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Survey

Smads and chromatin modulation

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Abstract

Smad proteins are critical intracellular effector proteins and regulators of transforming growth factor type β (TGFβ) modulated gene transcription. They directly convey signals that initiate at ligand-bound receptor complexes and end in the nucleus with changes in programs of gene expression. Activated Smad proteins seem to recruit chromatin modifying proteins to target genes besides cooperating with DNA-bound transcription factors. We survey here the current and still emerging knowledge on Smad-binding factors, and their different mechanisms of chromatin modification in particular, in Smad-dependent TGFβ signaling.

Keywords: Bone morphogenetic protein; Histones; Signal transduction; Smad; Remodeling

Contents

Abbreviations: AER, apical ectodermal ridge; ACF, ATP-utilizing chromatin assembly and remodeling factor; AML, acute myeloid leukaemia; AMT, arginine methyl transferase; ARC, activator-recruited cofactor; BAF, BRG1/hBRM-associated factors; BMP, bone morphogenic protein; BRG, brahma-related gene; CBFA, core-binding factor; CBP, CREB binding protein; Cdk, cyclin dependent kinase; CHD, chromo helicase-DNA binding; ChIP, chromatin immuno precipitation; CHRAC, chromatin-accessibility complex; CREB, cAMP-response element-binding protein; CtBP, C-terminal binding protein; CTF-1, CCAAT transcription factor 1; DNMT, DNA Methyltransferase; DRBP76, double-stranded (dsRNA)-binding proteins; EMSA, electric mobility shift assay; Evi-1, ecotropic virus integration site-1; FAT, factor acetyl transferase; GCN5, general control of amino-acid synthesis; HDAC, histone deacetylase; HIPK2, homeodomain-interacting protein kinase 2; HKMT, histone lysine methyl transferases; HMT, histone methyl transferas; HP1, heterochromatin protein 1; HPE, holoprosencephaly; LAT, lysine acetyl transferase; LSD1, lysine specific demethylase 1; MBD, methyl-binding protein; MeCP2, methyl-CpG-binding Protein 2; MH, Mad homology; MTA, metastasis-associated protein; NCoR, nuclear receptor co-repressor; NoRC, nucleolar remodeling complex; NuRD, nucleosome remodeling and histone deacetylation; NURF, nucleosome-remodeling factor; PARP, poly(ADP-ribose) polymerase1; pCAF, p300/CBP associated factor; PARG, poly (ADP-ribose) glycohydrolase; PARP, poly (ADP-ribose) polymerase; PEBP2, polyomavirus enhancer binding protein 2; PRMT, protein arginine methyltransferase; TGFβ, transforming growth factor β; RSF, remodeling and spacing factor; R-Smads, receptor regulated Smads; RSC, remodels the structure of chromatin; SAGA, Spt/Ada/Gcn5 acetyltransferase; Ski, Sloan kettering institute; SMAD, similar to mad; SMRT, silencing mediator for retinoid and thyroid receptors; SNF, sucrose non-fermenting; SNIP, Smad nuclear interacting protein; Sno, c-Ski-related novel gene; STAGA, SPT3-TAF-GCN5 acetylase; SUMO, small ubiquitin like modifier; Suv39h, suppressor of variegation 3–9 homolog; TBL, transducin beta-like protein 1; TFTC, TATA-binding protein-free TAF-containing complex; TGIF, 5′-TG-3′ interacting factor TIP60: Tat interactive 60 kDa protein; TLE, transducin-like Enhancer of split; TSA, Trichostatin A; TRRAP, transformation/transcription domain-associated protein; YY1, Yin Yang 1

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1. Introduction

The Transforming Growth Factor type β (TGFβ) family of ligands and receptors are important mediators of cell–cell communication, thereby determining the fate and steering the differentiation of various cell types during embryonic development in metazoans, and are essential for tissue homeostasis and repair in postnatal life as well. About one decade ago, Smad proteins were discovered as essential intracellular effector proteins in TGFβ signaling. All the Smads share two highly conserved domains (the MH1 and MH2 domain), which are separated by a variable linker region. Two distinct classes of Smad are required to convey the cellular responses to TGFβ signals: the receptor regulated Smads (R-Smads) and Smad4. R-Smad activation is triggered through phosphorylation by type I serine threonine-kinase receptors which themselves are targets for phosphorylation by type II receptors in the liganded receptor complex. R-Smads were classically divided into two groups based on the most intensively studied upstream ligands: Smad2 and 3 act downstream of TGFβs, nodals and activins, and Smad1, 5 and 8 act downstream of bone morphogenetic proteins (BMPs). In endothelial cells, the latter Smads can also be activated by TGFβ through Alk1, a type I receptor for TGFβ, and counteract the effect of Smad2 and 3 activated by TGFβ through another receptor, Alk5 [1]. Recent data illustrate that several non-Smad signaling cascades can emanate from liganded receptor complexes and direct targets for phosphorylation by the type II receptors, such as LIMK1/2 [2,3] and PAR6 [4], have been identified as well. Nevertheless, Smads remain critical TGFβ dependent regulators of gene transcription. Activated R-Smads bind to Smad4 and shuttle as a complex to the nucleus where they affect gene expression in a variety of ways. A third group of Smad proteins, the inhibitory Smads (with Smad6 and 7), is produced in response to cytokine signaling including TGFβ, activin and BMP themselves, and negatively regulate the cascade. Smads turn out to be extremely versatile proteins that can directly bind to regulatory sequences in target promoters. High affinity and specificity of DNA binding is mediated through the association of the Smads with other (and many) DNA-bound transcription factors [5]. These Smad-containing complexes mark a gene for activation or repression through additional Smad-dependent recruitment of co-activators and co-repressors.

Even before the Smad era, a direct link between TGFβ and regulation of chromatin structure was reported through the study of CCAAT transcription factor 1 (CTF-1). The activation domain of this transcription factor was found to interact with histone H3 in a TGFβ-sensitive way [6]. More recently, the ability of Smad4 to induce large scale chromatin unfolding has been visualized by tethering the protein (in a fusion with the lac-repressor) to a heterochromatic chromosome region containing lac operator repeats [7]. We summarize here the emerging knowledge on the new roles of Smads as docking proteins for chromatin modifying factors in the nucleus as well as their putative function as dynamic regulators of chromatin structure.

2. Chromatin modulation

In order to accommodate a large volume of genetic information into a small compartment, the DNA within the eukaryotic nucleus is complexed with histones and non-histone proteins into chromatin. The structural unit of chromatin is the nucleosome, in which 147 bp of superhelical DNA is wrapped around a histone octamer core containing two copies each of histones H2A, H2B, H3 and H4 [8]. Histones play an important role in the modulation of the chromatin structure. The amino-termini of histones (the tails) are subject to posttranslational modification including acetylation, phosphorylation,