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Review

Sp1: Regulation of gene expression by phosphorylation

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Abstract

As the prototype of a family of transcription factors, Sp1 has been extensively studied and widely reported for its role in gene regulation. The first evidence of Sp1 phosphorylation was reported more than a decade ago. Since then, an increasing number of Sp1 phosphorylation events have been characterized. Recent data demonstrate an important role for the phosphorylation state of Sp1 in the regulation of multiple genes. In this article, we review published literature in four specific areas relating to the phosphorylation of Sp1: (1) signal transduction pathways for Sp1 phosphorylation, (2) mechanisms of Sp1 dephosphorylation, (3) the functional implications of Sp1 phosphorylation, and (4) Sp1 phosphorylation in the lung.

Keywords: DNA binding; Lung; Promoters; Protein phosphatases; Signal transduction pathways; Transcription factors

1. Introduction

Research data of the past few decades indicate that transcription factors play a critical role in many biological events by virtue of their regulation of gene expression. It is well established that specific combinations of transcription factors exert unique effects on individual gene promoters, allowing spacio-temporal specificity of gene expression using only a small number of transcription factors under widely varying physiological and pathological conditions. In addition, the activities of individual transcription factors can be regulated at various levels such as post-translational modification (e.g., phosphorylation and glycosylation) and intracellular translocation. One mechanism worthy of our attention is phosphorylation, because it is a highly efficient and widely employed mechanism for regulating the function of proteins, including transcription factors. Also of note for this review is the transcription factor Sp1, because it is known to regulate a large number of genes. The phosphorylation of Sp1 has been shown to regulate target genes in both positive and negative directions. These properties suggest that Sp1 phosphorylation may exert broad and diverse effects in both cell and organ physiology. In this article, we review recent progress with the mechanisms and consequences of changes in the phosphorylation state of Sp1.

2. Overview of Sp1 and its phosphorylation

Sp1 is the founding member of a family of zinc finger transcription factors, which includes at least four Sp

Abbreviations: CCSP, Clara cell secretary protein; CDK, cyclin-dependent kinase; CK-II, casein kinase-II; CRH, corticotropin-releasing hormone; DNA-PK, DNA-dependent protein kinase; EGF, epidermal growth factor; ERK, extracellular signal-regulated kinase; FGF-2, fibroblast growth factor-2; GRE, glucocorticoid response element; HIV-1, human immunodeficiency virus; HSF/SF, hepatocyte growth factor; HSV1, Herpes Simplex Virus 1; LTR, long terminal repeat; MEK, MAPK/ERK kinase; OA, okadaic acid; PI-3, phosphatidylinositol 3-kinase; PKA, protein kinase A; PKC-ζ, protein kinase C-ζ; PP1, protein phosphatase 1; PP2A, protein phosphatase 2A; TTF-1, thyroid transcription factor-1; VEGF, vascular endothelial growth factor.

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Table 1
A list of reported Sp1 phosphorylation events with identified kinases or phosphatases in the signaling pathway

Signal	Kinase or phosphatase	Residues	DNA binding		Transcription activation		Cells	Reference
			Oligo probe	Change[a]	Promoter	Change[a]		
	DNA-PK	N-terminal 610 aa	Intergenic control region of SV40	No change			HeLa	(Jackson et al., 1990)
Terminal differentiation	CKII	C terminus, Thr579	Site II of the albumin D-box binding protein promoter	Decrease			Liver tissue	(Armstrong et al., 1997; Leggett et al., 1995)
Cyclin A	Cyclin-dependent kinase 2 (CDK2)	Ser59	Hamster DHFR promoter	Increase	Hamster DHFR	Increase	NIH 3T3	(Fojas et al., 2001)
Cyclin A, cell growth	Cyclin-dependent kinase 2 (CDK2)		Murine TK promoter	Increase	Contains 3 consensus Sp1 binding sites	Increase	U2OS (osteosarcoma), 3T6 (embryonic fibroblast)	(Haidweger et al., 2001)
EGF	ERK2, Sp1 kinase activity		Gastrin promoter	Increase	Gastrin	Increase	AGS (gastric carcinoma)	(Chupreta et al., 2000; Merchant et al., 1999)
	PKA		Sp1 consensus	Increase	SV-40	Increase	HL-60/AR (leukemia)	(Rohlff et al., 1997)
	PKC-ζ		Platelet-derived growth factor B-chain	Increase	Platelet-derived growth factor B-chain	Increase	WKY12–22 (rat aortic smooth muscle cells)	(Rafty and Khachigian, 2001)
HIV-1 Tat protein	DNA-PK	Ser131			HIV-1 minimal promoter	Increase	HeLa	(Chun et al., 1998)
Serum stimulation	Growth-related and Sp1-associated kinase activity	aa 612–678	Dihydrofolate reductase promoter	No change			Fibroblasts	(Black et al., 1999)
Neu differentiation factor (NDF)	A 60 kd kinase		NDF response element probe	Increase	AchR ε subunit promoter	Increase	P-19 teratocarcinoma cells	(Alroy et al., 1999)