Meeting report

Mice get their annual check-up

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A report on the 2004 meeting on Mouse Molecular Genetics, Cold Spring Harbor, USA, 1-5 September 2004.

The annual meeting on mouse molecular genetics, which alternates between Cold Spring Harbor and the European Molecular Biology Laboratory (EMBL) in Heidelberg, is the highlight of the meetings year for many mouse geneticists. It encompasses a wide spectrum of topics in mouse development and genetics and rewards participants with entertaining talks in areas they might not be following closely.

The Smads have it

The keynote address, the Rosa Beddington Lecture in honor of our late colleague, was delivered by Elizabeth Robertson (University of Oxford, UK). Her talk on Smad proteins, the downstream effectors of transforming growth factor beta (TGFβ) signaling, set the tone for the meeting, which this year had a decidedly developmental slant. Robertson reported a series of studies that used genetic manipulation to test the interrelationship of Smad proteins in regulating patterning in the early mouse embryo. Genetic studies had shown an interaction between Smad2 and Smad3 in down-regulating the pathway stimulated by the growth factor Nodal, indicating a functional redundancy between these two Smads. But this idea challenged the conventional wisdom based on differences in the biochemical activity of the proteins - that is, until it was discovered that alternative splicing of *Smad2* produces a minor transcript that is 95% identical to that for *Smad3*. To test experimentally whether this transcript could function like Smad3, Robertson removed an exon from the *Smad2* locus to make a mouse that expressed only the short form. The mice were indeed normal, even in the absence of Smad3. A clever genetic swap - putting the human *Smad3* gene into the mouse *Smad2* locus while at the same time knocking out the *Smad2* locus - showed that Smad3 adequately transduces Nodal signaling, indicating that Smad2 and Smad3 are functionally interchangeable. Finally, a knockout of Smad4, which acts as a cofactor for receptor-regulated Smads, revealed that only anterior patterning of the early embryo was affected, indicating a dedicated function for Smad4 in specifying the anterior region.

Patterning the early embryo from head to toe

In the session on embryonic patterning, several talks addressed anterior-posterior (A-P) axis formation in the pregastrulation-stage embryo, which consists of an inner layer of epiblast and an outer layer of visceral endoderm. The epiblast will form the entire body of the embryo following gastrulation, whereas the visceral endoderm will make extraembryonic membranes and also has a role in signaling positional information to the anterior epiblast. It is well known that the pregastrulation and early postgastrulation embryo, the 'egg cylinder', is flattened, and that after primitive-streak formation, this flattening coincides with the A-P axis. So it was natural to assume that the prestreak flattening coincided with the poststreak flattening, and thus also represented an early indicator of the A-P axis. Anterior and posterior molecular markers tell a different story, however. These markers indicate that the A-P axis is aligned with the short axis of the flattened cylinder in the pregastrulation embryo, not the long axis, and apparently shifts to the long axis as the primitive streak forms. How does this happen? Does the gene-expression pattern shift? Do cells migrate? Or does the egg cylinder change its shape?

Jérôme Collignon (Institut Jacques Monod, Université Paris VI, France) reported lineage-tracing studies that support the idea of a dramatic remodeling of the whole epiblast during the specific prestreak-to-poststreak transition as a mechanism for the shift in the A-P axis from the morphological short axis to the morphological long axis of the cylinder. He showed some mind-bending three-dimensional reconstructions of embryos made with wide-field optical coherence tomography that back up this idea. The tantalizing conclusion

from these images is that there is a dramatic change in shape of the embryo associated with the formation of a twist in the proamniotic cavity at the level of the boundary between embryonic and extraembryonic tissues. I, for one, am anxious to see how this twist is resolved.

And what might control this embryo shape change? Jeff Barrow (Brigham Young University, Salt Lake City, USA) supplied evidence for a candidate gene, *Wnt3*, that might play an important part. *Wnt3* is normally expressed in both the epiblast and the visceral endoderm in the posterior part of the embryo. Null mutant embryos fail to gastrulate and show a lack of posterior markers. Barrow used a conditional *Wnt3* allele and also chimeric analysis to show that it is the epiblast expression of *Wnt3*, and not the visceral endoderm expression, that is necessary for posterior identity and formation of mesoderm. Of interest to the control of A-P axis formation, he also observed that in *Wnt3* mutant embryos, the A-P axis is oriented along the short axis of the egg cylinder and apparently never shifts to the long axis. Could *Wnt3* be a causative factor for the shift?

Coming to your senses

Have you ever wondered why after you brush your teeth with menthol toothpaste even tepid water seems really cool? Or how certain odors elicit powerful memories and responses? Two entertaining and highly informative presentations in the Neurobiology session had everyone nodding in recognition of these phenomena. Linda Buck (Fred Hutchinson Cancer Research Center, Seattle, USA) chaired the session and also gave a talk on odorant receptors (ORs) in the nasal epithelium (in October, Buck, together with Richard Axel, was awarded the Nobel Prize in Physiology or Medicine for her work on these receptors).

About a thousand different ORs are expressed in the olfactory sensory neurons. Each neuron expresses a single OR and the receptors are used repeatedly and combinatorially, such that each odor has a distinctive OR code. But with billions of possible codes, how do we discriminate odors? Buck described the use of a transgenic tracer to investigate the spatial input of nasal epithelial cells to the olfactory bulb and the cortex. Although neurons with the same OR are scattered around in the nose, they converge on specific locations in the olfactory bulb, on a few glomeruli. In turn, inputs from one OR are targeted to clusters of neurons at specific sites in the olfactory cortex, creating a stereotypic spatial map that is not related to that in the bulb. This means that single cortical neurons may receive combinatorial inputs from many different ORs, resulting in a stereotypic sensory map. Using c-Fos expression as an indicator of neuronal activation, Buck has found that different odorants elicit different but partially overlapping activation patterns in the cortex and that the representation of each odorant is composed of a small subset of sparsely distributed neurons.

Ardem Patapoutian (The Scripps Research Institute, La Jolla, USA) described the mechanisms of temperature sensation in relation to a family of genes encoding thermosensitive ion channels that have been uncovered in the past four years. These temperature-activated transient receptor potential (TRP) ion channels, or thermo-TRPs, are differentially expressed in a subset of dorsal root ganglia neurons and some are specialized to detect distinct temperature ranges - for example, there are cool channels and hot channels. In addition, they also respond to certain non-thermal agonists such as chemical compounds. In what Patapoutian described as a "drugstore experiment", he combed the drugstore shelves inspecting lists of ingredients of toothpaste, gum and mouthwash, looking for compounds that activate these ion channels. Compounds such as 'hot' cinnamon or capsaicin (the heat in hot chili peppers) and 'cool' menthol activate the channels and can be used to study temperature sensation mediated by the different thermo-TRPs. Previous work has identified some family members that respond to different temperatures and others that sense a noxious temperature, whether it is hot or cold. There are also thermo-TRPs that are activated within the innocuous temperature range of 34-42°C.

Patapoutian reported new studies on mice mutant for *Trpv3*, a warm-sensitive ion channel that is activated at 33°C. Because the commonly used hot-plate test does not cover this temperature range, Patapoutian devised a hot plate with a difference: one half was a warm 35°C and the other was cooler, at room temperature. Normal mice prefer the warmer temperature and spend more time on that side of the hot plate, whereas mutants for *Trpv3* have no preference and spend equal time on either side, a nice demonstration that this ion-channel gene affects the sensing of warm temperature *in vivo*. It seems pretty obvious that temperature sensation within this range, as well as within the range of noxious temperatures, could have a selective advantage. Interestingly, *Drosophila* larvae have temperature preferences and will avoid a heated area; knockout of *TrpA* genes in *Drosophila* leads to loss of this avoidance behavior.

So why does menthol toothpaste make a drink of tepid water seem colder? The presence of menthol shifts the activation temperature of Trpm8 receptors to warmer temperatures, thus boosting the cooling effect and confounding the perception of absolute temperature. Like so much of the research at the conference, this rates as pretty cool.