observed in cerebral ischaemia and reperfusion.

The authors say that this NO-activated MMP mechanism "confers responsiveness of the extracellular matrix to nitrosative and oxidative stress", which are found in several conditions, including cerebral ischaemia and neurodegenerative diseases. The extracellular proteolytic cascades that are triggered by MMPs can disrupt the extracellular matrix, contribute to cell detachment and lead to anoikis (apoptosis due to cell detachment from the substrate). So, the authors conclude that preventing NO-activated MMP activity could be a novel way of tackling neurodegenerative diseases.

Simon Frantz,
Associate Editor (News),
Nature Reviews Drug Discovery

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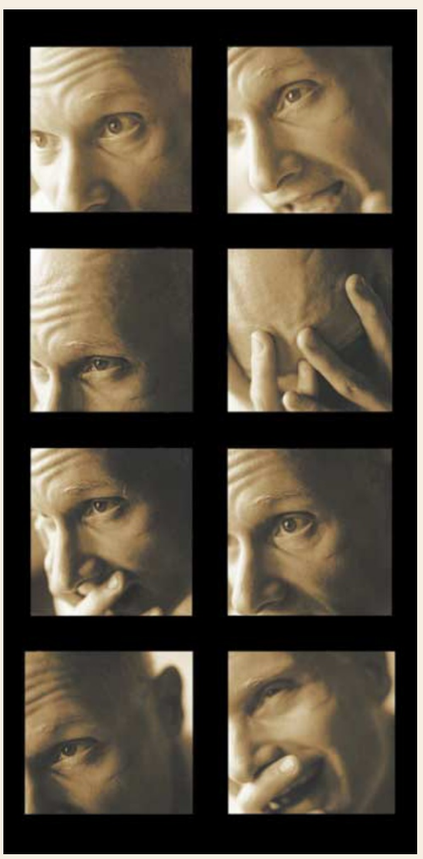

Courtesy of the Kobal Collection.

DEVELOPMENT

To branch or not to branch?

Dendrites come in a wide variety of shapes and sizes, ranging from a solitary process with no branches to an elaborately branched arborization. Because dendritic morphology is a vital factor in determining the pattern of inputs that a neuron will receive, its development has been the subject of many investigations. In neurons that are fated to produce branched dendrites, the structure of the arborization is controlled by a complex array of cell-intrinsic and cell-extrinsic factors. However, according to a new report in *Science*, the initial decision — to branch or not to branch — might be made at the flick of a genetic switch.

During development of the *Drosophila* peripheral nervous system, external sensory organ precursor (ESOP) cells divide to give two cells, one of which (IIB) generates a multidendritic (MD) neuron and a neuronal precursor called IIIB. The IIIB cell divides once more to generate an external sensory (ES) neuron and a glial cell. Although the MD and ES neurons are closely related by lineage, their dendrites could not be more different — the ES neuron has a single unbranched dendrite, whereas the multidendritic MD neuron, as its name implies, has a complex dendritic tree.

From a genetic screen that was designed to find mutations that cause defects in dendrite development, Moore *et al.* identified a gene that they named *hamlet* (or *ham*), after Hamlet's "To be or not to be" soliloquy in Shakespeare's play. This mutation caused ES neurons to adopt all the molecular and morphological characteristics of MD neurons. Conversely, ectopic expression of the HAM protein in the IIB precursor transformed its MD progeny into an ES neuron with a single dendrite.

The *ham* gene is expressed in the IIIB precursor, but not in the MD neuron, and its expression is maintained in the ES neuron as it differentiates, consistent with a role in preventing elaboration of the dendritic arborization in ES neurons. However, it is possible that HAM controls more fundamental aspects of neuronal identity, and that its effects on dendrite development are secondary. To find out, the authors expressed HAM in postmitotic MD neurons. They found that they could generate cells that continued to express MD-specific genetic markers, but had a single unbranched dendrite. So, in cells that are already committed to the MD lineage, HAM can suppress dendritic branching without completely switching the fate of the cell.

The *ham* gene seems to encode a transcription factor, which presumably initiates a cascade of events that culminates in the suppression of dendritic branching. The identification of the downstream targets of HAM should provide a fruitful line of research for the future. Genes with similar sequences to *ham* have been identified in higher organisms, including humans, so it will be interesting to see whether the binary switch from branched to unbranched dendritic morphology has been conserved during evolution.

Heather Wood

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