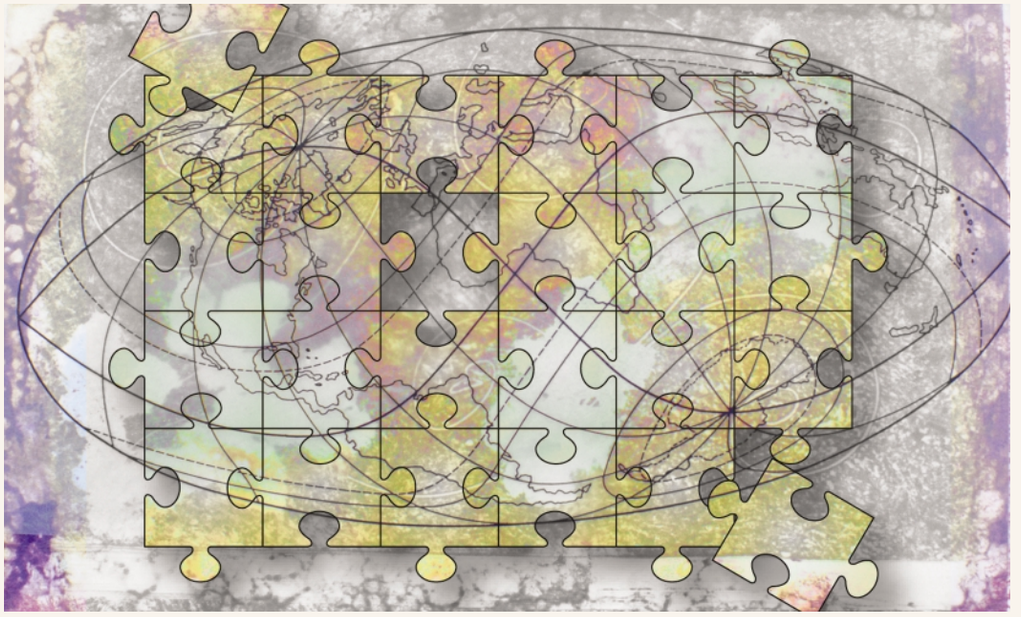

B-CELL DEVELOPMENT

Building the bigger picture

Lymphocyte development is a very complex process. Our understanding of such processes is often built up gradually, much like putting together the pieces of a jigsaw puzzle. Evidence is mounting that the recently identified members of the tumour-necrosis family (TNF) superfamily, BLyS (also known as BAFF, THANK, zTNF4 and TALL1) and APRIL (a proliferation-inducing ligand), and their receptors, transmembrane activator and CAML-interactor (TACI) and B-cell maturation protein (BCMA), are important regulators of B-cell development and function. BLyS and APRIL are very closely related, and each binds with high affinity to both TACI and BCMA. New work published in *Immunity* and *Science* now sheds further light on the role of these molecules in B-cell development.

Gross *et al.* and Schiemann *et al.* generated mice deficient in BAFF/BLyS. Phenotypic analysis of B-lymphocyte populations in these mice showed that B-cell development is arrested at the immature transitional T1 stage, and numbers of marginal zone, T2 and mature B cells are significantly reduced. Similar results were observed by Gross *et al.* in TACI–Ig transgenic mice and in normal mice treated with a TACI–Ig fusion protein, which can neutralize both BAFF/BLyS and APRIL. Interestingly, BAFF/BLyS-deficient mice had normal levels of B-1 B cells in the peritoneal cavity, but decreased numbers of conventional B-2 B cells. By contrast, the TACI–Ig-treated mice and TACI–Ig transgenics had reduced numbers of B-1 peritoneal B cells. These results indicate that BAFF/BLyS is not required for the development of B-1 B cells.

Initial studies by Thompson *et al.* on a human B-cell line indicated the existence of a third BAFF/BLyS receptor — this cell line binds with high affinity to BAFF/BLyS; however, surface expression of BCMA is not detectable and mRNA levels of TACI are low. Human BAFF receptor (BAFF-R) was isolated from an expression library and a mouse homologue was subsequently cloned. The extracellular domain of human and mouse BAFF-R contains four conserved cysteine residues, and the number and spacing of these cysteines is unique in the TNF superfamily. Transfection studies showed that human BAFF-R binds only to human and mouse BAFF/BLyS, and not to APRIL. This study also showed that A/WySnJ mice, which were previously characterized as having a similar phenotype to BAFF/BLys-deficient animals, have a mutation in the cytoplasmic tail of BAFF-R, which accounts for their lack of mature B cells.

Taken together, the results from this recent flurry of papers add further pieces to the jigsaw puzzle of our understanding of B-cell development. However, several pieces of the puzzle are still missing, and further work will be required to establish the precise roles of these molecules in B-cell development.

Elaine Bell

References and links

ORIGINAL RESEARCH PAPERS Gross, J. A. *et al*. TACI–Ig neutralizes molecules critical for B cell development and autoimmune disease: impaired B cell maturation in mice lacking BLyS. *Immunity* **15**, 289–302 (2001) | Thompson, J. S. *et al*. BAFF-R, a novel TNF receptor that specifically interacts with BAFF. *Science* **293**, 2108–2111 (2001) | Schiemann, B. *et al*. An essential role for BAFF in the normal development of cells through a BCMA-independent pathway. *Science* **293**, 2111–2114 (2001)
FURTHER READING Laabi, Y. & Strasser A. Lymphocyte survival-ignorance is BLyS. *Science* **289**, 883–884 (2000)

WEB WATCH

- (http://hiv-web.lanl.gov/immunology/index.html)

Virtual HIV

For the development of an effective human immunodeficiency virus (HIV) vaccine, further insights are needed into the nature of the virus and how an effective immune response can be mounted against it. The development of technologies, such as major histocompatibility complex (MHC)/peptide tetramers, has enabled the immune response to HIV to be studied in more detail, and data on the immunology of HIV is accumulating at a rapid rate.

The HIV Molecular Immunology Database, run by researchers in the Theoretical Biology and Biophysics Group at Los Alamos National Laboratory, enables the results obtained from numerous labs to be combined into a searchable database.

This regularly updated website, launched in 1995, contains annotated nucleotide and amino-acid alignment maps of HIV-1 and simian immunodeficiency virus (SIV) cytotoxic and helper T-cell epitopes and antibody-binding sites. Comparisons made between the immunology data and the sequence data provide new insights into the host–pathogen relationship and the evolution of these viruses. In addition to the sequences, other useful information, such as the location of the sequence in the genome and how the epitope was experimentally defined, is also available.

The site also provides useful tools, designed by the experts in Los Alamos, for carrying out sequence analysis such as HIV–BLAST, Treemaker and Vespa. And, for those who prefer the printed page, the data are also available in the HIV Molecular Immunology Compendium, which is published annually.

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