287
CRM-1 facilitates BMP signaling in *Caenorhabditis elegans*

Y.F. Wong, C.F. Ko, K.L. Chow
Hong Kong University of Science and Technology, Hong Kong

Proteins containing repeating cysteine-rich (CR) domains are known to be able to bind and sequester bone morphogenetic proteins (BMPs) in the extracellular space, thereby modulating the signaling activity. The vertebrate *Crim1* encodes a putative transmembrane protein with multiple CR domains. We have identified a spliced form of the *Caenorhabditis elegans* homologue of this gene, *crm-1*, with highly conserved C-terminal transmembrane domain and six conserved CR domains. In this study, we used the body morphology of *C. elegans* as an indicator to assess the regulatory role of *crm-1* on BMP signaling. Our results show that reduction of *crm-1* activity leads to a small body phenotype reminiscent to that of BMP pathway mutants. Epistatic analysis revealed that *crm-1* acts upstream of the *dbl/sma* pathway dependent of the presence of DBL-1, the homologue of vertebrate BMP4. The loss-of-function *crm-1* phenotype can be suppressed by constitutively supplying the *sma-4* activity. We also showed that *crm-1* is co-expressed with *dbl-1* in a subset of neurons in the ventral nerve cord, where DBL-1 is produced. We propose that *crm-1* is facilitating the BMP signaling in *C. elegans*. Potential model concerning this modulation event will be discussed. (The study is funded by Research Grants Council, Hong Kong.)

doi:10.1016/j.ydbio.2006.04.315

288
Mutation of an upstream cleavage site in the BMP4 prodomain leads to tissue-specific loss of activity

Devorah C. Goldman [1], Renee Hackenmiller [1], Takuya Nakayama [1], Shailaja Sopory [1], Crispin Wong [1], Holger Kulessa [2], L. Christian [1]
[1] *OHSU, Portland, OR, USA*
[2] *Vanderbilt Univ. Med. Center, Nashville, TN, USA*

ProBMP4 is initially cleaved at a site adjacent to the mature ligand (the S1 site) allowing for subsequent cleavage at an upstream (S2) site. BMP4 synthesized from exogenous precursor in which the S2 site cannot be cleaved is rapidly degraded, and thus less active when overexpressed in *Xenopus*. To study the physiologic relevance of cleavage at the S2 site, and to begin to test the hypothesis that tissue-specific cleavage of this site regulates BMP4 activity in vivo, we generated mice carrying a point mutation that prevents cleavage at the S2 site ($Bmp4^{S2G}$). $Bmp4^{S2G/S2G}$ mutants show severe loss of BMP4 activity in some tissues, such as testes and germ cells, whereas other tissues that are sensitive to *Bmp4* dosage, such as the limb, dorsal vertebrae and kidney, develop normally. In a haploinsufficient background, inability to cleave the S2 site leads to embryonic and postnatal lethality due to defects in multiple organ systems. These data demonstrate that cleavage of the S2 site is essential for normal development and suggest that this site might be selectively cleaved in a tissue-specific fashion.

doi:10.1016/j.ydbio.2006.04.316

289
BMP regulates multiple processes during retina regeneration

Tracy Haynes, Christian Gutierrez, Juan-Carlos Aycinena, Bret Lehman, Swati Reddy, Katia Del Rio-Tsonis
Miami University, Oxford, OH, USA

The embryonic chick is able to regenerate a complete neural retina after retinectomy between developmental stages 22 and 24 in the presence of fibroblast growth factor (FGF). The regeneration is complete 7days post-retinectomy and occurs via two distinct mechanisms: transdifferentiation of the RPE and by activation of retinal progenitor cells (RPCs) present in the anterior margin of the eye. Here, we focus on the role of the bone morphogenetic protein (BMP) pathway during retina regeneration from the RPCs. Overexpression of the BMP receptor, BMPR-IA, in the presence of FGF results in an increase in regeneration from the anterior margin and an expansion of the RPCs while inhibiting the BMP pathway by overexpressing noggin in the presence of FGF results in a decrease in regeneration from the anterior margin and a significant reduction in the number of RPCs. Differentiation of all cell types occurs when BMPR-IA is overexpressed with FGF; however, there is an increase in the number of ganglion and amacrine cells and Muller glia cells are disorganized. Overexpressing noggin affects differentiation even when FGF is present with only photoreceptors and Muller glia cells present in significant numbers. Apoptosis is significantly increased when BMPR-IA is overexpressed in the presence of FGF especially at later stages of regeneration while no cell death is detected when noggin is overexpressed along with FGF. These results suggest BMP plays multiple roles in the retina regeneration process by regulating proliferation, differentiation, and apoptosis of RPCs and their derivatives.

doi:10.1016/j.ydbio.2006.04.317

290
Understanding the mechanism of Wnt coreceptor LRP6 activation

He Huang, Xi He
Neurobiology Program, Department of Neurology, Children's Hospital, Boston, MA, USA

How the Wnt receptor complex is activated and inhibits β-catenin phosphorylation–degradation is a central question in Wnt signal transduction. Recent results revealed that Wnt in-