High-energy physics

Vote for Little Higgs

The Higgs boson has eluded detection for the moment, but theorists remain busy reconsidering what form or forms this object of much desire might take. The latest thinking was aired at the International Conference on High Energy Physics, held last month in Amsterdam.

The existence of the Higgs particle was first proposed in the 1960s. It is the manifestation of the Higgs mechanism that explains why fundamental particles, such as electrons and quarks, have mass. Mathematically, the particle can be formulated as part of the standard model of high-energy physics, or it could take a more exotic form that goes 'beyond the standard model' (BSM). But attempts to find evidence that the Higgs — any Higgs — exists have so far failed. An exhaustive search at CERN's Large Electron Positron (LEP) collider in Geneva ended in 2000 with the tantalizing hint of a signal, such as the candidate Higgs decay pictured here: the particle tracks shown in green and yellow may originate from a Higgs particle, created in an electron–positron collision at the centre. But no unequivocal signature has been identified.

So what now? Well, the experimentalists haven't given up. They will continue the search at the Tevatron collider, currently up and running at Fermilab, Chicago; and CERN's Large Hadron Collider (LHC) will take up the baton in 2007. Some theorists, however, have

gone back to the drawing-board. The basis of the Higgs mechanism remains, but tweaks to the model in the light of experimental data are altering what we might expect to see.

At the Amsterdam meeting, Martin Schmaltz (Boston Univ.) reported the results of a 'straw poll' he conducted among a gathering of theorists: what, he asked them, is the most exciting development in BSM theory? The clear winner was 'Little Higgs' theory, which many of the voters admitted to working on themselves. According to this theory, there should be one or more Higgs particles with masses around the 200-GeV range — the Higgs must be heavier than 114.4 GeV, according to the LEP data (<http://lepewwg.web.cern.ch/LEPEWWG>), and is probably lighter than a few hundred GeV. Moreover, the Little Higgs prediction is that there are other new particles to be discovered at about the 1,000-GeV scale. One of them could be a candidate particle for dark matter, the substantial mass that astronomical observations tell us is out there in the Universe, but is unseen.

So the goalposts have moved, but what is the significance of the new thinking? The theory of particles and interactions is beset with divergences — calculations that do not converge to a meaningful value. One solution is to invoke 'supersymmetry', a theory that predicts that every fundamental particle has a heavier, 'superparticle' partner. The Higgs mechanism and supersymmetry sit alongside each other quite happily, and physicists have even searched for a supersymmetric Higgs. But the Little Higgs theory can stand alone. It solves the problem of divergences in the standard model, without the need for supersymmetry.

A 200-GeV Higgs particle is an enticing prize, which Fermilab will no doubt race to find before CERN's LHC project comes into operation. The partner particles at 1,000 GeV are food for thought for proponents of the Linear Collider — a next-generation machine that has yet to get the go-ahead but that physicists hope will be operational within the next decade.

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expressed in cells at the centre of the disc, precisely where the Dpp and Wg signals intersect (Fig. 1c,d). This ligand also seems to be a target of Wg and Dpp but, once activated, no longer needs these signals for its expression². Yet removing *Vein* activity has only mild effects, if any, on the leg, so other ligands must also be involved. Indeed, Campbell shows that Rhomboid, which is required to process a different class of EGFR ligands, is also expressed in distal cells. In fact, it is not until *Vein*, Rhomboid and one of its relatives, *Roughoid*, are all simultaneously removed that a marked loss of distal structures occurs¹. So, although the specific ligands that Rhomboid and *Roughoid* activate are not known, the 'third signal' from the hypothesized distal organizer is likely to be a cocktail of EGFR ligands that are functionally redundant.

Thus, as often occurs in biology, both the direct and the organizer models seem to be correct, and each provides only part of the solution to how the proximal–distal axis is generated. The activity of Dpp and Wg apparently directly regulates *Dil* and *dac*, which define broad domains along the proximal–distal axis⁶. But the new papers^{1,2} provide strong evidence for a distal organizer, induced by Dpp and Wg, that is the source of EGFR ligands, which in turn works at a distance to help pattern the distal part of the leg.

The region of the leg that is patterned by this activity gradient — the tarsus — seems to be evolutionarily ancient¹⁰. This fact, together with the involvement of RTK pathways in both vertebrate and invertebrate^{1,2} leg development, makes it tempting to draw comparisons between the evolutionary origins of these limbs. However, the embryological differences are too plentiful to propose that the limbs are directly related to each other. Rather, the many developmental parallels, including RTK signalling, are more likely to reflect conserved regulatory relationships between signalling pathways that work together in many places in development. Alternatively, it is possible that vertebrate and invertebrate limbs were both derived from some type of outgrowth, perhaps not a limb¹¹, that grew from the body of a common ancestor. If this outgrowth had a primitive proximal–distal axis, it might have used many of the same genes and pathways that are active in the limbs we know today.

Beyond these evolutionary issues, other questions arise from this work. What are the EGFR ligands that Rhomboid and *Roughoid* process, and why are several different ligands required? Is activation of the EGFR pathway enough to generate an extra proximal–distal axis, or are other signals also required? To what extent is the regulation of the tarsal genes by the EGFR pathway direct and dependent on different thresholds of EGFR activity, as opposed to the result of cross-

If Wg and Dpp do not regulate the expression of these distal genes, what does? During vertebrate limb development, proteins from the fibroblast-growth-factor family are expressed at the distal edge of the growing limb. These proteins drive the formation of the proximal–distal axis by promoting the proliferation of underlying cells. They do this by activating receptors on the cell surface that are enzymes (receptor tyrosine kinases, RTKs), which transduce the signal through a well-characterized pathway to the cell nucleus⁸. Although fibroblast

growth factors do not seem to be involved in fly limb development, mutations in another RTK, the epidermal-growth-factor receptor (EGFR), cause the loss of the distal tip of the fly leg⁹. Campbell¹ has found that a gradient of EGFR signalling is likely to be at work, because a stepwise reduction in EGFR activity is correlated with a gradual loss both of leg structures and of leg-disc marker genes in a distal-to-proximal direction.

But which EGFR-activating proteins (ligands) are involved here? Both papers^{1,2} suggest the involvement of *Vein*, which is