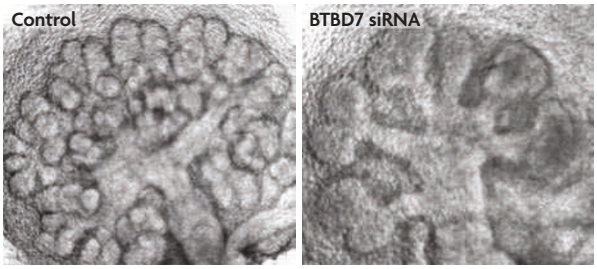

Small interfering RNA (siRNA)-mediated depletion of BTB/POZ domain-containing protein 7 (BTBD7) inhibits epithelial branching in salivary glands. Image courtesy of K. Yamada, National Institutes of Health, USA.

DEVELOPMENT

BTBD7 branches out

Epithelial branching is an integral part of embryonic development and requires the formation of clefts, which give rise to buds and eventually branches. One model postulates that clefts are formed when extracellular matrix (ECM) proteins accumulate between epithelial cells with loss of cell–cell adhesion, although how they drive cleft formation is unclear. Fibronectin is known to be required for branching in salivary glands, kidney and lungs, and Onodera *et al.* now show that it achieves this by activating BTB/POZ domain-containing protein 7 (BTBD7) at cleft-forming sites.

To identify genes that are involved in cleft formation, the authors compared gene expression in cleft and bud epithelial cells. *Btbd7* was highly expressed by cleft but not bud epithelial cells, and in salivary glands this expression was concentrated at the cleft base. This is where fibronectin and other ECM proteins are known to accumulate, suggesting that they might induce *Btbd7* expression. Indeed, fibronectin, but not collagen, induced *Btbd7* expression both in epithelial cell cultures and isolated salivary gland epithelia.

BTBD7 expression was accompanied by cell morphology changes reminiscent of cleft formation *in vivo*, indicating that it might have a role in this process. To investigate this, the authors transfected a kidney epithelial cell line with BTBD7, which resulted in labile epithelial cell–cell adhesions and cell dispersal associated with the loss of epithelial cadherin (E-cadherin). Cell dispersal, but not loss of E-cadherin, was achieved by the induction and nuclear accumulation of the transcription factor Snail 2 following *Btbd7* expression.

So does BTBD7 induce epithelial branching? In cultures of intact salivary glands, depletion of BTBD7 using small interfering RNA significantly inhibited cleft formation and, consequently, led to reduced bud formation and inhibition of branching. Similar observations were made following depletion of BTBD7 in lung cultures.

Together, these findings suggest a model of epithelial branching whereby fibronectin accumulates in forming clefts and induces the expression of *Btbd7*. BTBD7 in turn mediates epithelial cell dispersal by inducing Snail 2 expression and loss of cell adhesion by suppressing E-cadherin.

Rachel David

ORIGINAL RESEARCH PAPER Onodera, T. *et al.* Btbd7 regulates epithelial cell dynamics and branching morphogenesis. *Science* **329**, 562–565 (2010)
FURTHER READING Affolter, M., Zeller, R. & Caussinus, E. Tissue remodelling through branching morphogenesis. *Nature Reviews Mol. Cell Biol.* **10**, 831–842 (2009)