The study by MacBeth *et al.* also represents the first structural characterization of a monomeric metal-oxo complex of iron. The complex that is isolated is not the initially formed Fe(IV) species, which results directly from splitting O_2. Rather, it is an Fe(III)-O complex that forms after transfer of a hydrogen atom to the intermediate complex (see the figure). The long Fe–O bond (1.8 Å) is consistent with an Fe(III) ion and an oxide ligand, formally O^{2-} (*10*). The ligand provides a proton acceptor in the outer sphere of the complex that participates in the net hydrogen atom transfer process and stabilizes the oxide ligand by formation of hydrogen bonds.

The question of whether hydrogen atoms are transferred intact or with concomitant partitioning into an electron and a proton has important kinetic implications (*11*). The new iron compounds of MacBeth *et al.* are particularly well suited for probing these pathways because proton acceptors are intimately involved in the outer-sphere chemistry of their reactive metal ion centers. The complexes thus elegantly mimic the ability of some enzymes to influence both inner and outer coordination spheres of a metal ion.

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PERSPECTIVES: IMMUNOLOGY

Lymphocyte Survival—Ignorance Is BLys

Yacine Laâbi and Andreas Strasser

Members of the tumor necrosis factor receptor (TNFR) superfamily and their ligands are critical regulators of immune responses (*1*). They can be divided into two groups according to their intracellular structure and the types of signaling proteins that they activate. Death receptors (Fas, TNFR1, DR3, DR4, DR5, and DR6) contain a death domain through which they bind to adapter proteins such as TRADD (TNFR-associated death domain) or FADD (Fas-associated death domain)/MORT1, triggering apoptosis through recruitment and activation of caspase-8. Members of the other group (TNFR2, CD30, and CD40) lack a death domain. They bind TRAF (TNFR-associated factor) and activate c-Jun NH_2-terminal kinase (JNK) and the transcription factor Rel/NF-κB, thereby promoting cell survival, proliferation, and differentiation (*1*).

The functional distinction between these two groups is not absolute. Some receptors lacking death domains can trigger apoptosis by inducing the expression of membrane-anchored TNF ligand and by signaling through TNFR1 (*2*). Paradoxically, death receptors can also promote proliferation under certain circumstances. For example, TNFR1 is essential for liver regeneration after partial hepatectomy (*3*), and signaling through FADD is required for mitogen-induced T lymphocyte proliferation (*4–6*).

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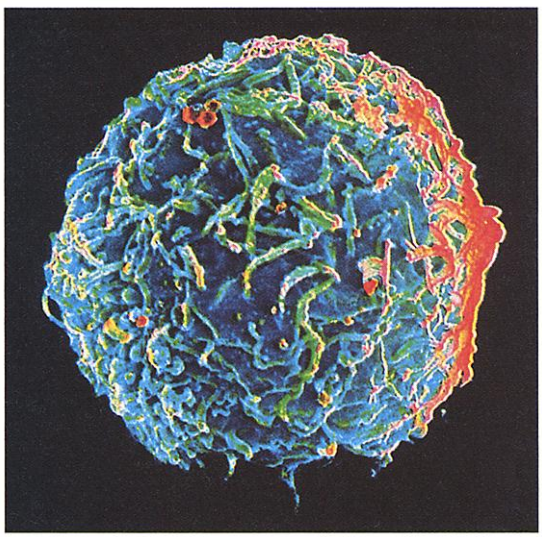
A flurry of recent papers now report that two newly identified receptors, TACI and BCMA, and their ligands BAFF/BLys (THANK/TALL-1) and APRIL (*7–11*), have joined the TNFR superfamily. These receptors and their ligands specifically regulate the survival, proliferation, and differentiation of B lymphocytes (*12–16*). Like CD40 ligand (CD40L), BAFF and APRIL promote survival of B cells, and, in collaboration with signals from the B cell antigen receptor (BCR), they also regulate their proliferation and differentiation. Both ligands are produced by monocytes, dendritic cells, and activated T cells. BAFF and APRIL are more closely related to each other than to any member of the TNF family, and each binds with high affinity to both BCMA and TACI (*12–16*). These two receptors are expressed on resting and activated B cells (*12–17*). In addition, TACI has been found on activated T cells (*18*), indicating that BAFF and APRIL may regulate T cell activity. Overexpression of BCMA activates the transcription factors Rel/NF-κB, JNK, Elk-1, and p38 kinase (*19*). When bound to its ligand, TACI activates Rel/NF-κB and NF-AT (*13–16, 18, 19*).



Scanning electron micrograph of a B cell.

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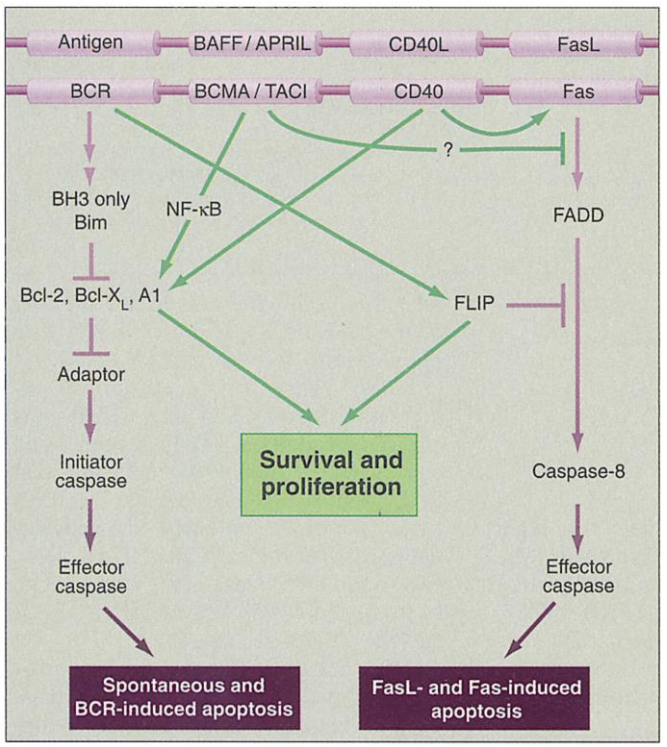
Distinct pathways leading to programmed cell death are activated through ligation of death receptors by ligand or through antigen receptor cross-linking in the absence of costimulatory signals. Fas-induced apoptosis requires FADD and caspase-8 and is not regulated by the Bcl-2 protein family (see the figure) (*4*, *20*, *21*). In contrast, apoptosis induced by ligation of BCR is mediated by different caspases and is controlled by Bcl-2 family members (*22*). Signals from antigen receptors and TNFR superfamily members synergize to promote lymphocyte proliferation and differentiation (*22*). In B cells, this is achieved (at least in part) by each signaling pathway inhibiting the proapoptotic activity of the other pathway. BCR ligation activates expression of FLIP (*23*), a competitive inhibitor of caspase-8 that blocks death receptor–induced apoptosis (*24*). Conversely, ligation of CD40, TACI, or BCMA triggers expression of Bcl-2–related proteins that inhibit apoptosis induced by BCR ligation (*7–9, 22*).

The transcription factor Rel/NF-κB is essential for survival and proliferation of B cells (*25*). It is likely that Rel/NF-κB–me-

diated activation of antiapoptotic members of the Bcl-2 family accounts for the ability of BAFF, APRIL, and CD40L to promote B cell survival. Expression of a *bcl-2* transgene inhibits apoptosis induced by BCR ligation in normal and Rel/NF-κB–deficient B cells (*22, 25*). Unlike the effects of BAFF, APRIL, or CD40L, Bcl-2 does not promote cell division or differentiation. The target genes of Rel/NF-κB that mediate the proliferative effects of TNFR superfamily members have not yet been identified.



A baffling view of a B cell's life. Multiple signaling pathways regulate B cell survival, proliferation, and differentiation. Fas-dependent apoptosis of B cells is triggered by signaling through the B cell antigen receptor (BCR) in the absence of costimulatory signals. Fas-independent apoptosis of B cells is triggered by cross-linking of BCR by antigen. BCMA and TACI receptors and their ligands, BAFF and APRIL, provide survival signals to activated B cells by inducing up-regulation of antiapoptotic proteins such as Bcl-2, down-regulation of proapoptotic proteins such as Bim, and possibly through blockade of the Fas-dependent apoptosis pathway.

During the antibody (humoral) immune response, some activated B cells develop into foci of primary (low affinity) antibody-secreting cells, whereas others enter the germinal centers of lymph nodes and spleen. In the germinal centers, activated B cells proliferate, their immunoglobulin (Ig) variable region genes undergo hypermutation, they undergo selection for high-affinity antigen binding sites, and they differentiate into memory cells and secondary (high affinity) IgG-secreting plasma cells (*26*). Mice or humans deficient in CD40 or CD40L lack germinal centers and high-affinity IgG antibodies to T cell–dependent antigens but have augmented IgM production (*20*). In contrast, neutralization of BAFF and APRIL by soluble TACI not only abolishes germinal center formation and high-affinity IgG production but also diminishes formation of mature B cells secreting low-affinity IgM (*12–14*). This suggests that CD40L may be critical for T cell–mediated B cell activation, whereas BAFF and APRIL are required to sustain proliferation of germinal center B cells and for survival of mature B cells secreting IgM as well as IgG.

The two distinct apoptotic pathways induced by BCR or Fas are both responsible for killing useless and potentially dangerous B cells. Upon ligation of BCR, autoreactive B cells that receive no T cell help (because of the induction of T cell tolerance) probably die because they are deprived of CD40L, BAFF, or APRIL. In contrast, when activated B cells no longer receive a BCR signal—either because the pathogen has been eradicated or because hypermutation has lowered the affinity of their BCR for the immunogen—they appear to be killed by Fas ligand (FasL) expressed on activated T cells (*27*). Elevated BAFF—whether due to injection, transgene expression, or genetic predisposition—causes B cell lymphadenopathy, plasmacytosis, or systemic lupus erythematosus–like autoimmune disease (*9, 12, 28, 29*). These diseases are probably caused by inhibition of BCR-induced apoptosis, similar to that seen in mice expressing a *bcl-2* transgene (*30*) or lacking the proapoptotic Bcl-2 family member Bim (*31*).

Abnormalities in cell death control predispose not only to autoimmunity but also to cancer. Deregulated Bcl-2 expression (whether due to chromosomal translocation or overexpression of a transgene) promotes the growth of lymphomas, particularly in combination with mutations that perturb cell cycle control (*32, 33*). It is possible that abnormal regulation of TACI or BCMA signaling may also contribute to the development of tumors. BCMA was originally identified in a human T cell lymphoma in which the *BCMA* gene was fused (through chromosomal translocation) to the interleukin-2 gene (*34*). Growth of this tumor may have been promoted by BAFF or APRIL through either autocrine or paracrine stimulation. Many MALT (mucosa-associated lymphatic tissue) B lymphomas are eliminated by eradication of *Helicobacter pylori* through antibiotic treatment. This indicates that tumor growth requires stimulation by inflammatory cells (*35*). The development of tumors from mature B cells (induced by injection of mineral oil into BALB/c mice) is thought to be due to production of a growth factor by the chronically inflamed tissue (*36*). Human Burkitt lymphoma cells require signals from monocytes to survive and proliferate in vivo and in vitro (*37*). It is possible that either BAFF or APRIL is the growth stimulus in these pathological conditions. This suggests that drugs that inhibit the action of BAFF and APRIL may be useful for the treatment not only of autoimmune diseases (*12*) but also of B lymphoid malignancies.

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