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50 & 100 YEARS AGO

50 YEARS AGO

To the young scientist making contact with industry or commerce fresh from school or university it comes as rather a shock to find that his general 'scientific' usage of the C.G.S. system has such small acceptance in the outside 'practical' world. True, he has used 'Winchester quarts' to hold his standard solutions made up in grams per litre, he has stirred with fractional h.p. motors and dabbled in foot-poundals and lb./sq. in. But he has learnt to think in metric units and centigrade degrees. He knows that engineers seem to be able to exist with other units, and he respects their attempts to decimalize the rather antique units that he finds them using. He will probably be surprised to learn that Great Britain narrowly missed adopting the metric system of weights and measures almost one hundred years ago by a handful of votes in Parliament.

From *Nature* 7 June 1958.

100 YEARS AGO

A poll has just been taken by the Geological Society to ascertain the opinion of the fellows resident in the United Kingdom as to the admission of women to the society. The number of voting papers sent out was 870, and 477 replies were received. An analysis of the votes shows that 248 fellows were in favour of the admission of women as fellows and 217 against their admission, but of this number only 133 voted against the admission of women at all, the remaining eighty-four being in favour of their admission as associates. The fact that there was a majority of thirty-one in favour of the admission of women as fellows should be an encouraging sign to the increasing number of women who are taking up scientific work and in other ways contributing to the extension of natural knowledge.

From *Nature* 4 June 1908.

planar bifurcation, but, between the two, a 90° rotation of the bifurcation plane leads to the arrangement of the resulting branches into a rosette (Fig. 2f on page 746). These simple branching modes are used iteratively to give rise to the labyrinthine network that constitutes the bronchial tree.

The repetitive nature of the branching modules, together with their hierarchical control and the fact that they are coupled, suggests that the genetic 'hard-wiring' for bronchial branching could actually be quite simple. Thus, determining how the genome encodes the early development of the lung might be more tractable than previously thought. It also gives hope that, some day, regeneration or engineering of damaged lung tissue might be possible.

How are the three branching modes regulated? Metzger *et al.* infer that, once left–right laterality of the lung is established, airway branching is driven by a 'master' branch generator, with three 'slaves' in the form of subroutines (series of discrete patterning events). Of these, one subroutine seems to instruct a periodicity clock, which times the appearance of subsequent branches; another determines the rotational orientation of the branches around the axis of the parent airway; and the third mediates bifurcation (Fig. 1).

The authors identify a protein called Sprouty2 as a candidate component of the periodicity-clock subroutine in mice. Sprouty2 is named after the excessive tracheal branching seen in fly mutants that lack this gene. In flies, branching of the tracheal airway is initiated and controlled by the *branchless* gene, the closest mammalian equivalent of which is the gene that encodes the signalling protein FGF10. Also, the receptor for the protein product of *branchless* is Breathless, whose mammalian counterparts are FGF receptors. Sprouty2 is an evolutionarily conserved, inducible downstream inhibitor of FGF-receptor signalling from flies to mice.

The *Fgf10* gene is expressed in the mesenchymal tissue, which overlies the epithelial-cell layer lining the emerging branch tip. The FGF receptor FGFR2 is expressed throughout the epithelium, and Sprouty2 is expressed locally at the branch tips[2]. Also, mutations in the *Fgf10* or *Fgfr2b* genes that prevent their expression completely abrogate lung branching, and either decreased FGF10 expression or enhanced expression of Sprouty2 produces a small, poorly branched lung. Thus, in both flies and mice — and probably in humans — Sprouty2 mediates fine regulation of FGF signalling at the correct time, place and dose to induce and control orderly airway branching.

Metzger and colleagues' observations further suggest that the balance between FGF expression, FGF-receptor activation and Sprouty2-mediated inhibition of FGF signalling is possibly a central component not only of the master branch generator but also of the periodicity-clock subroutine. The periodicity clock can be speeded up by increasing the internal pressure in cultured embryonic mouse lung tissue[3]. This gain-of-function effect, which involves a significant increase in the rate of branch extension, a reduction in inter-branch length and a shift from bifurcation to trifurcation of branch tips, is mediated by a pathway requiring FGF10, FGFR2b and Sprouty2[3–6]. Thus, the often-overlooked connection between physics and biology in developmental processes is clearly important.

Other crucial players involved in lung branching include a long list of gene transcription factors, such as Nkx2.1; major signalling pathways, including those mediated by retinoids, bone morphogenetic protein, Hedgehog and Wnt; and essential components of the extracellular matrix, especially fibronectin and laminin[6,7]. All these protein factors are expressed at the right time and place, and function in and around the tips of the airway branches. Equally important for structural reproducibility is suppression of branching at regions away from the tips. The signal protein Sonic hedgehog accomplishes this by negatively regulating *Fgf10* expression proximal to the tips, thus suppressing out-of-place branching.

Genes related to those encoding most, if not all, of these morphogenetic factors are thought to have been present even in *Urbilateria*, the common ancestor of the planarian flatworms[8]. So it is possible that conditions of relative oxygen shortage exerted strong evolutionary pressure on pre-existing groups of such genes, to select for tube formation and hence gas transport. In support of this idea, FGF signalling in flies is regulated by oxygen levels so as to match terminal tracheal branching to the local oxygen needs of a tissue[9]. In mice, and presumably in humans, the signalling pathway mediated by molecules such as hypoxia-inducible factor and vascular endothelial growth factor also plays a crucial developmental part with the FGF–FGFR–Sprouty2 pathway. Together, these pathways match the capillary vasculature to the epithelial layer in branches of the early lung, a process that is crucial for determining the eventual gas-diffusing capacity of the organ[10].

Whether a master branch generator controlling a select few slave subroutines represents a general developmental strategy that has been reused over evolutionary time, in different branched organs, remains an intriguing possibility. Also, solving the specific problem of gas diffusion as a limit on size, and discovering how simplified, genetically controlled branching routines interact with physical and biological factors to direct complex yet reproducible patterns of development, will be matters of great interest. To quote Charles Darwin as interpreted by biologist Sean Carroll, they will aid our understanding of how "endless forms most beautiful" have evolved from a relatively simple tool-box of genetic modules. ■

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