STRUCTURE WATCH

Get into the groove

Many mutations in the *BRCA1* tumour suppressor gene that lead to an increased susceptibility to breast and ovarian cancers are located in the tandem BRCA1 carboxy-terminal (BRCT) domains. These domains are known to function together as a phosphoserine/phosphothreonine-binding module, but how do they recognize phosphopeptides? And, might cancer-causing mutations in these domains specifically disrupt protein–protein interactions?

In *Nature Structural and Molecular Biology*, papers from Smerdon, Yaffe and colleagues and the Glover group now describe crystal structures of the BRCA1 BRCT domains bound to phosphopeptides that contain the pSer-X-X-Phe recognition motif (where pSer represents phosphoserine and X represents any amino acid). Both papers show that each BRCT domain forms a compact unit and that the phosphopeptides bind to a groove between these domains. The pSer residue of the motif binds to a basic pocket in the amino-terminal BRCT domain, whereas the Phe binds to a hydrophobic pocket between the domains. Smerdon, Yaffe and colleagues showed that a set of cancer-related BRCT mutations disrupt BRCA1–phosphopeptide interactions *in vitro* and BRCA1–phosphoprotein binding *in vivo*. The Glover group also showed that a large set of cancer-causing BRCT mutations disrupt phosphopeptide binding by using peptide-binding assays and by determining the crystal structures of two BRCT variants. These papers have therefore shown that a specific reduction in the phosphopeptide-binding ability of the BRCT domains, rather than a general disruption of the BRCT fold, might explain the increased cancer risks that are associated with BRCT mutations.

REFERENCES Clapperton, J. A. *et al.* Structure and mechanism of BRCA1 BRCT domain recognition of phosphorylated BACH1 with implications for cancer. *Nature Struct. Mol. Biol.* 9 May 2004 (doi:10.1038/nsmb775) | Williams, R. S. *et al.* Structural basis of phosphopeptide recognition by the BRCT domain of BRCA1. *Nature Struct. Mol. Biol.* 9 May 2004 (doi:10.1038/nsmb776)

No go for H_2O

Aquaporin-0 (AQP0) — a lens-specific water pore — is the only aquaporin that is known to form membrane junctions. In *Nature*, Walz and colleagues now describe the electron-crystallographic structure of an AQP0 membrane junction, which has given us our first insights into water-pore closure and gating.

The structure shows that the extracellular surface of AQP0 is relatively flat, and that the junction is formed by three specific interactions between AQP0 molecules in adjacent membranes. These interactions are mainly mediated by proline residues that are conserved in AQP0 molecules, but are not present in most other aquaporins. Compared to AQP1, the constriction site in AQP0 is narrower and longer, and prevents water permeation. Furthermore, AQP0 has a further, new constriction site in the cytoplasmic half of the pore, which is again too narrow for water to traverse. A tyrosine residue in this new constriction site seems mobile, which might constitute a gating mechanism for the AQP0 pore. Indeed, the authors suggest that junction formation might induce a series of conformational changes that result in pore narrowing at both constriction sites — a hypothesis for pore closure that can now be tested.

REFERENCE Gonen, T. *et al.* Aquaporin-0 membrane junctions reveal the structure of a closed water pore. *Nature* **429**, 193–197 (2004)

CELL PROLIFERATION

Tracing your roots

Where do postnatal pancreatic β-cells come from? During pancreatic maintenance and repair, do they arise from the differentiation of adult stem cells or from the duplication of differentiated cells? This controversial question has lacked a definitive answer, but the former theory has prevailed. The results now reported in *Nature* by Melton and colleagues are therefore a surprise.

The authors designed a genetic-lineage-tracing method that allowed them to trace the roots of postnatal pancreatic β-cells — more specifically, to distinguish between stem-cell-derived β-cells and β-cells that are the progeny of pre-existing β-cells. This method involved generating a transgenic mouse strain, in which adult β-cells were labelled in a heritable way.

The transgenic mice contained a gene that was under the control of the insulin promoter, which ensured that it was only expressed in β-cells. This gene encoded a recombinase that was inactive in the absence of the synthetic hormone tamoxifen. However, after tamoxifen injection, the transiently activated recombinase could remove a transcriptional stop signal from a reporter gene, such that this reporter gene is then expressed in a constitutive and heritable way.

Administering a 'pulse' of tamoxifen to these transgenic mice therefore resulted in reporter-protein production in the insulin-expressing cells that were present at the time of injection, as well as in their progeny. So, after a 'chase' period, during which cell turnover occurs, β-cells could be examined for the presence of the reporter-protein label. β-cells that are made after the pulse would only be labelled if they are the progeny of pre-existing β-cells; new β-cells that were derived from any non-β-cell source would not be labelled.

Using this approach, Melton and co-workers showed that pre-existing β-cells, rather than adult stem cells, are the main source of new β-cells in mice, both during normal adult life and after a partial pancreatectomy. "These results suggest that terminally differentiated β-cells retain a significant proliferative capacity *in vivo* and cast doubt on the idea that adult stem cells have a significant role in β-cell replenishment." The latter point has implications for cell-based therapies for type-I diabetes, although it remains to be shown that human β-cells replicate like mouse β-cells. Furthermore, this study has provided a way to assess how stem cells contribute to other organs during growth, normal turnover and regeneration.

Rachel Smallridge

References and links

ORIGINAL RESEARCH PAPER Dor, Y. *et al.* Adult pancreatic β-cells are formed by self-duplication rather than by stem-cell differentiation. *Nature* **429**, 41–46 (2004)
FURTHER READING Zaret, K. Self-help for insulin cells. *Nature* **429**, 30–31 (2004)