BYJU'S EXAM PREP

Full-Form of Bone Morphogenetic Protein (BMP)

BONE MORPHOGENETIC PROTEIN (BMPS)

Introduction- BMPs are a group of growth factors that induce the formation of bone and cartilage. They were originally discovered in their ability to induce bone formation and named as Bone Morphogenetic Proteins. This protein family is highly conserved across animal species; BMP-7 of humans and mouse share almost 98% similarity in their amino acid sequence.

BMPs constitute the largest part of the TGF-β superfamily. The members of the BMP family differ from other members of the TGF-β superfamily in having seven conserved cysteine residues in the polypeptide. The BMPs are synthesized as precursor proteins. The active BMP is released by proteolytic removal of the signal peptide and pro-peptide.

Types of BMPs

BMP	Function
BMP1	It is a metalloprotease that is involved in cartilage development
BMP2	It acts as a disulfide-linked homodimer and plays a key role in osteoblast differentiation
BMP3	It induces bone formation
BMP4	It regulates the development of teeth, limbs and bone. It also plays an important role in dorsal-ventral axis formation and ovarian follicle development
BMP5	It helps in cartilage development
BMP6	It plays an important role in controlling iron homeostasis by regulation of hepcidin
BMP7	It induces the production of SMAD1 and also plays a key role in renal development and repair
BMP8a	It plays an important role in bone and cartilage development
BMP8b	It is expressed in the hippocampus area
BMP10	It plays an important role in the development of the embryonic heart
BMP 11	It plays an important role in controlling the anterior-posterior patterning
BMP15	It controls oocyte and follicular development

Functions of BMP:

- Play an important role in embryonic development specifically in early skeletal formation.
- The main function of BMPs are to allow the undifferentiated pluripotent cells to differentiate into cartilage and bone forming cells.
- BMP signaling controls the early formation of Mullerian duct, which eventually gives rise to the female reproductive tract.

- BMP signaling is also involved in the formation of foregut and hindgut, intestinal villus patterning and endocardial differentiation.
- BMPS are also involved in the process of adipogenesis, by functionally regulating the adipose tissue. The process of white adipogenesis is favored by BMP4 while the process of brown adipogenesis is done by BMP7.

Mode of signaling:

- The members of the TGF-β family activate members of the Smad family of transcription factors.
- The TGF-β ligand binds to a type II TGF-β receptor, which allows that receptor to bind to a Type I TGF-β receptor.
- As the two receptors are in close contact, the Type II receptor phosphorylates a serine or threonine residue on the Type I receptor.
- This results in activation of the Type-I receptor.
- The activated Type- I receptor now phosphorylates the Smad proteins.
- There are three types of Smad proteins that function in the TGF-β signaling pathway:
  i. R-Smads (Receptor-regulated Smads) – Smad 2 and Smad 3
  ii. Co-Smads – Smad 4
  iii. I-Smads (Inhibitory Smads)- Smad 7

a) TGF-β proteins are stored in an inactive form in the extracellular matrix:

- The TGF-β is synthesized with a long N-terminal prodomain that is cleaved off in the Golgi complex.
- The monomeric form of TGF-β contains three intramolecular disulfide linkages.
- This prodomain remains noncovalently attached to the TGF-β growth-factor domain as the protein is secreted and prevents binding of the TGF-β to its cell-surface receptors.
- Certain mechanisms like protease digestion release the TGF-β from the extracellular matrix which leads to activation of cell signaling.

b) **Three separate TGF-β receptor proteins participate in binding TGF-β and activating signal transduction**:

- The three TGF-β receptor complexes were referred to as RI, RII and RIII respectively.
- The most abundant is the RIII, which is a β-glycan, which is a cell-surface proteoglycan.
- RIII is a transmembrane protein that binds and concentrates TGF-β molecules near the cell surface.
- The RI and RII receptors are dimeric transmembrane proteins with serine/threonine kinases as part of their cytosolic domains.
- RII exhibits constitutive kinase activity; that is; it is active even when not bound to TGF-β.
- Binding of TGF-β to RII generates a new molecular surface at the TGF-β-RII interface that docks to RI; which results in ligand-induced receptor hetero-oligomerization.

- An RII subunit then phosphorylates serine and threonine residues in a highly conserved sequence of the RI subunit adjacent to the cytosolic face of the plasma membrane, thereby activating the RI kinase activity.

c) Activated TGF-β receptors phosphorylate Smad transcription factors:

- In some cells, TGF-β binds to the Type III TGF-β receptor (RIII) , which presents the TGF-β to the Type II receptor
- In other cells, TGF-β binds directly to RII, a constitutively active kinase.
- Ligand-bound RII recruits and phosphorylates the type I TGF-β receptor (RI), which does not directly bind TGF-β.
- The RI kinase activity inhibition gets released as a result..
- Activated RI then phosphorylates Smad2 or Smad3 setting in motion a conformational change that unveils its nuclear localization signal (NLS).
- Two phosphorylated molecules of Smad 2/3 bind to a co-Smad (Smad4) molecule, which is not phosphorylated and to an importin; forming a large cytosolic complex.
- After the entire complex translocate into the nucleus; RAN-GTP causes dissociation of the importin
- A nuclear transcription factor (TFE3) then associates with the Smad 2/3/Smad4 complex forming an activation complex that binds to regulatory sequences of a target gene.
- Activation complex then recruits transcriptional co-activators and induces gene transcription.
- Smad 2/3 is dephosphorylated by a nuclear phosphatase and recycles through a nuclear pore to the cytosol; where it can be re-activated by another TGF-β receptor complex.

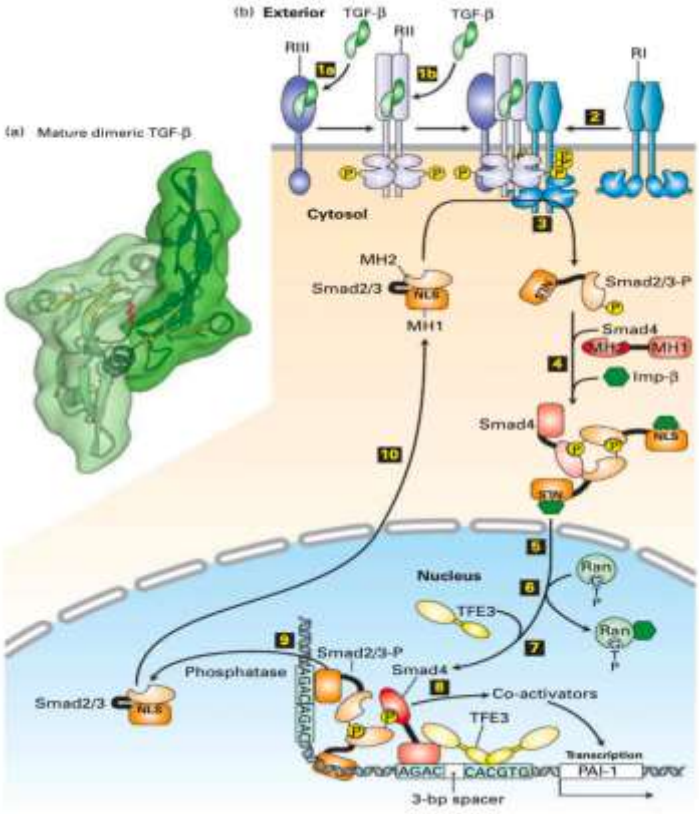

Fig: Mode of TGF-β signaling

d) Negative feedback loop regulates TGF-β/Smad signaling:

- Two cytosolic proteins SnoN and Ski are induced by TGF-β signaling in virtually all body cells.
- They down-regulate the TGF-β/Smad signaling pathway.
- Ski represses Smad function by directly binding to Smad4.
- Thus, binding of Ski disrupts the normal interactions between Smad3 and Smad4 necessary for transcriptional activation.
- Ski recruits the protein N-CoR which directly binds to mSin3A.
- mSin3A then interacts with histone deacetylase (HDAC).
- HDAC is an enzyme that promotes histone deacetylation on nearby promoters; thereby repressing gene expression.
- Thus, both the processes transcriptional activation induced by TGF-β and mediated by Smad complexes is shut down.
- Among the other proteins induced after TGF-β stimulation after the I-Smads, especially Smad7.
- Smad 7 blocks the ability of activated Type I TGF-β receptors (RI) to phosphorylate R-Smad proteins.
- Smad7 also targets TGF-β receptors for degradation.

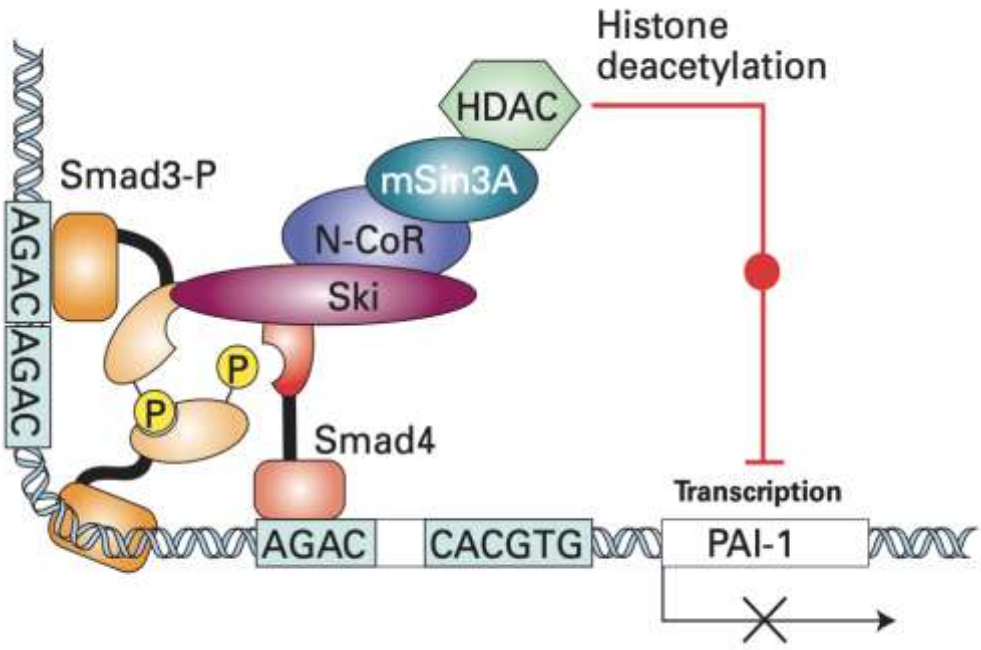

Fig : Model of Ski-mediated down-regulation of Smad transcription - activating function

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