

one of these planes. Most of the companions to Centaurus A are gas poor, but there are several systems that contain gas and in which star formation is occurring in each plane.

The situation in the Messier 81 Group is less compelling but still suggestive. Here, there is a distinction between the distribution of the gas-poor satellites and that of gas-rich satellites that are undergoing star formation. The gas-poor systems lie in a flattened distribution that have characteristic dimensions of 60×120 kpc, with the flattening coincident with the 'Local Sheet' structure⁶ that harbours all the galaxies mentioned above and which extends over a long dimension of 10 Mpc and with a thickness of 1 Mpc. The gas-rich satellites typically lie farther from Messier 81, and loosely align to a plane of their own.

This discussion of the organized distribution of satellites is anchored in the solid evidence reported by Ibata and colleagues for a thin plane with coherent kinematics. There are hints that structure in the distribution of satellites is the norm. The subject deserves further attention, but it should be noted that the planes that have been discussed on scales

of 300–500 kpc have a general alignment with the Local Sheet. This sheet forms a wall of an anti-structure, the 'Local Void', that strongly affects the development of nearby structure⁶.

Ibata *et al.* only touch on possible scenarios underlying the formation of the planar structures. The new information compounds a familiar galaxy-formation problem — a deficiency in the numbers of satellites found compared with theoretical expectations^{7,8}. Now, it seems, not only is there a paucity of satellites, but also most of those that do exist are in these organized structures. The very organization suggests that the structures (possibly as distinguished from their constituents) are not ancient.

Current ideas about galaxy formation propose that material (both gas and already constructed galaxies) falls into the extended haloes around galaxies as flows along filaments. The orbital angular momentum of the infalling material over time tends to cause motion that has the same direction of rotation as that of the dominant galaxy in the halo, resulting in the build-up of a spiral disk in the galaxy. It

is reasonable to assume that newly accreted satellites would share the sense of rotation, but that after a few orbits they would tend to become scrambled. Because infalling galaxies around Messier 31 adhere to such a thin plane, it would seem that they do not take many excursions before they are absorbed in the central galaxy. ■

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pole as the embryo elongates. In parallel with this, cell-autonomous oscillations in gene expression that are coordinated across the tissue define the timing of segment formation. The overall outcome is sequential segment formation in an anterior-to-posterior direction.

The predicted oscillations in gene activity have been visualized in chemically fixed and in live embryos, and correlate with the progressive pattern of somite formation. Furthermore, genetic manipulations of wavefront velocity or oscillation frequency modulate segment size³, as predicted by the clock and wavefront model.

In the intact embryo, oscillations are synchronized between adjacent cells, probably through the activity of the Notch signalling pathway. The frequency of oscillation in gene expression decreases towards the anterior PSM, so that anterior cells reach maximal signalling activity later than posterior cells. Therefore, the pattern of Notch activity seems to propagate from the posterior to the anterior PSM. This wave of molecular activity is not part of the original clock and wavefront model. So, what could be the function of such waves? Do they contribute to somite differentiation or scaling? And what is the molecular basis for these dynamics? Answering these and related questions is greatly facilitated by the ability to visualize⁹ and perhaps perturb the differentiation process as it progresses¹⁰.

Although methods for live imaging of intact embryos have been developed, they are limited, in part because of the complex geometry of the embryo. Lauschke *et al.* present an *ex vivo* (tissue culture) model that recapitulates

DEVELOPMENTAL BIOLOGY

Segmentation within scale

Irrespective of an organism's size, the proportional sizes of its parts remain constant. An experimental model reveals size-dependent adjustment of segment formation and gene-expression oscillations in vertebrates. SEE LETTER P.101

NAAMA BARKAI & BEN-ZION SHILO

Developing organisms face a major challenge: their body pattern must be adjusted — scaled — to their body size. But how is tissue size 'measured'? And what conveys general size information to the local settings of each cell? Despite intense interest, the mechanistic basis of scaling is poorly understood. On page 101 of this issue, Lauschke *et al.*¹ report that scaling persists in a tissue-culture model that simulates early segmentation in the vertebrate embryo. The simple, two-dimensional geometry of this system, and the fact that it can be visualized in real time and manipulated, opens exciting avenues for studying the formation and scaling of vertebrate segmentation*.

The segmented organization of vertebrates is set up in the early embryo. As the embryo elongates along an anterior–posterior axis, segmented structures called somites bud

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regularly from the anterior end of its immature presomitic mesoderm (PSM) tissue^{2–4}. The number of segments differs between species, but varies little between individuals of the same species. Seminal work by the developmental biologist Jonathan Cooke showed that surgical manipulations that reduce embryo size generate smaller yet well-proportioned embryos that are patterned normally along both anterior–posterior⁵ and dorso-ventral⁶ axes. In particular, somites become proportionally smaller, but their number and relative position are maintained⁵.

The observation that somite number and size are regulated independently prompted the 'clock and wavefront' model, which postulates that spatial and temporal inputs are combined to define somite size and position^{7,8}. According to this model, the position at which a somite can be formed at a given time is defined by molecular concentration gradients that are positioned at a fixed distance from the posterior pole (the wavefront), and that move posteriorly through the PSM towards the

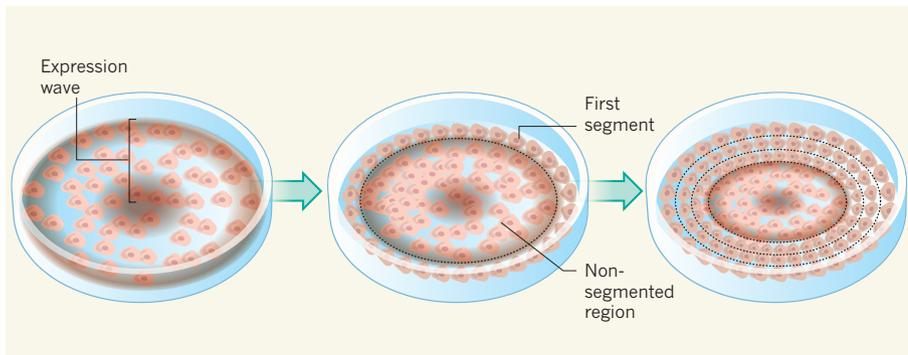


Figure 1 | Oscillating waves of gene expression in culture. Lauschke *et al.*¹ obtained presomitic mesoderm (PSM) tissue from the posterior region of a mouse at day 10.5 of embryonic development. They then plated this sample, which carried a Notch-signalling reporter molecule, on a culture dish. The reporter reveals waves of gene expression that progress in a central-to-peripheral direction. Some 20 hours after plating the cells, segments begin to form from the periphery towards the centre. Notably, segment size is adjusted (scaled) with the decreasing number of available cells, so that each new segment encompasses 20% of the remaining non-segmented region. Gene expression in cells at the centre and periphery oscillates at the same phase (darker shade of brown). Thus, the phase gradient between adjacent cells becomes steeper as the tissue size decreases.

the segmentation process in a simple two-dimensional geometry. They took a tissue slice from the posterior PSM of a mouse embryo and maintained it in culture. Cells grew out from this cultured tissue as a monolayer and began to show the hallmarks of segmentation. Most notably, periodic waves of a ‘reporter’ molecule for Notch activity seemed to propagate from the centre of the monolayer towards the periphery. After the tissue had grown to a certain size, segments began to form from the periphery, in a temporal sequence that was coordinated with the wave-like activity of the Notch reporter (Fig. 1). Altogether, the authors could detect up to 15 oscillations, at approximately 140-minute cycles, and the formation of five or more segments.

Strikingly, segment scaling was maintained under these *ex vivo* conditions. Formation of a segment decreased the size of the remaining unpatterned tissue. Consequently, the subsequent segments that formed within this smaller region had correspondingly smaller sizes — fixed at 20% of the remaining non-differentiated cells. Scaling was also observed in the velocity of the oscillatory waves of gene expression, which decreased in proportion to unpatterned-tissue size; this meant that the time it took the waves to propagate from the centre to the differentiation front in the periphery remained constant throughout the process.

The authors’ further analysis revealed that the best predictor of segment size is the phase gradient, namely, the rate at which the oscillation phase changes across the differentiating tissue. But what determines the phase gradient, and how does it scale with tissue size? The phase gradient is a kinetic property that is not directly linked to any physical entity. As such, scaling based on the phase gradient is different from scaling based on molecular gradients studied previously^{11–14}. The

correlation between phase gradient and segment size may imply a causal relationship. Alternatively, it could result from a mutual dependence on some other factor.

Perhaps in support of the latter possibility, Lauschke *et al.* observed a temporal increase in the steepness of the phase gradient even before segments had begun to form. One possibility is that both the phase gradient and segment size are dictated by gradients of Fgf or Wnt — signalling molecules that regulate development. The authors report that gradients of these morphogens are indeed established across the tissue, but further quantification is required to determine whether the gradients scale with tissue size, and to analyse their potential role in defining the phase gradient and segment formation.

Whether the segment scaling that Lauschke and colleagues observe in their *ex vivo* system reflects the scaling mechanism that compensates for size variations in live embryos deserves further investigation. Nevertheless, the intriguing *ex vivo* dynamics impinges on fundamental aspects of the clock and wave-front model. How are the clock genes of individual cells adjusted to generate a culture that shows coordinated oscillations in gene expression? Does this coordination involve long- or short-range interactions between the cells? What determines the initiation of segment formation? What is the role of Fgf and Wnt in this process? The authors’ model system holds the promise of providing answers to these questions, as well as additional quantitative insight into the process of segment formation in the vertebrate embryo. ■

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50 Years Ago

‘Education and the humanist revolution’. By Sir Julian Huxley — The knowledge explosion of the past hundred years has given us a new vision of human identity — of the world, of man, and of man’s role in the world ... It leads inevitably to a new dominant organization of thought and belief, and, after centuries of ideological fragmentation, to a new comprehensive idea-system, which I call ‘evolutionary humanism’ ... Our new system must itself be evolutionary, not change-resistant but change-promoting; it must transform as well as transmit. In part, it can be achieved by making girls and boys understand the moral duty of helping and guiding the evolutionary process in a desirable direction. But something more practical is also needed. If our aim be greater fulfilment, the next step in psychosocial evolution must be from the Welfare State towards a ‘Fulfilment Society’. A humanist educational system will put the idea of a fulfilment society before children, and will provide them with opportunities for actual personal fulfilment.

From *Nature* 5 January 1963

100 Years Ago

Perfect Health For Women and Children. By Elizabeth S. Chesser — Miss Chesser has to be commended for having treated a wide subject in such a sound, common-sense and practical manner as will make the book appeal to every class of reader, both lay and medical. The author does not mince matters when she finds fault with the unhygienic practices of the present day; and the work is full of good, telling sentences, such as, “if women paid as much attention to their teeth as they do to their complexions, they would be 50 per cent healthier and better looking.”

From *Nature* 2 January 1913

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complex. Their report provides a case study in how to approach the crystallization and structure determination of a membrane protein, an area of investigation currently at the frontier of structural biology.

The authors set out to identify a presenilin, or a presenilin-type protein, that could be overproduced in a bacterial host, purified in its active form and concentrated sufficiently for crystallization trials. After trying several proteins derived from a variety of organisms, they focused on a protease (mmPSH) from the archaean microorganism *Methanoculleus marisnigri*. This effort involved considerable protein engineering, leading to the identification of five mutations that improved the solubility of mmPSH, supported protease function and allowed the formation of high-quality crystals for structure determination.

The structure of mmPSH is only a snapshot, one stable conformation among a continuum of others. Even so, it confirms that presenilins contain nine TMDs and that two aspartate amino-acid residues — located in TMD6 and TMD7, and known to be essential for protease activity⁹ — are close to each other and buried in the membrane (Fig. 1). The structure seems to be consistent with previous biochemical studies of presenilins and γ -secretases regarding the arrangement of the TMDs, the water-accessibility of certain residues purportedly near the active site (the part of the enzyme where the cleavage reaction takes place), and the interaction with substrate proteins⁶. But it provides far more detail than previous studies and presents some surprises as well.

One surprise is that the mmPSH protease has a pore that goes through the entire transmembrane region; it may be one route for water to enter for the cleavage reaction. It

STRUCTURAL BIOLOGY

Membrane enzyme cuts a fine figure

Malfunction of presenilin enzymes, which cleave proteins in cell membranes, can lead to Alzheimer's disease. A crystal structure of a microbial presenilin provides insights into the workings of this enzyme family. [SEE ARTICLE P.56](#)

MICHAEL S. WOLFE

The interior of a cell membrane is a water-repelling environment. So the discovery¹ that some protease enzymes use water molecules to cut other proteins within membranes was surprising. Three types of such enzymes, which have a variety of roles in biology and disease, have been identified: zinc-containing site-2 proteases, rhomboid serine proteases and aspartyl proteases, such as presenilin. Atomic-resolution structures of site-2 protease and rhomboid enzymes^{2,3} have greatly improved our understanding of the mechanisms by which these proteases cleave their substrate proteins, but such a structure for a presenilin has remained elusive until now. On page 56 of this issue, Li and colleagues⁴ describe the first detailed structure of a presenilin-type protein, providing a framework for future mechanistic studies and drug-discovery programmes*.

There are two types of presenilin: those that function as single polypeptides, such as the signal peptide peptidase⁵, and those that require other proteins for activity. Presenilins of the second type assemble into γ -secretases, which are enzyme complexes, composed of four different proteins, that cleave many single-pass membrane proteins (each one containing a single transmembrane domain, or TMD), including the Notch receptor and the amyloid- β precursor protein (APP)⁶. The cleavage regulates the functions of the target proteins and releases peptides that can have various activities. Functional γ -secretases are essential for Notch signalling processes^{7,8}, which regulate cell differentiation

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during development and adulthood in multicellular animals. Moreover, mutations in genes encoding presenilins can cause early-onset Alzheimer's disease by altering how the amyloid- β protein is produced from APP cleavage.

Electron microscopy has provided low-resolution structural images of γ -secretase complexes, but the production of an atomic-resolution crystal structure will be highly challenging. Li *et al.* show that this is much more feasible (although still not easy) for a presenilin alone, representing an important step towards determining the structure of the entire enzyme

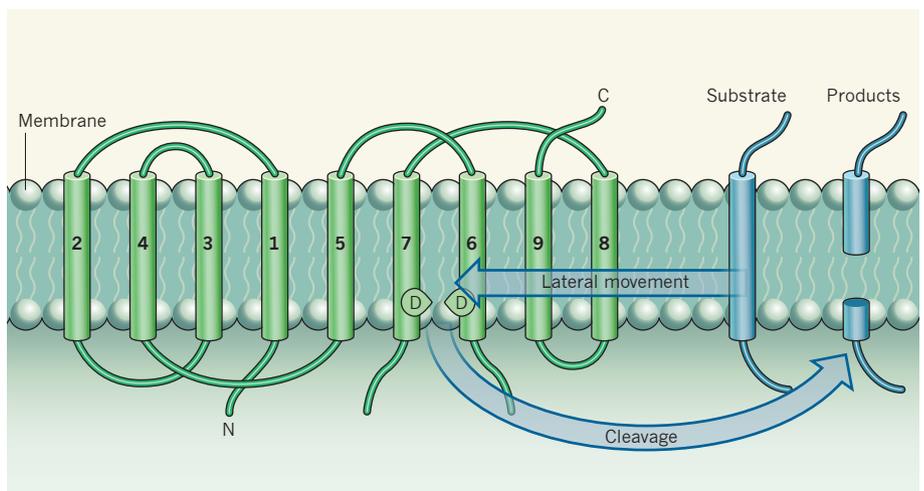


Figure 1 | Architecture of a presenilin enzyme. Presenilins are membrane-embedded protease enzymes that cleave other transmembrane proteins in a regulated manner. Li *et al.*⁴ show that a microbial presenilin-type protein, mmPSH, has nine transmembrane domains (TMDs; shown as columns). The active site, which drives the cleavage reaction, is composed of two aspartate amino-acid residues (denoted as D), one in TMD6 and the other in TMD7. The authors' results suggest that lateral movement of the substrate protein into the active site for cleavage is gated by TMD9. The mmPSH protein contains cavities (not shown) that might allow entry of water, which is activated by the catalytic aspartates for substrate cleavage into products. N and C represent the amino and carboxy termini of the protein.