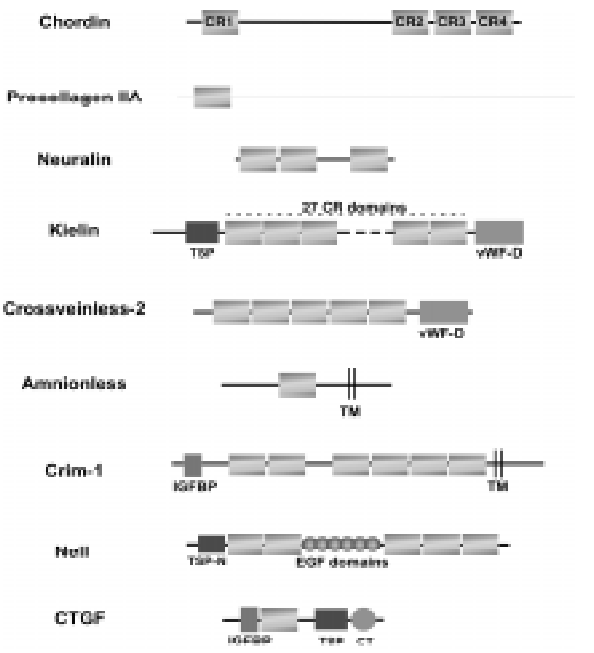
An evolutionarily conserved system that regulates dorsal-ventral patterning via the BMP, Chordin, Tolloid and Twisted gastrulation proteins

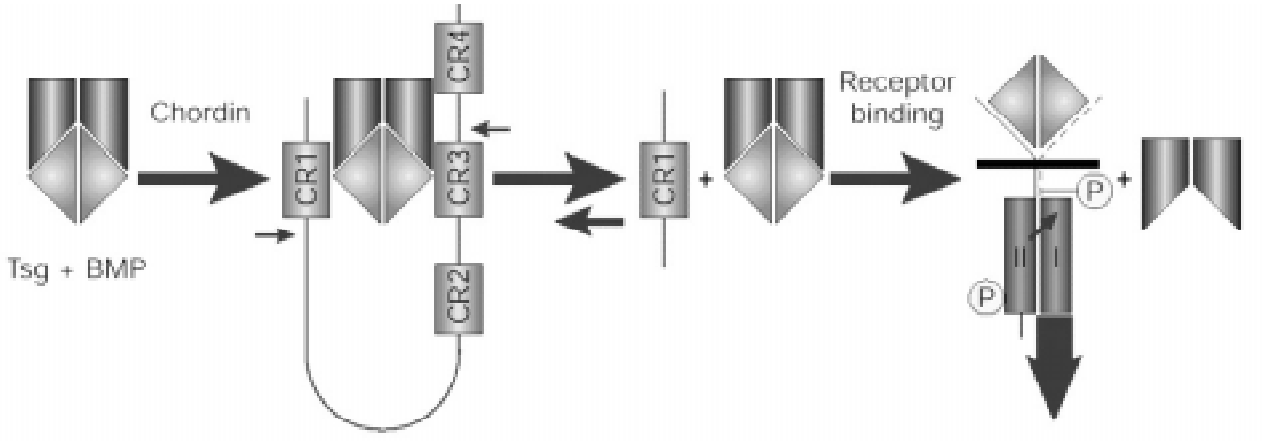
EDDY M. DE ROBERTIS*, EDGAR PERA, JOSÉ GARCÍA-ABREU, JUAN LARRAÍN, M. OELGESCHLÄGER and CATHERINE COFFINIER

Howard Hughes Medical Institute & Dept. of Biological Chemistry, University of California, Los Angeles, CA, USA

Dorsal-ventral patterning in vertebrate and *Drosophila* embryos is controlled by a system of interacting secreting proteins that include BMP, Chordin, Xolloid, Tolloid and Twisted gastrulation. Chordin, the molecule that generates the pattern, is a BMP antagonist that contains four cysteine rich (CR) domains that bind to BMP, blocking its binding to the receptor. Tolloid/Xolloid encodes a metalloproteinase that cleaves Chordin at two sites, restoring the ability of BMP to signal. Twisted gastrulation has two distinct and sequential activities in BMP signaling. First, Tsg makes Chordin a better BMP antagonist by forming a ternary complex that prevents binding of BMP to its cognate receptor. Second, after cleavage of Chordin by Xolloid, Tsg competes the residual activity of Chordin fragments and facilitates their degradation. This molecular pathway, in which Xolloid switches the activity of Tsg from a BMP antagonist to a pro-BMP signal once all endogenous full-length Chordin is degraded, helps explain how sharp borders between embryonic territories are generated during development.



CR domains of the type present in Chordin are found in many other extracellular space proteins. These include the fibrillar procollagens (type I, III and V), amnionless, neuralin-1 and 2, CRIM-1, crossveinless-2 and CTGF. Neuralins contain three cysteine-rich domains and can bind Tsg, which promotes their degradation, much in the same way as it does with Chordin. *Crossveinless-2* (*cv-2*) is a *Drosophila* gene required for maximal Dpp signaling in the wing. Interestingly, a second Tsg gene is encoded by *cv-1*, a gene that has a phenotype identical to that of *cv-2* in the fly wing. CR domains are not only associated with Tsg, but also are found associated with IGF-binding protein domains in some cases such as CRIM-1 (cysteine-rich motorneuron-1) and CTGF (connective tissue growth factor). The possibility that some of the CR extracel-



***Address correspondence to:** Eddy M. De Robertis. Howard Hughes Medical Institute & Dept. of Biological Chemistry, University of California, Los Angeles, CA, USA. e-mail: derobert@hhmi.ucla.edu

lular proteins may deliver combinations of growth factors to cell surface receptors will be discussed.

References

COFFINIER, C., TRAN, U., LARRAÍN, J. and DE ROBERTIS, E.M. (2001). Neuralin is a novel Chordin-related molecule expressed in the mouse neural plate. *Mech. Dev.* 100: 119-122.

DE ROBERTIS, E.M., LARRAÍN, J., OELGESCHLÄGER, M. and WESSELY, O. (2000). The establishment of Spemann's Organizer and patterning of the vertebrate embryo. *Nature Reviews Genetics* 1: 171-181.

OELGESCHLÄGER, M., LARRAÍN, J., GEISSERT, D. and DE ROBERTIS, E.M. (2000). The evolutionary conserved BMP-binding protein Twisted Gastrulation promotes BMP signalling. Nature 405: 757-763.