ONCOGENES

Transforming therapies

One aim of cancer research is to facilitate rational drug design by dissecting the molecular basis of malignancies to try and identify commonalities. Breast cancer is the most prevalent malignancy among women, and several genetic defects that are causally linked to this disease have been identified. Reporting in *Nature*, Qunyan Yu and co-workers have dissected the roles of several molecular lesions at the heart of this malignancy, opening up the prospect of more specific therapeutic intervention in the future.

One of the most frequently observed characteristics of breast cancer is overexpression of cyclin D1. This cell-cycle regulatory protein is one of three D-type cyclins, which interact with their kinase partners — cyclin-dependent kinases-4 and -6 — to drive cell-cycle progression by phosphorylating (and hence deactivating) the tumour suppressor retinoblastoma.

It is well established that overexpression of cyclin D1 is sufficient to initiate breast cancer — at least in mice. The same group had previously deleted the *cyclin D1* gene, and found that it had minimal phenotypic consequences, restricted to a defect in pregnancy-associated mammary-gland proliferation. This raised the possibility that ablation of cyclin D1 function might lead to attenuation of breast cancers without severe side effects in other proliferative tissues.

To address this issue, Yu and co-workers crossed mice deleted for the *cyclin D1* gene with mice engineered to overexpress one of a panel of transforming oncogenes known to induce breast cancer — *c-Myc*, *c-Neu*, *v-Ha-Ras* and *Wnt-1*. Remarkably, these mice were completely resistant to induction of breast cancers by the *Ras* and *Neu* oncogenes. However, the mice remained sensitive to cancers induced by deregulated *Myc* and *Wnt-1*.

The authors explain this striking result by showing that tumours arising as a result of overexpressing *Ras* and *Neu* express only cyclin D1. Tumours from *Myc* and *Wnt-1* transgenic mice, by contrast, tend to express cyclin D2 as well, which seems to compensate for the function of cyclin D1 in driving cell-cycle proliferation.

Yu and co-workers also find that the dependence on cyclin D1 for transformation of mammary epithelial cells by *Neu* and *Ras* only holds for breast tissues — *Ras* transgenic mice with deleted *cyclin D1* are still susceptible to salivary adenocarcinomas, and *cyclin D1*-negative fibroblasts are fully transformable by *Neu* and *Ras in vitro*. Consistent with their model, the authors found that tumours arising from such fibroblasts express compensating cyclin D2 and cyclin D3. It is well established that the signalling pathway involving Neu, Ras and mitogen-activated protein kinases leads to the induction of *cyclin D1* gene expression, and these experiments show that cyclin D1 expression provides the crucial link between this pathway and the cell cycle.

The requirement for cyclin D1 to transduce breast-cancer-inducing proliferative signals from the Neu–Ras signalling cascade raises the possibility that cyclin D1 could be a specific molecular target for therapy of the subset of breast cancers that arise from deregulation of this signalling pathway. Conversely, the data imply that breast cancers involving deregulated *Myc* and *Wnt-1* are unlikely to respond to anti-cyclin D1 therapy.

Undoubtedly, similar cases of tissue-specific transforming pathways will be discovered. This raises the hope that development of drugs aimed at targets specifically deregulated in cancers, combined with pre-therapeutic screening to provide molecular fingerprints of cancerous lesions, will provide a highly effective set of new clinical tools.

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References and links

ORIGINAL RESEARCH PAPER Yu, Q., Geng, Y. & Sicinski, P. Specific protection against breast cancers by cyclin D1 ablation. *Nature* **411**, 1017–1021 (2001)

FURTHER READING Bartek, J. & Lukas, J. Are all cancer genes equal? *Nature* **411**, 1001–1002 (2001)

ELECTROMOTILITY

Hear, hear

The sensitivity and selectivity of the human hearing organ rely on amplification of vibrations in the cochlea. Variation of the length of outer hair cells (OHC) in the cochlea in response to changes in transmembrane potential is central to sound amplification. But how do OHC change their length? Last year, prestin — a novel member of the family of pendrin-related transporters, found in the lateral membrane of OHC — was discovered to be the 'motor protein' responsible for OHC electromotility. Now, Oliver and colleagues report in *Science* that intracellular anions are the voltage sensor of prestin.

When sound travels through the cochlea, vibrations deflect the cilia on the apical side of OHC, opening mechano-sensitive ion channels. The resulting change in membrane potential induces cell lengthening in the case of hyperpolarization or shortening if the cell is depolarized. The motile response of OHC is accompanied by prestin-dependent charge movement, which can be measured experimentally.

Oliver and colleagues first assumed that a charged amino acid in prestin is likely to underlie the measured charge movement. They mutated the most likely candidates to non-charged residues and measured the gating current, but the characteristic bell-shaped electrical signature was not affected by any of these mutations.

The authors then reasoned that if the voltage sensor is not part of prestin, maybe it is an extrinsic charged particle. They tested intra- and extracellular ions and found that the charge movement is in fact due to the movement of cytosolic Cl^- or HCO_3^- ions across the membrane in response to changes in membrane potential.

A model emerges from this study. Many prestin molecules are embedded in the lateral membrane of OHC. When the transmembrane potential changes, it induces movement of intracellular anions into, or out of, a pocket in prestin, causing a switch between a wide and a narrow conformation. If all prestin molecules are in the narrow conformation, the cell shortens, whereas if they are in the wide conformation, the cell lengthens. From a cell biologist's point of view, prestin is an unusual 'motor protein', as it doesn't move relative to an anchorage point but rather changes the volume that it takes up within the plasma membrane, thereby indirectly changing the surface, and hence the length, of the cell.

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References and links

ORIGINAL RESEARCH PAPER Oliver, D. *et al.* Intracellular anions as the voltage sensor of prestin, the outer hair cell motor protein. *Science* **292**, 2340–2343 (2001)

FURTHER INFORMATION The authors' model