But if GSP1 regulates zygote-specific genes in mt$^-$ cells, why does it not affect zygotic gene expression in mt$^+$ gametes? Perhaps this is because, as the authors suggest, zygote-specific gene promoters are inaccessible to GSP1 in mt$^+$ gametes or because GSP1 associates with a pre-existing mt$^-$-specific partner molecule to form a transcription-regulatory complex that activates zygote-specific gene expression. The parallels between these events and those in budding yeast indicate that atypical, gamete-specific, homeodomain proteins, such as GSP1 and budding yeast's MATα2, might have evolved to act as regulators of zygotic gene expression before animals and plants diverged. If so, then such studies could inform our understanding of how zygote gene expression is controlled in mammals.

Jane Alfred

References and links

ORIGINAL RESEARCH PAPER Zhao, H. *et al.* Ectopic expression of a *Chlamydomonas* mt$^+$-specific homeodomain protein in mt$^-$ gametes initiates zygote development without gamete fusion. *Genes Dev.* **15**, 2767–2777 (2001)

WEB SITE

The *Chlamydomonas* genome database: http://www.biology.duke.edu/chlamy_genome/

associate with SGP cells, as if they had lost all sense of direction — consistent with loss of Hh. Conversely, *patched* or *protein kinase A* mutant germ cells, in which Hh signalling is constitutively active, clumped together in the middle of the embryo and failed to migrate at all.

Interest in germ-cell migration is not new and so several genes that affect this process, such as *wunen* and *Columbus*, have already been identified. How does Hh fit in with previous models of germ-cell migration? As there are countless sources of Hh in the embryo, how is specificity of migration achieved? This is probably only one leg of a longer journey to find out how germ cells reach their targets.

Tanita Casci

References and links

ORIGINAL RESEARCH PAPER Deshpande, G. *et al.* Hedgehog signaling in germ cell migration. *Cell* **106**, 759–769 (2001)

WEB SITE Paul Schedl's homepage: http://www.molbio.princeton.edu/labs/schedl/index.htm

HUMAN GENETICS

Closing in on palatal disorders

The formation of the lip and palate is a complex and delicate process in craniofacial development, requiring the careful joining of tissues from two opposite sides of the mouth. Cleft lip/palate (CL/P) — in which the lip and palate have failed to close — affects up to 0.2% of live births, with most instances occurring in families with no history of the disease. However, ~30% of cases occur as part of single-gene syndromes. Understanding the genetics behind this class of common birth disorder has not been easy, but the recent identification of two loci, one for CL/P and the other for isolated cleft palate (CP), has provided clues to the developmental defects that underlie these malformations. The importance of these studies is underscored by the finding that mutations at the same locus could be responsible for both the inherited and sporadic forms of CL/P, indicating a model that could lead to the identification of genes for other common, complex birth defects.

In the first of two studies, Claire Braybrook and co-workers went in search of the causative locus for a specific subclass of CP — cleft palate with ankyloglossia (CPX) — which is inherited as a semi-dominant X-linked disorder. The locus was delimited to a region of Xq21; of the three plausible transcripts within the candidate interval, only one, the conserved *TBX22* (T-box 22) gene, was mutated in affected males from an Icelandic family. Mutations in *TBX22* — missense, nonsense, splice site and frameshift — were also observed in individuals with CPX from five other families of different ethnic backgrounds, and are predicted to cause a complete loss of function of *TBX22*. This mutation distribution, the expression of *TBX22* in the palate and the involvement of T-box family genes in early development, make *TBX22* a likely determinant in palate morphogenesis.

The starting point for the second study, by Mehmet Sözen *et al.*, was their earlier finding of a gene responsible for the inherited CL/P-ectodermal dysplasia syndrome (CLPED1), an autosomal-recessive disorder attributable to mutations in the poliovirus receptor-related 1 gene, *PVRL1*. In the Venezuelan community on Margarita Island that they studied, CLPED1 is very frequent and is caused by homozygosity for the *PVRL1* nonsense mutation, W185X. Because the level of sporadic CL/P is also high on this island, the authors were curious to find out whether the same W185X variant was involved in both familial and sporadic forms of CL/P. Although there was no significant difference between the heterozygosity for W185X in sporadic CL/P patients and normal, unrelated islanders, a difference was observed in a population on the adjacent Venezuelan mainland. It seems likely that heterozygosity for W185X is a moderate genetic risk factor for sporadic CL/P, at least in this population, but is only one of many genetic and environmental contributors.

The story will not end here, as more susceptibility loci for CL/P defects will no doubt emerge. For all of them, the identification of the molecular lesion must be followed by a characterization of the resulting developmental pathology. In the case of *PVRL1*, which encodes nectin 1 — a cell–cell adhesion molecule important for cell fusion — this process has already begun. A key message to emerge from these two papers is that rare developmental syndromes can indicate candidate loci for more common disorders — a strategy that is especially welcome when standard mapping approaches are not an option.

Tanita Casci

References and links

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FURTHER READING Murray, J. Time for T. *Nature Genet.* **29**, 107–109 (2001)