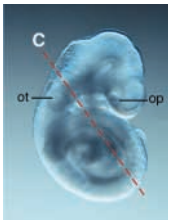
In this issue

By Jane Bradbury

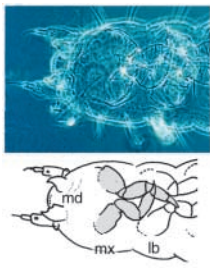
An embryological double act

Members of the transforming growth factor β (TGFβ) family of secreted growth factors regulate many embryonic processes. Now, Dunn et al. report (p. 1717) that Smad2 and Smad3, two closely related intracellular effectors of the TGFβ/activin/Nodal receptors, signal cooperatively in a dose-dependent manner to regulate mesoderm formation and patterning in the early mouse embryo. Although Smad2 and Smad3 are often functionally interchangeable, the development of mice lacking *Smad2* is severely disrupted, whereas *Smad3*-deficient mice have only subtle abnormalities. When the researchers genetically manipulated the expression ratio of Smad2 and Smad3, embryos with only one copy of each gene developed normally but loss of *Smad3* in the context of one wild-type copy of *Smad2* resulted in impaired production of anterior mesendoderm. *Smad2;Smad3* double homozygous mutants entirely lacked mesoderm and failed to gastrulate. This provides the first evidence that *Smad3* is essential during early post-implantation mouse development.



Mind the gap

Segmentation is well understood in *Drosophila*, a long germ insect in which all the segments are specified in the blastoderm. But most insects develop as short germ embryos and follow the ancestral mode of segmentation in which only the anterior segments are specified in the blastoderm. On p. 1729, Bucher and Klingler investigate segmentation in the flour beetle *Tribolium castaneum*, a short germ insect, by examining the expression and function of the gap gene *giant*. While the anterior domain of *giant* expression is similar in both insects, the posterior domain of *Tc'giant* expression is much more anterior than that of *Dm'giant*. The function of *giant* also differs between the two insects. For example, *Tc'giant* has a long-range effect on abdominal patterning, whereas *Dm'giant* functions only in its limited expression domain. The researchers suggest that changes in the abdominal gap gene system are central to the evolution from short to long germ insects.



A vital source

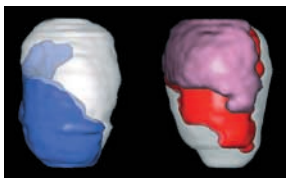
Platelet-derived growth factor-B (PDGFB) is necessary for microvasculature formation, and loss of PDGFB or its receptor – PDGF receptor β (PDGFRβ) – causes a wide range of abnormalities in mice, including defects of the heart, kidney and placenta. The formation of functional new vessels requires the recruitment of vascular-smooth muscle cells (VSMC) and pericytes, both of which express PDGFRβ and are thought to be primary targets for PDGFB. Bjarnegård and co-workers (p. 1847) have now determined the source of PDGFB involved in this process. PDGFB is produced from several cell types, including platelets and macrophages, but, using Cre-lox techniques, the researchers show that it is PDGFB from the endothelium that is crucial for pericyte recruitment. Furthermore, the phenotype of endothelium-restricted *Pdgfb* knockout mice resembles diabetic microangiopathy, prompting the authors to suggest that endothelium-restricted PDGFB mutants could provide a useful model for vascular complications of diabetes.

It's a hormonal thing

When times get bad – if food is limited, for example – *Caenorhabditis elegans* larvae enter the dauer larval stage 3 for several months, rather than racing through the normal larval stage 3 in a few hours. Attenuation of *daf-2* insulin/IGF or *daf-7* TGFβ-like signaling pathways causes developmental arrest at the dauer stage – as does loss of function of DAF-9, a cytochrome P450 related to steroidogenic hydroxylases. Two papers in this issue implicate DAF-9 in the production of important hormonal signals that regulate dauer diapause. On p. 1765, Gerisch and Antebi show that *daf-9* overexpressed constitutively in the hypodermis – the tissue in which endogenous *daf-9* expression is most visibly regulated by environmental cues – acts systemically to rescue the dauer phenotypes of *daf-9*, *daf-2* and *daf-7* mutants. This indicates that DAF-9 acts downstream of insulin/IGF and TGFβ signaling during dauer regulation. Mak and Ruvkun present similar results on p. 1777, and both research teams show that hypodermal *daf-9* expression is strictly dependent on *daf-12*, the nuclear receptor for the hormone produced by DAF-9.

Heard the news about Tbx1?

Inner ear sensory organs, which mediate balance and hearing in mammals, and the VIIIth cranial ganglion neurons, which innervate them, are derived from the otocyst, an epithelial vesicle formed by invagination of the otic placode. Raft et al. now report that Tbx1 differentially controls sensory organ and neural fate specification in the otocyst (see p. 1801). Tbx1 is a member of the T-box family of DNA-binding transcriptional regulators that control diverse aspects of embryogenesis, including cell-fate specification, in many organisms. The researchers show that while overexpression of *Tbx1* suppresses neurogenesis in the mouse otocyst epithelium, *Tbx1* loss of function results in ectopic neural precursor generation and sensory organ dysmorphogenesis. Together with expression data, these results indicate that *Tbx1* acts as a selector gene to specify regional identity in the otocyst.



In *Journal of Cell Science*

IGFBP-5 muscles in alone

IGFBP-5 is one of a family of proteins that bind to insulin-like growth factors (IGFs). It seems to regulate binding of IGFs to cell surface receptors, but may also have IGF-independent roles. IGFBP-5 is upregulated in certain tumours and, together with IGF2, is implicated in the control of muscle development. Pell and co-workers have examined the effects of both wild-type IGFBP-5 and a mutant form of the protein that cannot bind IGFs (mutIGFBP-5) on the differentiation of C2 myoblasts. They observe that the wild-type protein inhibits myogenesis but the mutant cannot. Interestingly, both forms of the protein inhibit apoptosis and, furthermore, protect cells from apoptosis induced by co-transfection of antisense *Igf2*. They conclude that the regulation of myogenesis by IGFBP-5 has two components: IGF-dependent inhibition of differentiation and IGF-independent promotion of cell survival. Given that IGFBP-5 is upregulated in tumours, its IGF-independent activity could also be an important factor in cancer progression.

Cobb, L. J. et al. (2004). Partitioning of IGFBP-5 actions in myogenesis: IGF-independent anti-apoptotic funtion. *J. Cell Sci.* **117**, 1737-1746.