

IMMUNOLOGY

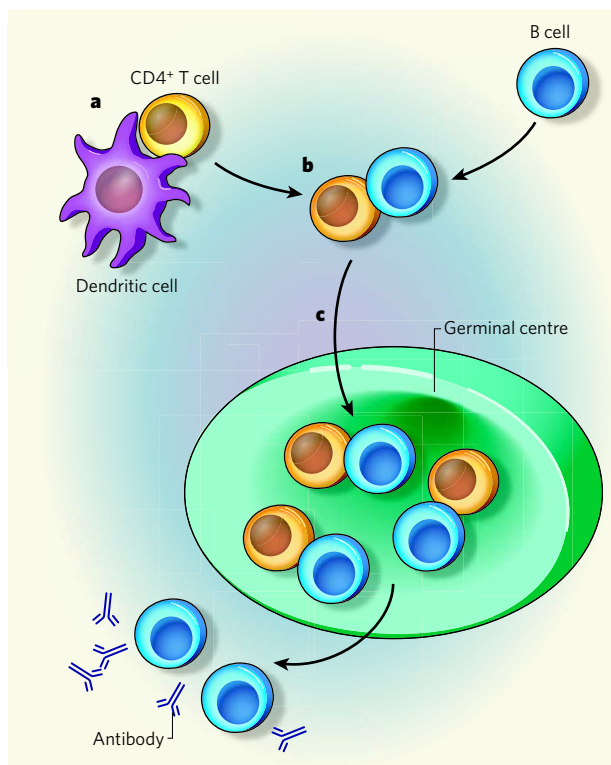
Helpful T cells are sticky

Elissa K. Deenick and Stuart G. Tangye

Prolonged physical interaction between helper T cells and antibody-producing B cells is crucial for efficient immune responses. Mutations in a protein that underlies this process cause human disease.

The production of antibodies by B cells is essential for protective immunity following vaccination or exposure to infectious pathogens. The development of antibody-secreting B cells occurs in discrete areas of lymphoid tissues called germinal centres^{1,2}, the formation of which depends on interactions between B cells and T cells bearing the CD4 molecule on their surface (CD4⁺ T cells). But several steps in the orchestration of T- and B-cell activation, differentiation and 'homing' to germinal centres during an immune response remain incompletely defined. For example, mutations in the protein SAP, which is involved in signalling by the SLAM family of cell-surface receptors³, leads to defects in the formation of germinal centres and the generation of long-lived antibody-secreting B cells. These defects result in a human immunodeficiency condition called X-linked lymphoproliferative disease³. But the mechanism associated with loss of SAP function has remained unknown. On page 764 of this issue, Qi *et al.*⁴ shed light on how SAP functions in CD4⁺ T cells to efficiently engage B cells and to provide appropriate signals for both the formation of germinal centres and the differentiation of B cells into antibody-secreting cells.

Figure 1 | Role of SAP in immune responses mediated by T and B cells. **a**, In lymphoid tissues, antigens on dendritic cells lead to these cells binding to, and activating, CD4⁺ T helper cells. **b**, The activated T cells then interact with antigen-specific B cells. Qi *et al.*⁴ show that, in the absence of the SAP protein, T and B cells manage only brief interactions. **c**, Activated B cells then form germinal centres, where they continue to receive help from CD4⁺ T cells. SAP-deficient T cells have limited ability to enter and remain in the germinal centres.



Several specialized immune cells mediate B-cell differentiation into long-lived antibody-secreting cells. Initially, dendritic cells capture foreign antigens and present them to CD4⁺ T cells, thereby activating them^{1,2}. These antigen-specific CD4⁺ T helper cells then interact with antigen-specific B cells, which undergo intense proliferation and eventually differentiate into long-lived antibody-secreting cells (Fig. 1). Qi *et al.* show that SAP is not required for dendritic cells to bind to and activate CD4⁺ T cells. Instead, the authors find that SAP-deficient, activated T cells cannot form stable interactions with B cells. The reduction in contact time between T and B cells probably explains the failure of SAP-deficient CD4⁺ T cells to deliver the necessary contact-mediated helper signals to B cells.

The authors also find that activated SAP-deficient CD4⁺ T cells show characteristics of functional follicular helper T (T_{FH}) cells, which are normally found in the germinal centres⁵. For instance, like T_{FH} cells, CD4⁺ T cells from SAP-deficient mice express high levels of specific surface molecules, including CXCR5, ICOS, CD40L and OX40. Nonetheless, these cells fail to efficiently enter or remain within germinal centres — a central requirement for



50 YEARS AGO

So far as men of science are concerned, the Lambeth Conference report follows much the same pattern as its immediate predecessor. The bulk of the report is concerned with topics which are not the immediate concern of scientists, as such, though they will note the resolution which gratefully acknowledges the work of scientists in increasing man's knowledge of the universe ... [T]wo sections of the report are concerned with problems with which men of science, as such, are equally concerned ... First are the problems involved in reconciliation of the conflicts between and within nations, and second are the group of problems centring around the family in contemporary society ... [T]he concluding section of the report, in which political conflicts are considered, merits close attention, because it poses a problem of action and of impartiality with which scientists are themselves familiar and which lies at the root of any attempt to apply scientific or technological knowledge impartially and objectively in public affairs.

From *Nature* 11 October 1958.

100 YEARS AGO

(1) *Selectionsprinzip und Probleme der Artbildung*: ein Handbuch des Darwinismus. By Prof. Ludwig Plate; (2) *Die Lehre Darwins in ihren letzten Folgen*. By Max Steiner — Prof. L. Plate's "Selectionsprinzip" has been so much expanded in its third edition that it deserves to be called a "handbook of Darwinism". It is a careful and thoughtful text-book by a thorough-going Darwinian, who is at the same time a believer in the transmission of acquired characters ... The author of the second volume before us seems to think that Darwinism has been too much discussed as a biological theory, artificially abstracted from its social consequences. If we understand him, he seeks to put things right by showing what terrible consequences the theory involves.

From *Nature* 15 October 1908.

50 & 100 YEARS AGO

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 — an observation that hints that signalling

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. ■

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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 molecular details of downstream signalling

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 program in a part of the outer body surface,