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Poster presentation

Crosstalk of cyclic GMP dependent kinase I and BMP signaling

Eva Heining*[1], Raphaela Schwappacher[1], D Horbelt[1], Otmar Huber[2] and Petra Knaus[1]

Address: [1]Institute for Chemistry/Biochemistry, Free University Berlin, Germany and [2]Institute for Biochemistry II, University Hospital Jena, Germany

Email: Eva Heining* - eva.heining@gmx.de

* Corresponding author

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Bone morphogenetic proteins (BMPs) are members of the TGFβ growth factor superfamily and have important roles in proliferation, development, differentiation of embryonic and adult cells, as well as in tissue regeneration. BMPs signal *via* two transmembrane serine/threonine kinase receptors, the BMP type I (BMPRIa and BMPRIb) and BMP type II (BMPRII) receptors which can form homo- and heterooligomeric complexes. They occur in distinct membrane areas, are differently modulated upon ligand binding and are subsequently endocytosed [1]. Upon ligand binding to the receptor complex a signaling cascade *via* Smad proteins or independent of Smads is initiated and results in expression of specific target genes.

cGMP-dependent kinase I (cGKI) was identified as a BMPRII interacting protein in a proteomics-based approach using the cytoplasmic BMPRII-tail region as bait [2]. cGKI is a cytoplasmic serine/threonine kinase and signals *via* the NO/cGMP/cGK pathway and is involved in regulation of growth, differentiation and apoptosis of cells [3].

The involvement of cGKI in BMP signaling could be validated as it positively influences receptor and Smad activation at the plasma membrane as well as it enhances the transcription of target genes in the nucleus [4]. New results hint towards the fact that cGKI is involved in endocytotic events in BMP signaling, as it dynamically interacts with BMPRII upon BMP-2 stimulation and enhances the internalization of the receptor. Interfering with endocytosis in the cell inhibits BMP signaling mediated by BMP-2 and cGKI.

Clinical evidence for the involvement of cGKI in BMP-signaling is given by the fact that mutations in the BMPRII are related to the development of *primary arterial hypertension* (PAH) [5]. Patients with PAH suffer from vasoconstriction and elevated pressure in the pulmonary arteries, but the distinct pathway leading to the specific phenotype is still unraveled. We could show that ineffective signaling caused by mutant BMPRII found in PAH could be compensated through cGKI [4].

References

1. Hartung A, Bitton-Worms K, Rechtman MM, Wenzel V, Boergermann JH, Hassel S, Henis YI, Knaus P: **Different routes of bone morphogenic protein (BMP) receptor endocytosis influence BMP signaling.** *Mol Cell Biol* 2006, **26:**7791-7805.
2. Hassel S, Eichner A, Yakymovych M, Hellman U, Knaus P, Souchelnytskyi S: **Proteins associated with type II bone morphogenetic protein receptor (BMPR-II) and identified by two-dimensional gel electrophoresis and mass spectrometry.** *Proteomics* 2004, **4:**1346-1358.
3. Hofmann F, Feil R, Kleppisch T, Schlossmann J: **Function of cGMP-dependent protein kinases as revealed by gene deletion.** *Physiol Rev* 2006, **86:**1-23.
4. Schwappacher R, Weiske J, Heining E, Ezerski V, Marom B, Henis YI, Huber O, Knaus P: **Novel crosstalk to BMP signaling: cGMP-dependent kinase I modulates BMP receptor and Smad activity.** *EMBO J*, 2009 in press.
5. Waite KA, Eng C: **From developmental disorder to heritable cancer: it's all in the BMP/TGF-beta family.** *Nat Rev Genet* 2003, **4:**763-773.