

a T_{FH} cell to fulfil its duty of helping B cells^{5,6}. So, in X-linked lymphoproliferative disease, defects in germinal-centre formation and antibody production seem to be due not only to inadequate communication between T and B cells but also to failed homing of T_{FH} cells to the germinal centres.

These findings have two noteworthy implications. First, they indicate that CD4⁺ T cells use different sets of molecules for each of the cell types with which they communicate and interact. Specifically, SAP — and, by inference, the SLAM family of cell-surface receptors — is required for the dialogue between CD4⁺ T cells and B cells but not for that between T cells and dendritic cells. Indeed, increased expression of specific SLAM proteins (CD84, SLAM, Ly108 and CD229) on B cells but not on dendritic cells⁴ supports this conclusion.

Second, the data⁴ suggest that the array of molecules involved in the dialogue between dendritic cells and T cells is insufficient to induce functional T_{FH} cells. Instead, it seems that B cells provide a unique signal that allows the appropriate CD4⁺ T cells to become fully functional T_{FH} cells — an idea supported by work in B-cell-deficient mice⁷. By inference, therefore, the definition of T_{FH} cells should be refined beyond their expression of molecules such as CXCR5. Indeed, earlier studies^{6,8} noted that the population of CXCR5-expressing cells includes CD4⁺ T cells found not only in germinal centres, but also outside them. Future work should determine the contributions of these different CXCR5-expressing CD4⁺ T-cell populations to B-cell responses and identify more specifically the T_{FH} cells that are truly located in germinal centres.

SAP binds to the cytoplasmic domain of SLAM-family cell-surface receptors. A crucial question arising from Qi and colleagues' study⁴ is which SLAM members are required for optimal adhesion of T cells to B cells. Although SLAM and CD229 are highly expressed on B cells, their deletion does not impair germinal-centre formation or T-cell-dependent antibody responses^{9,10}. CD84, however, could be a promising candidate, as it is highly expressed on both T_{FH} and B cells^{3-5,11}. So (presumably SAP-dependent) interactions between CD84 molecules on these cells might contribute to the formation of stable conjugates between T_{FH} and germinal-centre B cells, which seem to be essential for the efficient production of antibodies. Generation of CD84-deficient mice will clarify the role of this receptor in mediating interactions between T and B cells.

How does SAP itself contribute to adhesion between T and B cells? SAP-dependent signalling downstream of the SLAM-family receptors may induce changes in the expression of other adhesion molecules, such as integrins, that are involved in interactions between T and B cells. But the introduction of a signalling-deficient version of SAP into SAP-deficient CD4⁺ T cells can restore adhesion between B and T cells⁴

through SAP-associating receptors per se is not required for normal interactions between these cells. Alternatively, SLAM-family members may operate as adhesion molecules only in the presence of functional SAP (ref. 3). In other words, although SAP is unlikely to regulate the expression levels of SLAM receptors, it might stabilize interactions between these receptors on B cells and CD4⁺ T cells.

In mice, genes encoding SLAM-family receptors lie in a region known to be associated with susceptibility to the autoimmune disease systemic lupus erythematosus¹². So Qi and colleagues' results also have potential implications for understanding autoimmune diseases. Variations in the genes encoding SLAM proteins are predicted¹² to influence the strength of interactions between the extracellular domains of these cell-surface receptors or between their cytoplasmic domains and SAP. If reduced adhesion between B cells and SAP-deficient T_{FH} cells contributes to immunodeficiency, as occurs in X-linked lymphoproliferative disease, the converse — prolonged interactions between T and B cells through increased binding strength — might result in amplified T-cell

help and abnormal antibody responses characteristic of autoimmunity. By revealing more of the steps in the intricate dance of collaboration between T and B cells leading to antibody production, this study⁴ provides potential routes for modulating aberrant immunity in both immunodeficiency and autoimmunity. ■

Elissa K. Deenick and Stuart G. Tangye are at the Garvan Institute of Medical Research, 384 Victoria Street, Darlinghurst, 2010 New South Wales, Australia. e-mails: e.deenick@garvan.org.au; s.tangye@garvan.org.au

1. Liu, Y. J. & Banachereau, J. *Immunologist* **4**, 55–66 (1996).
2. MacLennan, I. C. M. *Annu. Rev. Immunol.* **12**, 117–139 (1994).
3. Ma, C. S., Nichols, K. E. & Tangye, S. G. *Annu. Rev. Immunol.* **25**, 337–379 (2007).
4. Qi, H., Cannons, J. L., Klauschen, F., Schwartzberg, P. L. & Germain, R. N. *Nature* **455**, 764–769 (2008).
5. Vinuesa, C. G., Tangye, S. G., Moser, B. & Mackay, C. R. *Nature Rev. Immunol.* **5**, 853–865 (2005).
6. Kim, C. H. et al. *J. Exp. Med.* **193**, 1373–1381 (2001).
7. Haynes, N. M. et al. *J. Immunol.* **179**, 5099–5108 (2007).
8. Ansel, K. M. et al. *J. Exp. Med.* **190**, 1123–1134 (1999).
9. Graham, D. B. et al. *J. Immunol.* **176**, 291–300 (2006).
10. McCausland, M. M. et al. *J. Immunol.* **178**, 817–828 (2007).
11. Chtanova, T. et al. *J. Immunol.* **173**, 68–78 (2004).
12. Chan, A. Y. et al. *Curr. Opin. Immunol.* **18**, 656–664 (2006).

DEVELOPMENTAL BIOLOGY

Teeth in double trouble

Georgy Koentges

Almost all vertebrates have teeth of some sort. But where, in developmental terms, do teeth come from? Results drawn from experimental embryology provide an illuminating perspective on this contentious question.

Teeth are made of some of the hardest stuff in organic nature, and many fossil vertebrates are known only from their dental remains. So teeth are central for systematic classification and reconstruction of animal life-histories, not to mention forensic science, horror movies and musicals. But we know all too little about the earliest cellular and molecular events that initiate teeth and define their position, shape and patterns — a deficiency that Soukup *et al.* (page 795 of this issue¹) have set out to remedy by first sorting out some basic embryology.

Three cell lineages in the vertebrate embryo pertain to tooth development — ectoderm and endoderm, organized as epithelia, and mesenchyme, derived from the so-called neural crest. Tissue interactions between embryonic epithelia and mesenchyme are known to be needed to form teeth². In all bony fish, for example, the epithelia form specialized cells that make the tooth enamel, whereas the mesenchyme makes the underlying dentine. But vertebrate hard tissues are complex: the same neural-crest cells can also form bone, and it is not known how such differences are established. A substantial body of work³ has elucidated the

systems that sculpt teeth. But the very earliest events that determine tooth patterning remain obscure.

In evolutionary terms, tooth-like structures — such as the denticles that appear as a ubiquitous feature on the body armour of early vertebrates — might have preceded the advent of jaws proper⁴. The staggering histological diversity of such structures has led to byzantine systems of classification of vertebrate hard tissues, and in turn to serious differences of opinion. The acrimony of these debates has scaled linearly with the lack of experimental embryological evidence about the underlying process.

The presence of denticles on the body of early jawed vertebrates led to speculation that, early in vertebrate evolution, embryonic ectoderm moved into the mouth and initiated organized tooth rows there. In contrast to this 'outside-in' view of events is the 'inside-out' theory. This theory holds that the evolutionary origins of teeth started in the mouth or pharynx and are linked to the presence of embryonic endoderm. An outward migration of cells, or a co-option of a pharyngeal tooth-forming

would have to occur to explain the presence of denticles on the outer covering of sharks and other more basal vertebrates^{5,6}.

Both theories hinge on the idea that there is an inherent difference in the inductive power of ectoderm and endoderm, and that migration of one or the other is the crucial factor in tooth formation. Implicit in this is the notion that tooth and denticle anatomy reflects embryonic origins — that is, that actual tooth or denticle histology can reveal which embryonic tissue was the key source.

Soukup *et al.*¹ now provide experimental grounds to debunk such ideas by testing the spatial distribution of ectoderm and endoderm in relation to erupting teeth. They took advantage of a line of transgenic axolotls⁷ — a group of amphibians that have ample teeth in their mouth — in which cell lineages can be fluorescently labelled. By grafting ectoderm or endoderm labelled with a marker known as green fluorescent protein from transgenic into normal axolotls, and vice versa, the authors show that there is no relationship between ectodermal and endodermal origin and the shape or nature of the resulting teeth — at least at the point when such teeth become visible. The enamel of teeth can be of ectodermal, endodermal or mixed origin. This is a dramatic finding. It means that one cannot infer relative distributions of ectoderm and endoderm from tooth or denticle anatomy even in a living species, let alone in a fossil.

The caveat here is that a lack of relationship between the later position of these epithelia and teeth does not mean that these tissues do not influence tooth position. It may well be that, at some early critical moment, an ecto–endo–dermal boundary provides positional information or orientation for some teeth. Many early signalling centres in the body (such as the apical ectodermal ridge for limb development) are known to disassemble once they have done their job⁸.

Nonetheless, Soukup and colleagues' study removes the basis for theories depending on 'co-option' processes that would require migration of epithelial cells, and redirects future research. We need to study the molecular co-option of tooth or denticle genetic programs, a process that might have occurred several times independently in the history of jawed vertebrates. Which gene-regulatory regions are involved in switching on key regulators of tooth or denticle initiation in both epithelial and mesenchymal tissue? How, where and when did these genomic regions evolve? Are the same regions driving expression in ectoderm and endoderm? Are the regions involved in patterning denticle fields also used for organizing feathers and hair? And where are the 'atoms of information' that initiate, position and shape a tooth or denticle, and make its internal structure different from that of a dermal bone?

One can expect that there are combina-

to unique tooth or denticle genetic regulatory elements, that drive the earliest molecular inducers of teeth or denticles. Such combinations, and their phylogenetic distribution and history, will be the ultimate arbiters of palaeontological arguments over dental and denticle homology⁹.

Discovery of the underlying tooth- or denticle-forming molecular programs will require transgenic analyses in paddlefish, catfish and sharks. Such analyses are not yet possible; nor are in-depth reconstructions of gene-regulatory sequences or bound transcription factors, necessitating the development of new experimental and bioinformatics approaches. Cracking such hard technical nuts will require strong intellectual teeth as well as robust

body armour, given the vigour of opinion on this subject. ■

Georgy Koentges is at the Systems Biology Centre, University of Warwick, Coventry CV4 7AL, UK.

e-mail: g.koentges@warwick.ac.uk

1. Soukup, V., Epperlein, H.-H., Horáček, I. & Cerny, R. *Nature* **455**, 795–798 (2008).
2. Sellman, S. *Odontologist Tidskrift* **54**, 1–28 (1946).
3. Thesleff, I. *Am. J. Med. Genet.* **140A**, 2530–2535 (2006).
4. Janvier, P. *Early Vertebrates* (Oxford Sci. Publ., 1996).
5. Johanson, Z. & Smith, M. M. *Biol. Rev.* **80**, 303–345 (2005).
6. Young, G. C. *J. Vert. Paleontol.* **23**, 987–990 (2003).
7. Sobkow, L., Epperlein, H.-H., Herklotz, S., Straube, W. L. & Tanaka, E. M. *Dev. Biol.* **290**, 386–397 (2006).
8. Guo, Q., Loomis, C. & Joyner, A. L. *Dev. Biol.* **264**, 166–178 (2003).
9. Koentges, G. *Nature* **451**, 658–663 (2008).

GEOMORPHOLOGY

How Tibet might keep its edge

Lewis A. Owen

The stability of the margins of the Himalayan–Tibetan mountain belt constitutes a puzzle. Repeated damming of major Tibetan rivers by glaciers, so controlling river erosion, is a possible explanation.

The collision of the Indian and Asian continental plates is the most dramatic tectonic event that Earth has experienced in the past 50 million years. It resulted in the formation of the Himalayan–Tibetan mountain belt, the growth of which initiated the south Asian monsoon, created some of the world's greatest rivers and gorges, and established the most highly glaciated realm outside polar regions. The combi-

nation of high topography, monsoon climate and great rivers and glaciers has produced intense erosion at the margins of these mountains, bringing deeply buried rocks quickly to the surface, most rapidly at the western and southeastern edges¹. Defining landscape development in the Himalaya and Tibet, and the factors involved, is among the greatest challenges facing geoscientists, and it is one tackled



Figure 1 | River deep, mountain high. At this site, which is just above where the Yarlung Tsangpo River (just off the photograph to the right) enters its gorge and slices its way through the Himalaya, impressive moraines extend from the flanks of the Namche Barwa massif and mark the limit of glaciation. The location corresponds to the place just upstream of the knick point shown in Figure 2.

B. HALLET