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Review

The uncertain glory of APRIL

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Abstract

The tumour necrosis factor (TNF) family is intimately connected to the regulation of cellular pathways. A PRoliferation-Inducing Ligand (APRIL) is a rather new member of that family, named for its capacity to stimulate the proliferation of tumour cells *in vitro*. Subsequent publications also called this ligand TRDL-1 or TALL-2, respectively. APRIL and B-lymphocyte stimulator (BLyS; also termed BAFF, TALL-1, THANK, zTNF4) form a new subfamily of TNF-like ligands that are expressed in haematopoietic cells. Both ligands can bind the two members of the TNF receptor family, namely the transmembrane activator and calcium modulator cyclophilin ligand interactor (TACI), as well as B-cell maturation antigen (BCMA). BLyS has recently been the subject of several reviews (for an extensive review, see Mackay *et al*.). The present review will thus focus on APRIL, and discuss BLyS only briefly for the sake of clarity.
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Abbreviations: APRIL, A PRoliferation-Inducing Ligand; BCMA, B-cell maturation antigen; BLyS, B-lymphocyte stimulator; DC, dendritic cell; IAP, inhibitor of apoptosis; JNK, c-Jun NH_2-terminal kinase; MAPK, mitogen-activating protein kinase; PBL, peripheral blood leucocytes; SEB, *Staphylococcus* enterotoxin B; TACI, transmembrane activator and calcium modulator cyclophilin ligand interactor; Tg, transgenic; TI, T-cell-independent; TNF, tumour necrosis factor; TRAF, TNF receptor-associated factors; XIAP, X-linked inhibitor of apoptosis.

BLyS and its receptors

The crucial role of BLyS in B-cell homeostasis became evident through the following observations: (i) *in vivo* administration of a soluble form of BLyS disrupts spleen architecture due to increased B-cell numbers,[1] (ii) mice that express BLyS as a transgene have enlarged spleens and lymph nodes; prolonged survival of normally deleted B cells results in B-cell expansion and autoimmunity,[2–4] and (iii) BLyS-deficient mice have a phenotype comparable to TACI-Fc- or BCMA-Fc-treated mice, that is, almost complete loss of mature B cells and a severely-decreased humoral response.[5,6] BCMA and TACI are expressed mainly in B lymphocytes and were originally thought to induce BLyS signalling in B-cells. TACI-deficient mice nonetheless show B cell expansion rather than death, whereas BCMA knockout mice have no overt phenotype.[6–9] These apparently contradictory findings in BLyS, TACI and BCMA knockout mice were clarified mainly by the identification of BR3/BAFF-R, the third receptor for BLyS.[10,11] This receptor appears to mediate most of the B-cell survival signals elicited by BLyS, and to a large extent explains the phenotype of BLyS transgenic and knockout animals.[5,6]

APRIL and its receptors

APRIL and BLyS share a higher sequence identity with each other than with any member of the TNF family, explaining why both ligands can bind to the BCMA and TACI receptors.[3,12–16] With BR3, one specific receptor for BLyS has been identified; however, evidence is also accumulating for the existence of at least one specific receptor for APRIL, as the Jurkat human leukaemia T-cell line is susceptible to APRIL stimulation, but not to BLyS,[17] and neither BCMA nor TACI were detectable by RT-PCR in Jurkat cells (M Hahne, unpublished data). Concurring with this is a report that BCMA and TACI are not detectable in Jurkat cells by Northern blot analysis.[13] Taken together, these data strongly suggest that APRIL-susceptible tumour cells express at least one additional receptor for APRIL. It has also recently been reported that fibroblast and epithelial cell lines express a new, yet uncharacterized, APRIL receptor that does not crossreact with BLyS.[13] Besides BCMA and TACI, none of the other currently known TNF-like receptors binds APRIL.[17,18,13]

The signal transduction pathways used by BCMA and TACI have been partially characterised. BCMA binds TNF receptor-associated factors (TRAF) 1, 2 and 3, which appear to mediate NF-κB, p38, mitogen-activating protein kinase (MAPK) and c-Jun NH2-terminal kinase (JNK) activation,[19] whereas TACI engagement results in activation of transcription factors NF-κB, AP-1 and NF-AT via TRAF 2, 5 and 6.[20]

APRIL and tumorigenesis

APRIL transcript levels are reported to be low in normal tissues, among which the highest levels are found in peripheral blood leucocytes (PBLS).[17] In contrast, higher mRNA levels have been detected in tumour cell lines and in a variety of primary tumour tissues.[17,21–23] In addition, endogenous APRIL protein has been detected in human myeloid leukaemia cell lines, including U937 and Mono Mac 1.[24] The effect APRIL exerts on tumours has been explained in two ways. First of all, a glioblastoma cell line was described to have been made resistant to death-induced apoptosis by transfection with APRIL;[23] this was associated with upregulation of X-linked inhibitor of apoptosis (XIAP), a member of the inhibitor of apoptosis (IAP) family that blocks death via

inhibition of downstream caspase activity and/or activation. APRIL apparently acts as a protective agent in this glioblastoma line. Most available data nonetheless suggest that APRIL promotes tumour cell proliferation. For instance, addition of APRIL to Jurkat T cells increases their proliferation.[17] Similarly, APRIL-transfected NIH-3T3 cells show an increased *in vitro* growth rate and, more importantly, an enhanced tumour growth rate in nude mice.[17] This conclusion is supported by a report of Rennert *et al*.,[13] demonstrating that a soluble form of BCMA, an APRIL receptor, blocks the growth of APRIL-expressing colon carcinoma and lung carcinoma cell lines in nude mice.[13] These results suggest that APRIL is involved in the regulation of tumour growth. It is unclear, however, whether APRIL acts solely as a growth factor of established tumours or whether it also induces tumour formation. To determine whether APRIL has such a tumorigenic role, studies must be performed on spontaneously developing tumours in mice with an intact immune system.

The cellular regulation of APRIL

Although TNF ligand family members are synthesised as type II transmembrane proteins, cleavage is frequently observed at the plasma membrane. Cleavage occurs in the stalk region between transmembrane and receptor-binding domains. In contrast to this membrane processing, APRIL is cleaved intracellularly, which leads to its secretion and not to a membrane-bound form.[25] Cleavage occurs in the Golgi as blockage of protein transport from the endoplasmic reticulum to the Golgi apparatus by brefeldin A treatment-abrogated APRIL processing, whereas monensin, an inhibitor of post-Golgi transport, did not interfere with APRIL cleavage, but blocked secretion of processed APRIL.[25] APRIL processing is mediated at an arginine-rich motif by furin, a ubiquitously expressed pro-protein convertase that processes many inactive precursors including hormones, growth factors and receptors.[26] BLyS and TWEAK, two other TNF family members, are also cleaved proteolytically at a multibasic motif, probably by furin.[27,28] In contrast to APRIL, however, these ligands are not processed intracellularly, but are instead released from the cell surface, where they appear as membrane-anchored proteins.[29,30] In conclusion, APRIL acts as a secreted factor and thus possesses a unique maturation pathway among TNF ligand family members, which resembles that of many growth factors.

The formation of biologically active BLyS/APRIL heterotrimers has been reported.[31] Whether these heterotrimers form intracellularly or after secretion is not yet clear, although they have been detected in serum from patients with systemic immune-based rheumatic diseases.[31] After lymphotoxin-α/lymphotoxin-β heterotrimers, BLyS/APRIL is the second example of such endogenous heterotrimerisation in the TNF ligand family.

APRIL in immune regulation

Some reports described the potential of recombinant APRIL to act as a costimulator of primary B and T cells *in vitro* and to stimulate immunoglobulin M (IgM) production by peripheral blood B cells *in vitro*.[12,16] The observation that anti-APRIL antibodies prevent T-cell stimulation *in vitro* supports the proposed implication of APRIL in primary T-cell activation *in vitro* (Dr. M Lenardo, personal communication). The status of APRIL knockout mice nonetheless remains unclear for the moment, as there are conflicting reports on the viability of APRIL-deficient mice[18] (A. Ashkenazi, personal communication). Most data presently available on the role of APRIL *in vivo* are therefore derived from analysis of APRIL transgenic (Tg) mice,[32] which display detectable transgene protein levels in peripheral T cells. Moreover, sera from these mice showed detectable circulating APRIL protein, underlining APRIL's activity as a secreted, systemic factor in the Tg mice.

APRIL and T cells

T cells derived from APRIL Tg mice show significantly increased proliferation after *in vitro* activation; this was especially evident after activation with anti-CD3/anti-CD28.[32] This concurs with reports that propose a role for APRIL as an *in vitro* T cell stimulator.[16,33] Increased proliferation is due at least in part to increased cell cycling, as Tg T cells divide more rapidly than their non-Tg counterparts (JP Medema, unpublished data). Elevated IL-2 production was observed in *in vitro* activated Tg T cells, which probably contributes to their increased proliferation. The APRIL-induced proliferative effect can be mediated by TACI, whose cell surface expression is up-regulated following T-cell activation.[20] Alternatively, T cells may express a new, yet-undefined APRIL receptor that could mediate these effects.

In addition to the effect on proliferation, a highly significant increase in *in vitro* survival of Tg APRIL-expressing T cells is observed under conditions in which cells are deprived of survival factors and receive suboptimal or no activation signals. Survival coincides with increased Bcl-2 expression in APRIL Tg T cells, which would explain the protection against growth factor deprivation-induced apoptosis, since Bcl-2 Tg T cells show comparable survival in such assays.[34] Nevertheless, one cannot exclude other survival-supporting molecules in APRIL Tg T cells. In contrast to the effect of APRIL on proliferation, this survival signal cannot be blocked by addition of TACI-Fc or BCMA-Fc *in vitro*; it is therefore likely that the survival signal is already in place prior to isolation of the cells. Furthermore, recombinant APRIL addition neither upregulated Bcl-2 nor protected T cells from *in vitro* death (JP Medema, unpublished data). This suggests that APRIL-induced survival is either an indirect effect of *in vivo* APRIL expression and not directly mediated by an APRIL receptor on the T cell, or that an APRIL receptor-mediated survival signal synergises with other factors present *in vivo* but not *in vitro*.

Despite the fact that APRIL Tg T cells show increased proliferation and survival *in vitro*, no clear differences are detected in total T-cell numbers in APRIL Tg mice. Moreover, increased T-cell proliferation *in vitro* is not mirrored by an increase in the *in vivo* growth kinetics of *Staphylococcus* enterotoxin B (SEB) superantigen-activated T cells. Whether this reflects a difference in signal requirements between *in vitro* and *in vivo* proliferation, similar to that reported for IL-2-induced T-cell proliferation,[35] is presently unclear.

An interesting alteration observed in the Tg T-cell pool is the reduction in T cells in peripheral lymph nodes and an increased number of $CD62L^-$ T cells. These features are probably related, as CD62L participates in lymphocyte recruitment from the blood to lymph nodes. It is thus possible that the decreased percentage of T cells in peripheral lymph nodes of APRIL Tg mice is a consequence of diminished homing capacity due to decreased CD62L expression on T cells. Moreover, the increased *in vitro* survival and proliferation capacity of Tg T cells is not linked to the increased $CD62L^-$ T-cell numbers, as these features are also detected in sorted $CD62L^-$ Tg T cells. Despite the difference in CD62L expression, T cells in the APRIL Tg mice show no further signs of activation.

This contrasts with a report that five consecutive injections of recombinant APRIL resulted in full T-cell activation.[16] The exposure to relatively large amounts of APRIL protein, as is the case upon injection, may thus induce signals in addition to those observed with Tg APRIL expression (see also B cells next paragraph). It therefore appears that Tg APRIL expression on T cells does not result in their activation, but rather in specific loss of CD62L.

APRIL and B cells

Transgenic APRIL expression does not result in B-cell expansion, which again contrasts to the observation that *in vivo* administration of recombinant APRIL leads to mature B-cell accumulation in the spleen.[16] The physiological relevance of these effects remains to be determined. It is important to note that APRIL is unable to compensate for the B-cell maturation defect observed in BLyS-deficient mice.[4,5] Conversely, the viable APRIL-deficient mice show no defects in B-cell homeostasis (A. Ashkenazi, personal communication). That APRIL does not contribute to mature B-cell survival was also concluded following analysis of murine BCMA-Fc Tg mice. Murine BCMA-Fc bound only weakly to murine BLyS, but with high affinity to murine APRIL.[36] The murine BCMA-Fc Tg mice were thus considered to reflect an APRIL-deficient situation, and revealed no alterations in B-cell homeostasis.[36]

Although transgenic APRIL expression did not alter B-cell numbers in Tg mice, we observed a significant (approximately two-fold) increase in serum IgM levels in APRIL Tg mice, while serum IgG levels were unaffected. TACI-deficient mice were shown in one report to have the opposite phenotype, that is, decreased serum IgM but not IgG concentrations.[7] Combined with the observation that APRIL can promote IgM secretion *in vitro*,[16] this suggests that APRIL–TACI interactions may have a role in this secretion. Studies of BLyS Tg mice showed significantly elevated serum IgM and IgG levels (up to 10-fold).[2–4] This difference between Tg APRIL and BLyS expression can be attributed to the capacity of BLyS to bind to TACI and promote IgM secretion, as well as to the BLyS-specific receptor BR3, promoting massive expansion of the B-cell compartment.

In addition to increased serum IgM levels, an elevation has been observed in T-cell-dependent humoral responses in APRIL Tg mice using the vaccinia virus. An increase was observed in antiviral B-cell responses only for IgM, since antigen-specific IgG levels were similar in Tg mice and littermates. It thus appears that APRIL promotes B-cell secretion of IgM, but does not induce class switching in a T-cell-dependent response, or promote IgG secretion. As well as the effect on the T-cell-dependent humoral response, APRIL Tg mice had a clear increase in IgM and IgG responses to a typical T-cell-independent (TI)-2 antigen.[32] Recent reports suggest that dendritic cells (DCs) may also be an important source for APRIL and/or BLyS in regulation of TI humoral responses (see below).

In contrast to the APRIL Tg mice, TACI-deficient mice display a greatly diminished TI-2 humoral response.[7,11] As TACI-deficient mice fail to develop IgM or IgG responses after challenge with TI-2 antigens, and Tg APRIL expression results in elevated IgM and IgG levels during TI-2 responses, it is likely that TACI receives this stimulatory signal from APRIL. Whether BLyS contributes to TACI signaling in this setting is not clear, but is plausible, as BLyS sequestration following BR3-Fc injection is reported to affect TI-2 IgG responses.[11] However, in this setting, it is not clear whether the observed effect is due to a block in B-cell activation or to disappearance of B cells, as BLyS is essential for the development of these cells.[5,6] As such, this effect could be mediated via BR3 and not TACI. In agreement, A/WySnJ mice, which lack functional BR3 and as a result lack mature B cells, also show severely affected IgG responses to the TI-2 antigen NP-Ficoll.[37] It is therefore too early to conclude that BLyS will actually signal through TACI in TI responses.

In contrast to the stimulatory role of TACI in TI-2 responses, an inhibitory role has been proposed for TACI in B-cell activation, based on the observation that the TACI-deficient mice showed B-cell expansion.[7,8] These findings were recently extended to show that these mice develop fatal lymphoproliferation and autoimmunity, and that the TACI intracellular domain can induce apoptosis in the murine A20 B-cell line.[38] This led to the conclusion that TACI can act as a negative regulatory receptor. Since APRIL and BLyS bind TACI, both could mediate these negative regulatory effects. In one study, APRIL was also reported to induce apoptosis in Jurkat cells.[21] It would be of interest to determine TACI expression in this specific Jurkat clone, as the results contrast with other studies of Jurkat cells (see above).

The source of APRIL and/or BLyS in TI humoral responses has not yet been clarified. Spleen marginal zone B cells have an important role in the response to TI-2 antigens by retaining these antigens.[39,40] As APRIL is expressed in monocyte/macrophages,[41] it can be envisioned that endogenous APRIL secreted by macrophages within the marginal zone mediates a stimulatory signal to B cells during a TI-2-type humoral response. Several recent reports describe a role for APRIL- and BLyS-expressing DC in the TI response.[42–44] Litinskiy *et al*. showed that (i) IFNα released by antigen-loaded DC or macrophages induces BLyS and APRIL expression in DC[43] and (ii) recombinant BLyS or APRIL induce an appropriate cytokine environment that allows class switching in B cells. Furthermore, DCs also induce class switching through BLyS and/or APRIL expression, as the presence of TACI-Fc blocked this effect. This suggests that APRIL and BLyS produced by DC promote CD40L-independent class switching. Craxton and coworkers share this vision of a macrophage/DC role in TI B cell activation; however, they conclude that this response is regulated by BLyS, as TACI-Fc blocked macrophage-mediated enhancement of B-cell stimulation, whereas an antagonistic anti-APRIL antibody did not.[44] The distinct results might be explained by the different *in vitro* situations under which these experiments were performed. Balázs *et al*.[42] investigated an *in vivo* model and showed that a subset of blood-derived CD11^{lo} DC efficiently captures and transports antigen to the spleen marginal zone, where plasma cell differentiation takes place. Supernatant from antigen-primed blood-derived CD11^{lo} DC induced plasmablast differentiation *in vitro*, and administration of TACI-Fc partially blocked TI antigen-specific plasmablast survival *in vivo*. The authors concluded that these DC are critical for TI humoral responses by inducing plasmablast differentiation in a TACI ligand-dependent manner, that is, by using APRIL and/or BLyS.

Combining these observations, it is clear that APRIL can promote TI-2 responses and that, under physiological conditions, it is probably produced by macrophages and or DC that reside near the triggered B cells. The exact contribution of APRIL and BLyS remains elusive at this point, however, and will await further inbreeding of specific knockouts and Tg mice.

TWE-PRIL

TWEAK is, like APRIL, a TNF ligand family member, and was first identified as a factor that induces apoptosis in several tissues and cell lines.[27] In agreement with this, a recent report shows that TWEAK is expressed on human peripheral blood monocytes after IFNγ stimulation and appears to be involved in IFNγ-stimulated cytotoxicity against TWEAK-sensitive tumour cells.[29] In contrast to this cytotoxic effect,

TWEAK was reported to induce proliferation of endothelial cells and subsequent angiogenesis.[45] Whereas APRIL acts solely as a secreted factor, TWEAK is a transmembrane protein expressed on the cell surface, where it can be proteolytically cleaved by furin.

Using RACE and RT-PCR techniques, cDNA library screening and RNase protection assay, a novel transcript was identified that did not correspond to any of the reported APRIL splice variants.[21] This mRNA was identified as a hybrid transcript between TWEAK and APRIL.[25] The human TWEAK gene is situated 878 bp upstream of the APRIL transcription start site. TWE-PRIL mRNA encompasses TWEAK exons 1–6 fused to APRIL exons 2–6, using the splice donor/acceptor sites of TWEAK and APRIL. The TWE-PRIL protein encoded is composed of TWEAK cytoplasmic and transmembrane domains fused to the APRIL C-terminal receptor-binding domain. TWE-PRIL mRNA is expressed and translated in human primary T cells and monocytes, and endogenous TWE-PRIL protein has been detected in primary human T lymphocytes and monocytic cell lines.[24] TWE-PRIL is membrane-anchored and presents the APRIL receptor-binding domain at the cell surface. It is a biologically active ligand, as it stimulates cell division in T- and B-lymphoma cell lines. TWE-PRIL is thus the first example of a functional, endogenous fusion protein between two genes of the same family. Alternatively, TWEAK and APRIL could be considered as a single gene with two distinct promoter regions.

In comparison with other ligand–receptor interactions within the TNF family, it is conceivable that APRIL and TWE-PRIL have different affinities for their cognate receptors. That soluble and membrane-bound ligands can trigger distinct signals was clearly demonstrated for membrane-bound and soluble TNFα, the former of which is a more potent activator of TNF receptor 2.[46]

So far, several members of the TNF ligand family–including BLyS and TWEAK, the former of which shares two receptors with APRIL–are expressed as membrane-anchored proteins that can be cleaved into a soluble form. In the case of BLyS and TWEAK, both forms are biologically active.[29,30] No distinct function can yet be attributed to either form of BLyS or TWEAK, so that the biological significance of their processing remains obscure. Distinct roles for membrane-anchored and soluble TNFα are nonetheless well documented;[47–49] it was recently reported that membrane-bound TNFα supports many features of lymphoid organ structure, whereas secreted TNFα is needed for optimal proinflammatory functions.[49] By analogy, it can be envisaged that APRIL and TWE-PRIL also exert complementary functions.

APRIL and BLyS are two intimately connected ligands of the TNF superfamily, both involved in the regulation of humoral responses. As exemplified in this and other reviews, we now understand some of the interplay that occurs in this subfamily. It is clear that BCMA and TACI are shared by these two ligands: yet, the distinct phenotypes of APRIL and BLyS Tg mice suggest that these proteins are used to exert different biological functions. Both ligands appear to have a unique receptor, although that for APRIL has not yet been identified. The recent report of a membrane-bound form of APRIL, termed TWE-PRIL, opens up new possibilities for additional regulatory mechanisms. Further studies of this complex family will undoubtedly reveal more important features of its impact on immune regulation as well as on tumour development.

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'O, how this spring of love resembleth The uncertain glory of an April day!W Shakespeare, The Two Gentleman of Verona

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