formation may be generated within the cell by internal processes or obtained from external signals. Storing information in a signaling pathway that functions as a gate allows the information to be used in a conditional manner. Information storage within a transmittal pathway requires sustained activation of components of the pathway, a process that is almost always deleterious. For example, continuous activation of Ras or Raf contributes to malignant transformation. Continuous activation of the gating pathway, however, would not cause potentially harmful overstimulation but would only modify the response generated by the signaling pathway upon receipt of external signals. Thus interactions between signaling and gating pathways could provide a biochemical basis for information storage and processing within the cell.

References and Notes

1. E. W. Sutherland and W. D. Wosilait, *Nature* **175**, 169 (1955); E. G. Krebs and E. H. Fischer, *J. Biol. Chem.* **218**, 483 (1956); M. Rodbell, L. Birnbaumer, S. L. Pohl, H. M. J. Krans, *ibid.* **246**, 1877 (1971); T. Pfeuffer, *ibid.* **252**, 7224 (1977); E. M. Ross and A. G. Gilman, *ibid.*, p. 6966.
2. J. D. Rothermel *et al.*, *J. Biol. Chem.* **258**, 12125 (1983); J. D. Rothermel *et al.*, *ibid.* **259**, 8151 (1984); J. D. Rothermel *et al.*, *ibid.*, p. 15294.
3. S. E. Egan and R. A. Weinberg, *Nature* **365**, 781 (1993); J. Avruch *et al.*, *Trends Biochem. Sci.* **19**, 279 (1994).
4. Signaling pathways can also interact with one another to produce a coordinated response. Sometimes, each pathway contributes a portion of the end-point signal. The contributions may be additive but are usually synergistic. Signaling proteins, including some isoforms of adenylyl cyclase capable of receiving such multiple inputs, are called coincidence detectors. T. W. Abrams, K. A. Karl, E. R. Kandel, *J. Neurosci.* **11**, 2655 (1991); H. R. Bourne and R. Nicoll, *Cell* **72** (suppl.), 65 (1993).
5. J. Wu *et al.*, *Science* **262**, 1065 (1993); S. Hafner *et al.*, *Mol. Cell. Biol.* **14**, 6696 (1994).
6. J. Chen and R. Iyengar, *Science* **263**, 1278 (1994).
7. S. Cowley, H. Paterson, P. Kemp, C. J. Marshall, *Cell* **77**, 841 (1994); S. J. Mansour *et al.*, *Science* **265**, 966 (1994).
8. C.-M. Fan *et al.*, *Cell* **81**, 457 (1995).
9. J. Jiang and G. Struhl, *ibid.* **80**, 563 (1995); W. Li *et al.*, *ibid.*, p. 553.
10. U. Frey, Y.-Y. Huang, E. R. Kandel, *Science* **260**, 1661 (1993); P. V. Nguyen, T. Abel, E. R. Kandel, *ibid.* **265**, 1104 (1994).
11. R. D. Blitzer *et al.*, *Neuron* **15**, 1403 (1995).
12. A. Myer-Franke *et al.*, *ibid.* **15**, 805 (1995).
13. J. P. Pieroni *et al.*, *J. Biol. Chem.* **270**, 21368 (1995).
14. D. L. Pettit, S. Perlman, R. Malinow, *Science* **266**, 1881 (1994); J.-H. Wang and P. Kelly, *Neuron* **15**, 443 (1995).
15. Although both coincidence signal detection and gating involve multiple pathways, there are fundamental differences between the two. For coincidence signal detection, both transmittal pathways must share a component capable of receiving and processing multiple signals. In contrast, the gating capability of a pathway is determined solely by the components of the target transmittal pathway. If they cannot be regulated, the pathway cannot be gated.
16. P. J. Roach, *J. Biol. Chem.* **266**, 14139 (1991).
17. F. L. Huang and W. H. Glinsmann, *Eur. J. Pharmacol.* **70**, 419 (1976); S. Shinolikar and A. C. Nairn, *Adv. Second Messenger Phosphoprotein Res.* **23**, 1 (1991).

BMP-1: Resurrection As Procollagen C-Proteinase

A. H. Reddi

Bone morphogenetic proteins (BMPs) are bone-inducing molecules that have been isolated and cloned from the extracellular matrix (ECM). Unlike the other bone morphogens, BMP-1 is not a member of the transforming growth factor–β (TGF-β) family, but rather looks more like a protease—some researchers have suggested that it cleaves and activates TGF-β. In last week's issue of *Science*, Kessler *et al.* (*1*) reported that BMP-1 is indeed a protease, but that its substrate is procollagen, not TGF-β. BMP-1 is identical to procollagen C–proteinase (PCP), an enzyme essential for the proper assembly of collagen within the ECM.

The ECM is a supramolecular assembly of collagens, proteoglycans, and glycoproteins (*2*) that holds cells together. Its appearance in evolution coincided with that of multicellular Metazoa. The ECM and its interaction with cells allowed the organization of cells into tissues. The ECM has an intimate relation with cells. It is secreted as a cellular product, but can itself act upon cells and tissues. For example, implantation of demineralized ECM derived from bone results in the formation of new bone (*3*).

The active factors in the ECM that mediate this morphogenetic effect comprise a family of proteins—the BMPs. A simple bioassay facilitated their cloning (*4*, *5*). Reconstitution of a soluble extract of the matrix with insoluble collagen allows bone formation (*6*). Almost all of the dozen or so members of the BMP family are members of the TGF-β superfamily, the one exception being BMP-1. The black sheep status of BMP-1 may be a result of flaws in the original bioassays for osteogenesis (*4*). From the photographs in the published report (*4*), the cartilage observed in the bioassay actually appears to be growth plate cartilage contaminating the insoluble bone matrix. Thus, old cartilage may have been misidentified as newly formed tissue.

The author is in the Departments of Orthopedic Surgery and Biological Chemistry, Johns Hopkins University School of Medicine, Baltimore, MD 21205–2196, USA. E-mail: ahr@welchlink.welch.jhu.edu

The deduced amino acid sequence of the human BMP-1 protein reveals a domain structure of a metalloprotease from the astacin family, an epidermal growth factor (EGF)–like domain, and three domains with considerable sequence similarity. Thus, BMP-1 is related to the *Drosophila* gene *tolloid*, which is implicated in the patterning controlled by the *decapentapeptide* gene by virtue of its ability to activate TGF-β–like morphogens.

If BMP-1 is not a true TGF-β family member, how does it function? Is it actually a protease that activates TGF-β, as its homology to *tolloid* would suggest? The incisive work of Kessler *et al.* (*1*) shows unexpected similarities between BMP-1 and a protease they have been studying (PCP). These investigators expressed a recombinant BMP-1 in a baculovirus system and purified the protein. The recombinant BMP-1 and purified mouse PCP yielded similar COOH-terminal procollagen peptides.

Morphogenesis is the culmination of the cascade of pattern formation, body plan establishment, and attainment of adult form. An integral part of the morphogenetic cascade is the assembly of the ECM. The supramolecular self assembly of triple-helical collagen is triggered by the processing of COOH-terminal procollagen peptide by the newly discovered function of BMP-1. The recent work by Kessler *et al.* presents a new solution to the old riddle of the biological function of BMP-1 and places it directly at an essential control point of morphogenesis.

References

1. E. Kessler, K. Takahara, L. Biniaminov, M. Brusel, D. S. Greenspan, *Science* **271**, 360 (1996).
2. K. A. Piez and A. H. Reddi, *Extracellular Matrix Biochemistry* (Elsevier, New York, 1984).
3. M. R. Urist, *Science* **150**, 893 (1965); A. H. Reddi and C. B. Huggins, *Proc. Natl. Acad. Sci. U.S.A.* **69**, 1601 (1972).
4. J. M. Wozney *et al.*, *Science* **242**, 1528 (1988).
5. A. H. Reddi, *Curr. Opin. Genet. Dev.* **4**, 737 (1994); N. E. Cunningham *et al.*, *Growth Factors* **12**, 99 (1995); E. Ozkaynak *et al.*, *EMBO J.* **7**, 2085 (1990).
6. T. K. Sampath and A. H. Reddi, *Proc. Natl. Acad. Sci. U.S.A.* **78**, 7599 (1981).