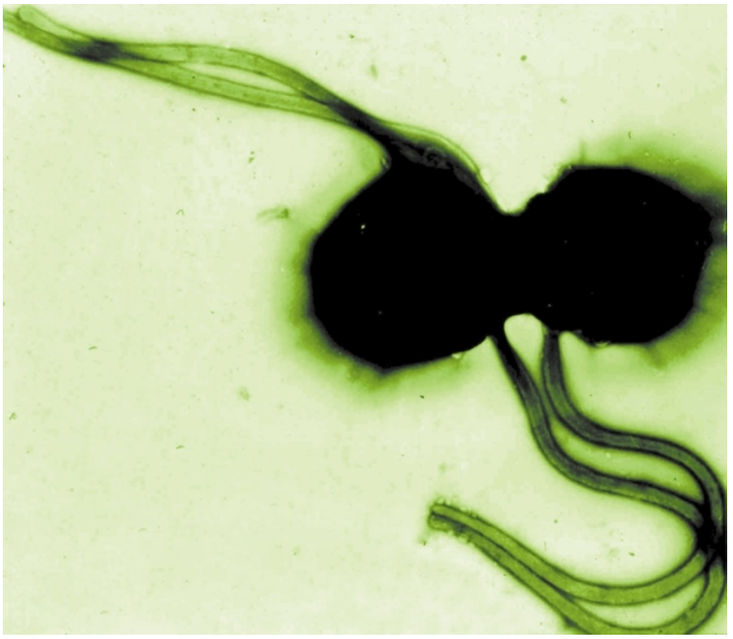
GENE REGULATION

Probing zygotic gene control



Courtesy of William Snell, University of Texas Southwestern, USA.

Although it is known that fertilization triggers events that ultimately lead to the transcriptional activation of the zygotic genome, we know surprisingly little about these events — a factor that probably contributes to the low success rates of current mammalian-cloning efforts. So, to investigate the mechanisms that control zygotic gene transcription, Zhao *et al.* turned to *Chlamydomonas reinhardtii* — a unicellular alga — in which early zygotic development is easier to study. Here they report that the gamete-specific, homeodomain protein GSP1 can activate the transcription of some zygotic genes in the absence of gamete fusion. Their findings show that both gametes contribute proteins that are required for zygote development.

Chlamydomonas's quirky life cycle makes it amenable to studies of fertilization. Upon nutrient starvation, its haploid vegetative cells of two mating types — mt^- and mt^+ — undergo gametogenesis. When gametes of opposite mating type meet, they fuse together (see picture), triggering rapid zygote-specific gene expression. This expression occurs independently of protein synthesis, indicating that pre-exisiting factors in one or both gametes regulate the expression of these genes. As zygote maturation continues, zygotes clump together to form large aggregates and mt^--derived choloroplasts are selectively degraded — zygotes germinate on return to a nutrient-rich medium.

The previous finding that GSP1 is present only in mt^+ gametes led the authors to consider it as a candidate regulator of zygotic gene transcription in *Chlamydomonas*. To test this, they expressed *gsp1* in mt^- cells, and found that although the vegetative mt^- transformants appeared normal, they formed zygote-like aggregates on undergoing gametogenesis — a behaviour not seen in transformed mt^+ cells. The transformed mt^- gametes expressed six out of seven zygote-specific genes — the unexpressed gene, *ezy1*, is thought to be required for mt^- chloroplast destruction. Its lack of expression in mt^- transformants indicates that it is under separate regulatory control or perhaps is imprinted in mt^- gametes.

DEVELOPMENTAL BIOLOGY

Hedgehog shows the way

Cells that originate in one place in the embryo often have to migrate some distance to reach their ultimate place of residence. A good example of this is the *Drosophila* germ cells. These cells are specified by maternal factors and lie outside the posterior of the embryo, segregated from the soma until gastrulation. At this stage, they undergo a complex pattern of migration that brings them inside the embryo and into contact with two lateral clusters of somatic gonadal precursor (SGP) cells — an association that creates a functional gonad. But how do germ cells know where to go? In their study of this process, Girish Deshpande and colleagues have found that, by secreting Hedgehog (Hh), SGP cells could provide the attractive cue that guides germ cells to their destination.

The study, published in *Cell*, was based on the premise that germ cells would follow attractive signals derived from the SGP cells, and that the identity of such molecules could best be found by looking at genes involved in specifying SGP cell fate. Of several such genes, Hh seemed a particularly promising candidate — it is expressed in the SGPs (as shown by the distribution of Hh–*lacZ*) and is known to be a short- and long-range signalling molecule. A crucial experiment reinforced this prediction: when Hh was ectopically expressed in the embryo, using four different Gal4 drivers, it redirected the migration of a subset of germ cells towards the new source of Hh. An alternative explanation for these results — that germ cells were drawn to ectopic SGP cells newly induced by Hh — is unlikely, as the Hh-expressing cells were negative for a SGP-cell-specific marker.

If germ cells respond directly to Hh, rather than to a secondary signal, then it follows that the germ line should require cell-autonomous components of the Hh pathway for proper migration. Indeed, when mutant for positively acting members of the pathway (such as *smoothened* or *fused*), germ cells scattered randomly and failed to

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

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