

VOLUME 1

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Autoimmune Diseases

- ▶ [Systemic Lupus Erythematosus, Autoantibodies](#)
- ▶ [Therapeutic Considerations in Kidney Diseases Due to Glomerulonephritis](#)

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B7 and CD28 Families

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Synonyms

B7-1; B7-2; B7-H3; B7-H4; B7S1; B7x; CD152; CD273; CD274; CD276; CD278; CD279; CD80; CD86; CTLA-4; CTL antigen-4; ICOS; inducible costimulator; ICOS-L; ICOS ligand; PD-1; programmed death-1; PD-L1 and PD-L2; PD-1 ligand 1 and 2

Definition

T cell costimulation is a signal required for the full activation of naïve T lymphocytes in the presence of T cell receptor signal. T cell coinhibition is a signal required for inhibition of activated T lymphocytes in the presence of T cell receptor signal.

Introduction

According to the two-signal model, optimal activation of a naïve T cell requires the simultaneous occurrence of two signals. Signal 1 is an antigen-specific signal generated by T cell receptor (TCR) recognition of peptide-MHC presented by an antigen-presenting cell (APC) (Bour-Jordan et al. 2011; Zang and Allison 2007). Signal 2, called costimulation, is an antigen-independent signal produced by the interaction between CD28 on T cells and ligand B7-1 (CD80) or B7-2 (CD86) on APC. Activation through the TCR (Signal 1) in the absence of costimulation (Signal 2) leads to functional inactivation or clonal deletion of T cells. After activation, T cells express CTLA-4 (CD152), a homolog of CD28. CTLA-4 also binds B7-1 and B7-2, which results in coinhibition attenuating T cell responses. T cell

B7 and CD28 Families, Table 1 Structure, expression, and function of the B7 ligand family and the CD28 receptor family

Ligands			Receptors and binding partners			Function
Name	Structure	Expression	Name	Structure	Expression	
B7-1 (CD80)		APC, activated T cells	CD28		T cells, Treg, NK	Costimulation
			CTLA-4 (CD152)		activated T cells, Treg	Coinhibition
			PD-L1			
B7-2 (CD86)		APC, activated T cells	CD28		T cells, Treg, NK	Costimulation
			CTLA-4		activated T cells, Treg	Coinhibition

ICOS-L (CD275, B7h, B7RP-1, GL50, B7H2, LICOS)		APC, tissues	ICOS (CD278)		activated T cells, Treg	Costimulation

PD-L1 (CD274, B7-H1)		APC, T cells, tissues, tumors	PD-1 (CD279)		activated T and B cells, Treg myeloid cells, thymocytes	Coinhibition
			B7-1			
PD-L2 (CD273, B7-DC)		DC, macrophages	PD-1		activated T and B cells, Treg myeloid cells, thymocytes	Coinhibition

B7-H3 (CD276)		DC, macrophages, tissues, activated T cells, tumors	unidentified receptors		activated T cells, NK	Costimulation
						Coinhibition

B7x (B7-H4, B7S1)		tissues, tumors	unidentified receptors		activated T cells	Coinhibition

costimulatory and coinhibitory pathways are essential orchestrators and regulators of the adaptive immune response. In recent years, the CD28 receptor and B7 ligand families have been expanded to include a total of four [CD28, CTLA-4, ICOS (CD278), and PD-1 (CD279)] and seven members [B7-1 (CD80), B7-2 (CD86), ICOS-L (CD275), PD-L1 (CD274), PD-L2 (CD273), B7-H3 (CD276), B7x (B7-H4 or B7S1)], respectively (Table 1).

The B7-1/B7-2/CD28/CTLA-4 Pathway

This pathway is the most extensively characterized T cell costimulatory and coinhibitory pathway. Ligands B7-1 and B7-2 have extracellular IgV-IgC domains, and it is the IgV domain that is responsible for receptor binding and dimerization (Chattopadhyay et al. 2009). Both B7-1 and B7-2 are mainly expressed on APC such as dendritic cells (DCs), macrophages, and

B cells, but their expression kinetics differ. APC activation is necessary for induction of B7-1 expression, whereas B7-2 is constitutively expressed on resting APC in low levels and is enhanced upon APC activation. Similarly, B7 receptors CD28 and CTL antigen-4 (CTLA-4) are both expressed on T cells, but differ in their expression kinetics as well. CD28 is constitutively expressed on naïve and activated T cells, whereas CTLA-4 expression is induced in response to TCR signal, so it is detectable on activated T cells and regulatory T cells (Treg) but not on naïve T cells. Both CD28 and CTLA-4 have an extracellular IgV domain, but they differ markedly in their localization in T cells (Rudd et al. 2009). CD28 is localized on the cell surface. By contrast, the majority of CTLA-4 is found in intracellular compartments such as the trans-Golgi network, endosomes, and lysosomes. Therefore, factors that regulate CTLA-4 protein access to the cell surface can spatially and temporally determine the extent to which CTLA-4

regulates T cell function. Although B7-1 and B7-2 can bind both CD28 and CTLA-4 via the same MYPPPY motif, the affinity of CTLA-4 for these ligands is much higher compared to that of CD28. Clearly, expression kinetics, location, and binding affinity are diverse among the ligands and receptors in this pathway.

In the presence of TCR signal, CD28 co-localizes with TCR in the central region of the immunological synapse, where the interaction between B7-1/B7-2 on APC and CD28 on T cells leads to costimulation. The costimulatory pathway not only amplifies phosphorylation of TCR-dependent kinases but also establishes a distinct signaling and transcriptional program (Rudd et al. 2009). CD28-mediated costimulation can also drive the formation of a mature immunological synapse partially via the recruitment of lipid rafts to the synapse. The cytoplasmic tail of CD28 contains several motifs responsible for binding of signaling molecules. The proximal motif can be phosphorylated by Src family kinases and then binds PI3K, Grb2, and GADS; the distal motif can be phosphorylated by Lck and Fyn kinases and then binds Grb2 and Filamin-A; a proline-rich region is associated with Itk binding. One of the most important functions of CD28-mediated costimulation is to markedly promote the production of T cell growth factor IL-2 and the expression of the high-affinity IL-2 receptor, which is pivotal for optimal clonal expansion of naïve T cells. CD28-mediated costimulation also controls T cell survival by enhancing expression of the anti-apoptotic factor Bcl-X_L. Finally, CD28-mediated costimulation is able to increase glucose uptake and glycolysis in order to meet the elevated metabolic requirement following T cell activation. B7-1/B7-2/CD28-mediated costimulation is essential for the initial activation of naïve T cells, while effector and memory T cells are less dependent on this pathway to maintain their function. Most normal tissue cells do not express B7-1 or B7-2, and immature APC express only low levels of B7-2, so these cells cannot provide enough ligands to bind CD28 on naïve T cells that may recognize MHC-peptide complex presented by these cells. The consequence is that these tissue cells will not

fully activate the naïve T cells they bind, but rather, results in anergy, functional inactivation of T cells. This is one of the fundamental mechanisms the immune system has to maintain self-tolerance and prevent autoimmune responses against self-tissues.

In contrast to the costimulatory activity of CD28, the interaction of B7-1 or B7-2 with CTLA-4 is essential for limiting the proliferative response of activated T cells to antigen and CD28-mediated costimulation (Egen et al. 2002). The importance of CTLA-4 function is evidenced by the fact that *CTLA-4* gene knockout mice develop a lethal lymphoproliferative disorder and human *CTLA-4* gene polymorphisms are strongly linked with some autoimmune diseases (Scanduzzi et al. 2011). T cell coinhibition by CTLA-4 is achieved mainly through two mechanisms: competition for ligands and induction of an inhibitory signal. Like CD28, CTLA-4 also moves to the immunological synapse, but its accumulation in the immunological synapse is proportional to the strength of the TCR signal (Egen et al. 2002). At the immunological synapse, CTLA-4 can compete with CD28 for B7-1/B7-2 engagement. Because CTLA-4 has greater affinity for B7 ligands than does CD28, CTLA-4 can sequester B7-1/B7-2 molecules, which in turn reduces CD28-dependent costimulation. Crystal structures reveal that CTLA-4 and B7 pack in a strikingly periodic arrangement in which bivalent CTLA-4 homodimers bridge bivalent B7 homodimers, therefore allowing the formation of a zipper-like protein lattice that could, in theory, assemble in the immunological synapse to compete with CD28 and/or to initiate inhibitory signal (Chattopadhyay et al. 2009; Schwartz et al. 2002). CTLA-4 can induce an inhibitory signal through its cytoplasmic tail that is 100 % conserved among mammalian species. The cytoplasmic tail of CTLA-4 contains two tyrosine residues that can be phosphorylated and subsequently recruit phosphatases like SH2 domain-containing phosphatase-2 (SHP-2). These phosphatases then dephosphorylate TCR- ζ as well as other components of the TCR proximal signal molecules such as linker for activation of

T cells (LAT), tyrosine kinases Fyn and Lck, and ζ chain-associated protein kinase of 70 kDa (ZAP-70). CTLA-4's cytoplasmic tail also contains a lysine-rich motif which can be bound by the serine/threonine protein phosphatase 2A (PP2A) resulting in thereby repression of CTLA-4 inhibitory function. In addition, CTLA-4 can inhibit the CD28 signal. Some signaling molecules such as PI3K and PP2A are able to bind cytoplasmic tails of both CTLA-4 and CD28, and CTLA-4 may sequester these molecules thereby reducing availability to induce CD28-dependent costimulation. CTLA-4 may also bring phosphatases in proximity to CD28's cytoplasmic tail, thereby repressing CD28-mediated costimulation. Although the precise nature of the signals transmitted through CTLA-4 remains controversial, it is likely that CTLA-4 can antagonize both TCR-dependent and CD-28-dependent signals (Rudd et al. 2009). In addition to activation of naïve T cells, B7/CD28 interactions are needed for the development and maintenance of regulatory T cells (Treg). Treg constitutively express high levels of CTLA-4 on their surface, and CTLA-4 may have an important cell-autonomous inhibitory function in Treg. In summary, the pathway of B7-1/B7-2/CD28/CTLA-4 has critical roles in naïve T cell activation and Treg homeostasis.

The ICOS-L/ICOS Pathway

ICOS (inducible costimulator, CD278) is the third member of the CD28 family (Nurieva et al. 2011; Zang and Allison 2007). Unlike CD28, ICOS is not expressed on naïve T cells but is induced after T cell activation. Both TCR and CD28 signals enhance ICOS expression, whereas the RING-type ubiquitin ligase family member Roquin mediates degradation of ICOS mRNA. ICOS-L (also called B7h, B7RP-1, GL50, B7H2, and LICOS) is the ligand for ICOS and is constitutively expressed on B cells, macrophages, and DCs and can be induced in nonlymphoid tissues by inflammatory stimuli. ICOS-L expression on B cells is downregulated by signaling through the B cell receptor and IL-4

receptor or after interaction with ICOS as a negative feedback loop.

The cytoplasmic tail of ICOS has an YMFM motif that, after tyrosine phosphorylation, binds to the P85 α and P50 α subunits of PI3K. Compared to CD28, ICOS stimulates greater PI3K activity and a concomitant increase in Akt signal. However, unlike CD28, the ICOS YMFM motif does not bind Grbs which is critical for IL-2 production. Therefore, ICOS engagement has little effect on IL-2 secretion, but increases production of IL-4, IL-5, IL-6, IL-10, interferon- γ (IFN- γ), and granulocyte-macrophage colony-stimulating factor (GM-CSF) by T cells. The ICOS signal promotes T cell activation, differentiation, and effector responses.

The ICOS-L/ICOS pathway provides critical T cell help to B cells. Chemokine CXC motif receptor 5 (CXCR5)-positive follicular helper CD4 T (Tfh) cells are a unique T cell subset which provide help to B cells and promote the formation of long-lived antibody responses, and ICOS-L engagement of ICOS on CD4 T cells provides signals required for initiation and maintenance of Tfh differentiation (Crotty 2011). At the time of DC priming, the expression of ICOS on CD4 T cells is required for the expression of transcription factor Bcl6, a master regulator of Tfh differentiation. After priming, Bcl6⁺CXCR5⁺ Tfh cells express an elevated level of ICOS and migrate to the T-B border where the B cell-dependent phase of Tfh differentiation occurs. B cell-expressed ICOS-L and Tfh-cell expressed ICOS are required for the production of IL-21, a cytokine for B cell maturation, as well as the formation of a germinal center. Due to the vital role of the ICOS-L/ICOS in Tfh generation and promotion of humoral immunity, deficiency of ICOS or ICOS-L results in substantially reduced numbers of Tfh cells, impaired germinal center formation, and dysfunctional isotype switching.

ICOS deficiency accounts for the full spectrum of manifestations in a proportion of patients with common variable immunodeficiency (CVID) (Scanduzzi et al. 2011; Yong et al. 2009). Specifically, a homozygous partial deletion of the *ICOS* gene in some CVID

patients results in deficiency in the expression of ICOS protein on activated T cells. As a consequence, the patients cannot generate or sustain normal numbers of memory B cells and have markedly reduced levels of serum IgG and IgA. Even after vaccination these patients lack detectable amounts of specific IgG. The genetic linkages between ICOS deletion and the clinical features of CVID emphasize the critical role of the ICOS-L/ICOS pathway in antibody production.

The PD-L1/PD-L2/PD-1 Pathway

PD-1 (programmed death-1, CD279) is a member of the CD28 family (Keir et al. 2008; Okazaki and Honjo 2007). The extracellular part of PD-1 contains a single IgV domain but lacks the membrane proximal cysteine that mediates the interchain disulfide bond, so it is monomeric on the cell surface (Chattopadhyay et al. 2009). PD-1 is expressed during thymic development but is absent on mature naïve T cells. In contrast to the restricted expression of other CD28 family members to T cells, PD-1 is induced on T cells, B cells, and some myeloid cells after activation. PD-1 has two ligands, PD-L1 (B7-H1, CD274), which also binds B7-1, and PD-L2 (B7-DC, CD273). PD-L1 is widely expressed on hematopoietic cells including APC and on several parenchymal tissues including the vascular endothelium and epithelium of several organs, whereas PD-L2 expression is mostly restricted to DCs and macrophages. IFN- γ is a major regulator of PD-L1 expression for a wide range of cell types (Barach et al. 2011). The different expression patterns of the PD-1 ligands may relate to their distinct functional abilities. Although both ligands have extracellular IgV-IgC domains and PD-L2 has greater affinity for PD-1 than PD-L1, PD-L1 is usually more effective than PD-L2 at triggering PD-1-mediated T cell inhibition.

The PD-L/PD-1 pathway plays an important role in the control of tolerance and autoimmunity (Sharpe et al. 2007), which was first revealed when

it was observed that *PD-1* gene knockout mice slowly developed spontaneous autoimmune diseases. PD-1 engagement during TCR signaling can inhibit T cell proliferation, cytokine production, cytolytic function, and T cell survival. PD-1 is more effective at attenuating weak TCR signals than strong ones. Unlike CTLA-4, PD-1 function solely depends on its cytoplasmic tail which contains an immunoreceptor tyrosine-based switch motif (ITSM) (Okazaki and Honjo 2007; Sharpe et al. 2007). Ligation of PD-1 and TCR leads to tyrosine phosphorylation of the ITSM which can then be bound by SHP-1 and SHP-2; these phosphatases can dephosphorylate TCR-associated CD-3 ζ and ZAP-70, resulting in inhibition of PI3K and downstream Akt. In contrast, CTLA-4 inhibits Akt activation but does not alter PI3K activity. PD-1 ultimately decreases induction of cytokines and cell survival proteins. During autoimmune responses, this pathway limits the initial phase of activation and expansion of self-reactive T cells and restricts self-reactive effector T cells and targets organ damage.

The PD-L1/PD-1 pathway contributes critically to T cell exhaustion and viral persistence during some chronic infections (Hofmeyer et al. 2011). Cytotoxic CD8 T lymphocytes (CTLs) play a pivotal role in the control of infection by killing infected cells. During chronic viral infection, the persistent presentation of antigen causes highly upregulated PD-1 on CTLs and upregulated PD-L1 on APC or resident tissue cells. As a consequence, activated CTLs become exhausted, lose effector function, and are unable to eliminate infection. Therefore, the PD-L1/PD-1 pathway is emerging as one of major regulators converting effector CTLs into exhausted CTLs during chronic infection with human immunodeficiency virus, hepatitis B virus, hepatitis C virus, and other pathogens capable of establishing chronic infections.

The B7-H3 and B7x Pathways

B7-H3 (CD276) and B7x (B7-H4 or B7S1) are the most recently discovered members of the B7 family, and their contribution to immune

response has not yet been clearly defined. Furthermore, the receptors for B7-H3 and B7x are currently unidentified.

B7-H3 has two major isoforms. Mouse B7-H3 contains extracellular IgV-IgC domains, whereas human B7-H3 has tandemly duplicated IgV-IgC-IgV-IgC domains because of exon duplication (Collins et al. 2005). However, no functional difference has been observed between these two isoforms. B7-H3 protein is induced on APC, NK cells, T cells, fibroblasts, fibroblast-like synoviocytes, and some epithelial cells. microRNA-29 represses B7-H3 translation. The physiological function of B7-H3 on T cell proliferation and cytokine production remains controversial (Hofmeyer et al. 2008); B7-H3 binds activated T cells, leading to costimulation in some cases and to coinhibition in others. Similarly, studies in *B7-H3* gene knockout mice support a costimulatory role in some disease models and a coinhibitory role in others. The function of B7-H3 in cancer immune responses is also controversial (Barach et al. 2011; Zou and Chen 2008). In some murine models of cancer, expression of B7-H3 on cancer cells activates tumor-specific CTLs and slows tumor growth. In contrast to mouse tumor studies, the majority of studies with human cancers demonstrate that patients with strong B7-H3 expression on cancer cells are more likely to have poor clinical outcome, suggesting a coinhibitory role. It remains to be determined whether the contrasting roles of B7-H3 in T cell function are attributed to multiple receptors.

B7x, like most other B7 family members, is composed of extracellular IgV-IgC domains linked by a transmembrane region to a very short cytoplasmic tail. B7x mRNA is broadly expressed across a wide range of organs but exhibits an expression pattern inverse of that of B7-2 mRNA, with higher B7x mRNA expression in peripheral nonlymphoid tissues and very low expression in the hematopoietic compartment. B7x protein is hardly detectable on immune cells even after culture in various stimulating, suppressive, and maturation conditions, but is found on epithelial cells of some organs and β cells of the

pancreas. B7x inhibits both CD4 and CD8 T cell proliferation and cytokine production in vitro (Zang and Allison 2007; Zou and Chen 2008). The combination of the in vivo expression pattern and the in vitro T cell coinhibitory capability of B7x suggests that the B7x pathway may be important in regulating tolerance and autoimmunity in nonlymphoid organs. The in vivo function of the B7 pathway, however, remains largely unknown. Although B7x protein expression is rare in healthy tissues, it is abundant in human malignancy (Barach et al. 2011), including cancers of the prostate, ovary, brain, lung, breast, kidney, pancreas, gut, esophagus, uterus, and skin. Importantly, overexpression of B7x in cancer often correlates with disease progression and poor clinical outcome, suggesting the B7x pathway may be exploited by cancer cells to evade antitumor immune responses.

Drugs Developed Based on the B7 and CD28 Families

The fundamental importance of costimulatory and coinhibitory signals for lymphocyte activation have spurred a large amount of effort in developing new immunotherapies by manipulating the pathways of the B7 and CD28 families. In 2005, the US Food and Drug Administration (FDA) approved Abatacept (CTLA-4-Ig) for the treatment of adult rheumatoid arthritis; a few years later, its use was extended to juvenile idiopathic arthritis (Felix et al. 2010). Abatacept is a fusion protein consisting of the extracellular domain of human CTLA-4 and the Fc portion of human IgG1, which has been modified and does not bind complement nor the Fc receptors. Compared to CD28, CTLA-4 has much higher affinity for B7-1 and B7-2; therefore, Abatacept can hamper B7-1/B7-2/CD28-mediated costimulation, resulting in increased cell death, anergy induction, and blockade of cell differentiation of T cells. Belatacept, the second generation of Abatacept, has higher affinity and is being tested in clinical trials for use in organ transplantation. In 2011, the US

FDA approved ipilimumab for the treatment of metastatic melanoma (Sharma et al. 2011). Ipilimumab, a human monoclonal antibody against CTLA-4, functions to block the interaction of CTLA-4 with B7-1 and B7-2, while leaving TCR and CD28 signals intact, which results in increased T cell function against cancer cells. Ipilimumab is currently in clinical trials in patients with other types of cancers. Clearly, research on T cell costimulation and coinhibition holds promise for the development of novel therapies and diagnoses.

Conclusion

Costimulation and coinhibition control appropriate T cell activation, proliferation, differentiation to effector function, and memory cell generation. The intense efforts towards understanding B7 and CD28 molecules over the past two decades have shaped much of our understanding regarding the immune system and disease mechanisms. The B7-1/B7-2/CD28/CTLA-4 pathway serves as the main switch regulating the clonal expansion of activated naive T cells as well as Treg homeostasis; the ICOS-L/ICOS pathway provides critical T cell help to B cells and germinal center formation; the PD-L1/PD-L2/PD-1 pathway controls effector T cell function and T cell exhaustion. PD-L1, B7-H3, and B7x are expressed in the peripheral tissues and may therefore act as gatekeepers for immune cells in nonlymphoid organs to prevent self-attack, whereas cancer and chronic infectious pathogens exploit these pathways to achieve immune evasion. While further studies are required to better understand the molecular mechanisms of these pathways and their particular roles in various diseases, the pathways of T cell costimulation and coinhibition are promising drug targets and already being developed for their therapeutic potential.

Cross-References

- ▶ CTLA-4
- ▶ CTLA4-Ig

- ▶ Cytotoxic T Lymphocytes
- ▶ Genetics of Juvenile Idiopathic Arthritis
- ▶ Juvenile Idiopathic Arthritis: Pathogenesis, Presentation, and Treatment
- ▶ PI3K
- ▶ Rheumatoid Arthritis, Treatment
- ▶ SH2 Domain-containing Inositol Phosphatase-1 (SHIP)
- ▶ T Cell Memory
- ▶ Therapeutic Considerations in Kidney Diseases Due to Glomerulonephritis
- ▶ Tregs in the Liver
- ▶ Tumor-Infiltrating T Cells

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BAFF and APRIL and Their Receptors

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Synonyms

APRIL (a proliferation ligand): TALL-2, TNFSF13; BAFF (B cell activating factor): zTNF4, BlyS, TALL-1, THANK, TNFSF13B; BAFF-R: Bcmd1, BR3, TNFRSF13C, CD268; BCMA: TNFRSF13A, CD269; TACI: TNFRSF13B, CD267

Definition

BAFF and APRIL are homologous homotrimeric cytokines belonging to the TNF family.

BAFF and APRIL Ligands and Receptors

BAFF (B cell activating factor: also named zTNF4, BlyS, TALL-1, THANK, TNFSF13B) and APRIL (a proliferation ligand: also named TALL-2, TNFSF13) are homologous TNF-like cytokines that are made by a wide variety of cell types including myeloid cells, stromal cells, activated lymphocytes, epithelial cells, and some cancer cells. Their major function is to support the survival and differentiation of B cells. BAFF binds to three receptors, BAFF-R (also named Bcmd1, BR3, TNFRSF13C, CD268), TACI (TNFRSF13B, CD267), and BCMA (TNFRSF13A, CD269), that are expressed on B cells at different developmental stages, whereas APRIL binds only to TACI and BCMA (Fig. 1a). BAFF-R is the predominant receptor on transitional, naïve, and memory B cells; TACI, the predominant receptor on marginal zone B cells and short-lived plasma cells, and BCMA, the predominant receptor on long-lived plasma cells (reviewed by Davidson (2010); Mackay et al. (2010); Mackay and Schneider (2009)). BAFF receptors may also be expressed on other immune cell types including activated T cells and dendritic cells (DCs) as well as on non-immune cells such as cancer cells (Vincent et al. 2013).

BAFF and APRIL are type II transmembrane proteins that are cleaved either at the cell membrane (BAFF) or in the Golgi apparatus (APRIL) to generate soluble forms. Several splice isoforms of both cytokines exist including ΔBAFF, a transmembrane form lacking an exon that may act as a negative regulator of BAFF function, and TWE-PRIL, a fusion protein of the extracellular domain of APRIL with the intracellular domain of TWEAK, thereby yielding a transmembrane form of APRIL. BAFF and APRIL may also form a small amount of heterodimers (reviewed by Mackay and Schneider (2009); Vincent et al. (2013)).

In mice, BAFF-R is a high affinity receptor for BAFF and binds to BAFF in its trimeric form. Although the BAFF trimer can bind to TACI, activation of the TACI receptor by BAFF requires multimerization to a 60-mer form