detectable levels were detected in stromal or normal glandular cells within or surrounding the tumour. The results also showed that the survival of patients with high Sp1 expression was significantly decreased compared to patients with weak to non-detectable Sp1 expression. Since Sp1 also regulates VEGF expression, there was a positive correlation between Sp1 and VEGF expression in gastric cancer patients, and patients with high VEGF levels also had decreased survival times [36]. Shi and coworkers [37] showed that Sp1 was overexpressed in pancreatic tumours compared to normal tissues, and overexpression of Sp1 in tumours and pancreatic cancer cell lines correlated with elevated VEGF levels. These results were consistent with molecular biology studies showing that Sp1 plays a major role in regulation of VEGF. Sp1 protein expression was elevated in 11 out of 14 breast carcinomas, whereas only 1 in 5 benign breast lesions expressed detectable Sp1 [38], and Sp1 was overexpressed in thyroid tumours compared to normal tissues [39]. DNA-dependent protein kinases Ku70 and Ku80 are upregulated in colon tumours compared to adjacent normal tissues, and this also correlated with increased levels of Sp1 expression in these tumours [40]. Moreover, promoter analysis studies confirm that constitutive expression of these kinases is regulated by Sp1 interaction with GC-rich promoters in these genes. These data link elevated Sp protein expression in tumours to upregulation of genes that are involved in tumour growth and metastasis. Additional research is required to determine direct linkages between overexpression of Sp1 and other Sp family members in various tumour types since Sp proteins may be important prognostic factors and therapeutic targets.

3. Regulation of growth promoting and cell survival genes by sp proteins in cancer cells

Sp family proteins regulate basal/constitutive expression of genes involved in multiple functions in both normal and cancerous tissues [18]. Genes that regulate