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Of ITIMs, ITAMs and ITAMis, revisiting Immunoglobulin Fc Receptor signaling

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Summary

Receptors for immunoglobulin Fc regions play multiple critical roles in the immune system, mediating functions as diverse as phagocytosis, triggering degranulation of basophils and mast cells, promoting immunoglobulin class switching and preventing excessive activation. Transmembrane signaling associated with these functions is mediated primarily by two amino acid sequence motifs, ITAMs (Immunoreceptor Tyrosine-based Activation Motifs) and ITIMs (Immunoreceptor Tyrosine-based Inhibition Motifs) that act as the receptors' interface with activating and inhibitory signaling pathways, respectively. While ITAMs mobilize activating tyrosine kinases and their consorts, ITIMs mobilize opposing tyrosine and inositol-lipid phosphatases. In this review we will discuss our current understanding of signaling by these receptors/motifs and their sometimes blurred lines of function.

Keywords

Fc receptors; signal transduction; ITAMs; ITIMs; SHIP; SHP

Introduction

Most effector functions of antibodies are dependent on interaction of their constant regions, usually hinge and CH2, with Fc receptors (FcR). This engagement can initiate immunologic responses provided FcR contains Immunoreceptor Tyrosine-based Activation Motifs (ITAMs) and the immune complexes or opsonized particles aggregate receptors due to multivalency. Initiating the function of inhibitory Fc receptors, those containing Immunoreceptor Tyrosine-Based Inhibitory motifs (ITIMs), generally requires co-aggregation of the ITIM-containing receptor with an activating, ITAM-containing, receptor that provides tyrosine kinase activity that phosphorylates the ITIM. Particularly in the case of members of the more recently described Fc-receptor-Like molecules, receptors can contain both ITAMs and ITIMs, which may obviate coaggregation requirements.

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The magnitude and duration of responses to Fc-containing ligands is controlled at multiple levels by both passive and active regulatory signaling. Most activating receptors interact directly with phosphatases that passively counteract kinase effects, creating negative feedback loops. The function of the inhibitory FcR, FcγRIIb, is only actively invoked by coaggregation. Passive and active regulatory signaling by ITAMs and ITIMs, respectively, seem to use the same phosphatases. However, actively invoked regulatory signaling involves quantitatively greater activation of phosphatases and therefore is more potently regulatory. Finally, a conundrum is presented by a situation in which activating Fc receptors containing only ITAMs, e.g. FcαR1, can, under certain circumstances of stimulation, behave as inhibitory receptors. While these “circumstances” and the underlying mechanisms by which they act are unclear, they are associated with low affinity/avidity and chronic stimulation. In this review we discuss our current understanding of these inhibitory signaling events that regulate Fc receptor-mediated cell activation.

Activating signaling by Fc receptors

Most but not all biological effects of Fc receptors require the Immunoreceptor tyrosine-based activating motif (ITAM) in the cytoplasmic portion the Fc receptor or associated signaling proteins such as the FcRγ chain and the FcεRI β chain. Depending on the cell type, these biological effects include phagocytosis, degranulation, ADCC, cytokine and superoxide production. In the case of canonical (or type I) Fc receptors, the initiating event in signaling is receptor clustering, which leads to the activation of associated Src family kinases, Lyn and/or Fyn. When these kinases phosphorylate both conserved tyrosines in the ITAM motif, the tyrosine kinase Syk binds via its tandem SH2 domains and becomes activated. Depending on the cell type, specific adaptors are then phosphorylated by Syk and these in turn participate in signaling by proteins such as PLCγ, Btk, Vav and PI3K. PLCγ hydrolysis of PtdIns(4,5)P2 produces IP3 and DAG, that initiate calcium mobilization and PKC activation respectively. Calcium influx and PKC activation affect a number of downstream effectors altering gene expression and promoting biologic responses such as degranulation and cytokine production. Vav is important in remodeling of the actin cytoskeleton to accommodate phagocytosis and activation of superoxide production by NADPH oxidase. PI3K catalyzes the conversion of PtdIns(4,5)P2 into PtdIns(3,4,5)P3 in the inner plasma membrane leaflet. Pleckstrin homology (PH) domain containing proteins such as PLCγ, Gab2, Akt and Btk bind PtdIns(3,4,5)P3 retaining them at the inner leaflet of the plasma membrane leaflet at the site of active signaling resulting their phosphorylation and activation.

Type II Fc receptors, including CD209, (DC-SIGN (human), SIGN-R1 (mouse)) and CD23, the low affinity IgE receptor, belong to C-type lectin receptor family. These receptors bind antibodies differently, preferring Fc domains in the closed conformation. Glycosylation of the Fc domain induces a conformational change of the Fc domain that occludes the binding site for type I Fc receptors lying near the hinge-proximal surface (open conformation) and reveals a binding site at the surface of the CH2-CH3 interface (closed conformation). These receptors bind antibodies in a 2 receptors to 1 antibody stoichiometry that may influence signal initiation (1). Although signaling by these receptors is not as well described as canonical Fc receptors, studies of CD23 have provided some insight. On B cells CD23

crosslinking can lead to increases in cAMP (2) and intracellular ionic calcium (3) as well as activation of the Src-family kinase Fyn, the Erk pathway and the PI3K pathway (4). CD23 signaling differs somewhat depending on the cell type. Monocytes CD23 is not coupled to activation of Fyn, the PI3K pathway or elevation of intracellular calcium, but does activate the Erk pathway (4). CD23 does stimulate tyrosine kinase activity, although its identity is unknown, and initiate the NFκB pathway by phosphorylation and degradation of IκBα (5, 6).

Phosphatase regulation of Fc receptor signaling

Functions of ITAM-bearing receptors are actively counteracted by the action of Immunoreceptor Tyrosine-based Inhibitory Motif (ITIM)-bearing receptors. Upon co-aggregation with activating receptors, associated kinases phosphorylate the conserved ITIM tyrosine, which then recruits the tyrosine phosphatases SHP-1 and SHP2 and the inositol phosphatases SHIP-1 and SHIP2. Below we will summarize key characteristics of these phosphatases before discussing their role in regulation of Fc receptors.

SH2-containing adaptors and phosphatases; SHIP-1 and SHIP-2

SHIP-1 and SHIP-2 are adaptor proteins and inositol 5-phosphatases that convert PtdIns(3,4,5)P3 to PtdIns(3,4)P2. This has two effects on retention of signaling molecules at the plasma membrane inner cell leaflet: 1) by reducing the PtdIns(3,4,5)P3 levels it prevents retention of molecules containing PH domains that bind PtdIns(3,4,5)P3, thus reducing, for example, activation of PLCγ and AKT. By increasing local PtdIns(3,4)P2 levels it promotes retention and activity of signaling proteins such as TAPP1, TAPP2 and Bam32 that have PH-domains that preferentially bind PtdIns(3,4)P2. While their precise function is still unclear, the TAPP proteins negatively regulate B cell activation and are important for maintenance of B cell tolerance (7). In contrast Bam32 appears to aid in B cell activation (8). The SHIP proteins contain several functional domains that control their function and enable them to interact with other signaling proteins. SHIP-1 contains a N-terminal SH2 domain, a PH-like domain, a phosphatase domain, a C2 domain, two NPXY domains and a C-terminal proline-rich region (PRR). The SH-2 domain can interact with several proteins including phosphorylated Dok family proteins, Shc, ITIMs and ITAMs. Once phosphorylated, the NPXY motifs can also bind Dok family proteins and Shc via their PTB domains (9, 10). The PRR confers the ability to interaction with adaptors like Grb2 via their SH3 domains. Resultant Grb2 association promotes SHIP-1 binding to phosphorylated FcγRIIb. While it has suggested previously that SHIP-1 might require association with a PH-domain containing adaptor to localize to its substrate (11) recently a PH-like domain was identified within SHIP that allows SHIP-1 to localize to PtdIns(3,4,5)P3 directly (12). Finally the C2 domain associates with the SHIP-1 phosphatase product PtdIns(3,4)P2, an interaction that has been suggested to increase phosphatase activity, providing a positive feedback mechanism for further SHIP-1 activation (13). Unlike SHIP-1, which is restricted in expression primarily to hematopoietic cells, SHIP-2 is ubiquitously expressed. The two have significant sequence homology and both function as inositol phosphatases. However there is great amino acid sequence divergence in their C-terminal region, including one less

NPXY motif and the addition of a sterile α-domain in SHIP-2 that is likely to alter the protein's adaptor functions, as discussed below.

Tyrosine Phosphatases, SHP-1 and SHP-2

The SH2-containing tyrosine Phosphatases SHP-1 and SHP-2 have two N-terminal SH2 domains (N-SH2 and C-SH2), a tyrosine phosphatase domain and a C-terminal tail that contains 2 tyrosine phosphorylation sites. SHP-2 also contains a proline-rich domain that may bind to SH3 domain-containing proteins. SHPs have been reported or have been suggested to dephosphorylate a number of (putative) substrates, including CD79α/β (Igα/β, Syk, FcR ITAMs, SHIP, PI3K. Structural studies have revealed that the N-SH2 domain obstructs the catalytic domain of the enzyme. Upon binding of the two SH2 domains to p-tyrosyls, SHPs undergo conformational changes that expose the catalytic domain (14, 15). The exposed C-SH2 domain binding is thought aid the binding of the more hidden N-SH2 domain. Accordingly the enzymatic activity increases drastically when the enzymes are bound to two phosphorylated ITIMs. This non-covalent regulation suggests that SHP-1 would only be able to dephosphorylate substrates within close range of the SHP-1-associated receptor. Other findings suggest that phosphorylation of either or both of the tyrosines in the C-terminal tail of SHP-1 may lead to intramolecular interactions with the N-SH2 domain that increase the phosphatase activity. Thus when this tyrosine is phosphorylated, binding of SHP-1 to a single phosphorylated ITIM might suffice to de-repress its activity (16, 17).

SHP-2 has been reported to influence signaling both negatively, by its phosphatase function, and positively, as an adaptor protein that recruits proteins that aid in cell activation. An interesting recent study suggests the existence of a more prominent activating function that could be of importance for Fc receptor biology. A family of innate sensing C-type lectin receptors called dectins have a family member, dectin 2/3, that uses the FcRγ chain as an adaptor. The authors showed that to trigger Syk-mediated cytokine production through this molecule, SHP-2 must be recruited to phosphorylated ITAMs in FcRγ While bound to the pITAM, SHP-2 is phosphorylated on a previously unidentified C-terminal ITAM-like motif. This phosphorylated ITAM-like motif then directly recruits Syk to the receptor (18).

Inhibitory signaling by FcγRIIb

Immune complexes that contain IgG (and possibly other immunoglobulin isotypes) have the ability to recruit FcγRIIb to co-engaged activating receptors. This would occur on B cells, which among FcR express only FcγRIIb, if the immune complex contains unhindered antigen epitopes to which the antigen receptor is specific. If the immune complexes contain complement-activating immunoglobulin isotypes, FcγRIIb can also inhibit complement receptor signaling (19). FcγRIIb has an ITIM motif that is phosphorylated by Lyn (or other Src-family kinases) activated by co-aggregated ITAM-containing receptors (20). Initially controversy existed over the identity of the phosphatases recruited to the FcγRIIb pITIM. SHP-1 was first identified as being recruited to the ITIM of FcγRIIb and to be essential for FcγRIIb function based on studies in SHP-1 deficient (moth-eaten viable) mice (21). Shortly thereafter SHIP-1 was identified as being recruited to the ITIM of FcγRIIb and to be essential for FcγRIIb function (22). As discussed below subsequent studies confirmed a

primary role for SHIP-1 in FcγRIIb mediated inhibition, although under circumstances of highly efficient receptor coaggregation SHP-1 also plays a role. Most ITIM-bearing receptors utilize the SHPs. However the FcγRIIb ITIM has a leucine in the Y+2 position that determines its ability to bind SHIP-1 and SHIP-2. The canonical isoleucine on the Y-2 position enables SHP-1 and SHP-2 binding (23), thus the FcγRIIb ITIM has the ability to bind both SHIPs and SHPs. While pull-down studies with pITIM peptides confirm binding of SHIP-1, SHIP-2, SHP-1 and SHP-2 (24, 25), surface plasma resonance analysis demonstrated that SHIP-1 binds with the highest affinity to FcγRIIb pITIM peptide (26). At least two factors may contribute to preferential binding of FcγRIIb to SHIP *in vivo*. The ITIM distal C-terminal region of FcγRIIb contains a second tyrosine that can be phosphorylated and serves as a binding site for SH2-domain of Grb2. Grb can stabilize the SHIP-FcγRIIb interaction by forming a stable complex by bridging the SH3 domain of Grb2 and the PRR in SHIP-1 (27). Accordingly, upon FcγRIIb-BCR colligation, Grb2 associates more with Dok-3 and SHIP-1 and less with activating proteins such as CD19, PI3K and Vav (28). A second reason for SHIP-1 preference likely lies in the fact that FcγRIIb contains one ITIM. As discussed above, SHP-1 must bind via its two SH2 domains simultaneously to achieve optimal activation, while SHIP-1 requires interaction with its single SH2 domain. In agreement with this, Lesourne et al., used beads with increasing density of pITIM peptides to demonstrate that SHP-1 binding only occurs at high pITIM density. Thus at low ligand concentrations, FcγRIIb may only be aggregated and phosphorylated sufficiently to allow binding of SHIP. Only when phosphatase inhibitors were used to achieve high levels of phosphorylation could SHP-1 binding to FcγRIIB be observed (29). This model would predict that only under conditions leading to efficient FcγRIIB –BCR crosslinking would SHP-1 be recruited by binding to single pITIMs of neighboring FcγRIIbs. Indeed supercrosslinking of the BCR with FcγRIIb does induce both SHIP and SHP-1 recruitment (30). SHP-1 may play a role in other cell types as it has been found to associate with FcγRIIb on human monocytes (31). In addition of SHIP-1, SHIP-2 utilized in inhibitory signaling by FcγRIIb in activated B cells (32).

FcγRIIb coengagement with the BCR leads minimally to inhibitory signaling at least three qualitatively distinct levels. SHIP-1 recruitment results in enhanced hydrolysis of PtdIns(3,4,5)P3 reducing membrane localization and activation of PH domain-containing proteins such as Btk (33) and Vav (34). Dok binding to pSHIP and its subsequent phosphorylation leads to RasGAP activation, inhibiting Erk (10). Finally, besides counteracting the PI3K pathway by hydrolysis of PI3K product, FcγRIIb crosslinking also reduces PI3K activation by reducing phosphorylation of CD19 (35). The mechanism by which the latter occurs is unclear, it is independent (36) of both SHP-1 and the ITIM and c-terminal domain of FcγRIIb (37). These mechanisms are not unique to FcγRIIb function in B cells, crosslinking of FcγRIIb with FcεRI on mast cells also leads to SHIP recruitment and phosphorylation, association with Shc and Dok, and downstream effects such as inhibition of calcium responses and Erk activation (38).

Aggregation of FcγRIIb on B cells independent of antigen receptors has been shown to have biological effects under certain circumstances, although the operative mechanisms appear to differ depending on developmental stage. Initially reported in mature B cells, FcγRIIb

crosslinking can mediate apoptotic signaling that is SHIP-1 (39). This is thought to play a role during affinity maturation in germinal center reactions when there is plenty of antigen-bound IgG on FDCs to engage FcγRIIb on B cells, while only antigen-specific B cells with the highest affinity will be able to compete for the available antigen. FcγRIIb-BCR induced SHIP-1 activation is thought to somehow counteract the apoptotic signal in high-affinity B cells. The signaling pathway by which FcγRIIb homotypic-aggregation induces apoptosis is still unclear. This pathway is independent of the ITIM, SHIP-1 and Src family kinases, but FcγRIIb is phosphorylated and, though their exact role is unclear, the c-Abl family kinase pathway members, c-Abl and Arg were shown to be of importance (40). Pre-B cells respond to FcγRIIb aggregation by undergoing apoptosis, but also display impaired cell migration due to SHIP-1 activation. How SHIP-1 becomes activated is unclear because in these cells FcγRIIb does not seem to become phosphorylated (41). Finally in IgM^+ human B cells FcγRIIb crosslinking causes ITIM phosphorylation and SHIP recruitment. In these cells FcγRIIb crosslinking does not induce apoptosis but it does inhibit B cell proliferation and Ca mobilization (42). Phosphorylation of FcγRIIb under condition of receptor aggregation in isolation may indicate association of the receptor with second receptor/adaptor capable of recruiting tyrosine kinases.

Regulatory signaling by FCRL

Over the past decade a family of novel receptors sharing homology with Fc receptor has been identified and designated Fc receptors-like receptors (FCRL)(reviewed in (43, 44). While the physiologic ligands for most family members are unknown, FCRL4 and FCRL5 were recently shown to be bona fide Fc receptors. Initial analysis showed that FCRL4 binds heat aggregated IgA and FCRL5 binds heat aggregated IgG (45). Subsequent studies demonstrated that FCRL5 binds native and complexed IgG with affinity comparable to the canonical low affinity FcγR, although it binds IgG differently than classical Fc receptors (46). FCRL5 is expressed on most B cells (47) while FCRL4 is expressed only on subset of tissue memory B cells (48). FCRL4 contains a switch motif and two ITIMs in its cytoplasmic tail while FCRL5 contains a noncanonical ITAM and two ITIMs. Switch motifs bind SHP-2, but upon binding of a small adaptor SH2D1A, also binds SHIP-1, thus both receptors have the potential to signal positively and negatively. To begin characterization of the signaling function of these FCRLs, fusion proteins were constructed in which the extracellular domain of FcγRIIb was fused with the cytoplasmic domain of FCRL4 or FCRL5. Crosslinking of FcγRIIb-FCRL4 fusion with the BCR led to phosphorylation of the ITIM motifs and recruitment of SHP-1 and SHP-2, and complete inhibition of BCR-mediated signaling (49). Subsequent studies using intact FCLR4 confirmed these findings and expanded them, demonstrating a requirement for all 3 FCRL tyrosines (including the one in the switch motif) and inhibition of Syk phosphorylation. SHP-1 and SHP-2 are associated with FCRL4 in resting cells as well, suggesting that they may regulate basal signaling levels. Finally, FCRL4 positively influences TLR9 signaling (50).

Crosslinking of FcγRIIb-FCRL5 chimeric receptors and FCRL5 with the BCR leads to phosphorylation of the tyrosines in the ITIMs, as well as the ITAM-like sequence, although only the former are required for associated suppression of BCR signaling. Only SHP-1 is recruited to the ITIM motifs and is responsible for dephosphorylation of Igα/β and

downstream signaling proteins (51). Subsequent studies showed that co-crosslinking of FCRL5 has both positive and negative effects on BCR signaling, occurring via recruitment of Lyn to the ITAM-like motif and SHP-1 to the ITIMs. Interestingly the balance tipped depending on B cells differentiative state, in marginal zone B cells the overall outcome was stimulatory but in B1 cells it was suppressive (52).

Feedback signaling by activating Fc receptors

Early studies of signaling by "activating" Fc receptors indicated that these receptors can also recruit phosphatases. Best described is the high affinity receptor for IgE, FcεRI, which contains two ITAM-containing subunits, the FcRγ chain and the FcεRI β chain, that function as signal transducers. Each contains a single ITAM. Association studies suggest a division of labor as FcRγ chain primarily recruits Syk and possibly SHIP-1 assuming a more activating role, while the FcεRI β chain can associate with SHIP-1, SHP-1, Lyn, Grb2 and Shc thus likely having a more regulatory role (53–57). Association of these phosphatases with an "activating" complex may have two functions; to control the magnitude of the biological response and to diversify the signal. As is seen in B cells, Lyn has both positive and negative signaling functions in mast cells. Upon stimulation with high concentrations of crosslinking ligands, FcεRI chain-activated Lyn phosphorylates SHIP-1 and SHP-1, while at low ligand concentrations it initiates cell activation (58). Further, SHP-1 has been shown to dephosphorylate the FcRγ chain ITAM tyrosines at different rates, creating monophosphorylated ITAMs that are unable to bind Syk (59). Dephosphorylation of ITAMs and Syk, and, possibly, phosphorylated adaptors, results in reduced receptor-mediated gene transcription and cytokine production. However, studies using mast cells derived from SHP-1 deficient bone marrow have revealed that in this context SHP-1 also has positive functions. Decreased calcium mobilization, PLCγ phosphorylation and degranulation were observed in SHP-1 deficient cells and this could be attributed to decreased association of SLP-67 and PLCγ, suggesting an adaptor function for SHP-1 (60). Under supraoptimal ligand conditions, SHIP is also recruited to FcεRI and suppresses degranulation (61, 62). By combining mathematical modeling with electron microscopic and biochemical analysis, the Wilson group proposed a model in which SHIP becomes associated with FcεRI at both suboptimal and supraoptimal ligand stimulation conditions, causing inhibition, and that only at optimal ligand concentrations is Syk recruited (63). The authors suggested that this differential recruitment results from differences in ITAM phosphorylation, with dual phosphorylation required for Syk recruitment occurring only following optimal stimulation. Under other conditions ITAMs would likely be inhibitory due to monophosphorylation, either due to inefficient phosphorylation (suboptimal stimulation) or selective dephosphorylation (supraoptimal stimulation). These authors also demonstrated opposing roles for SHP-1 (inhibitory) and SHP-2 (activating) in the degranulation response. Finally, SHIP-2 reportedly associates constitutively with the FcεRI β chain and, while it does not appear to affect receptor-mediated calcium mobilization or PLCγ activity, it does negatively regulate cytoskeletal function and degranulation (64).

These relationships are much less well-defined in IgG Fc receptor signaling. However, SHIP-1 is reported to be recruited, along with Shc, to FcγRI, FcγRIIa and FcγRIII, and to

become phosphorylated following stimulation (65–68). In addition, SHP-1 has been shown to associate with the N-terminal ITAM tyrosine in hFcγRIIa, and to inhibit signaling (69).

Inhibitory signaling by activating Fc receptors

While ITAM-bearing Fc receptors recruit phosphatases in the normal course of transduction of signals that lead to cell activation, recently findings indicate that under appropriate conditions signals emanating from these receptors can be solely inhibitory. This phenomenon has come to be known as ITAMi or inhibitory ITAM signaling. Originally described for FcαRI, it was observed that low-level engagement of FcαRI by serum IgA suppressed, in trans, the activation signaling though independently stimulated FcγRs or FcεRI. An explanation may exist in the fact that dimeric IgA molecule binds two FcαRI (70). Based on the discussion above (63), and very early findings using FcεR1, receptor dimerization may generate inhibitory signals by stimulating biased ITAM monophosphorylation known to propagate inhibitory signals (71). Finally, it has been shown that by a poorly understood mechanism involving actin depolymerization, FcαRI-SHP-1 complexes translocate into lipid rafts with activating receptors, possibly enabling SHP-1 trans-dephosphorylation of neighboring receptors (72). This non-covalent co-localization would allow SHP-1 to have a wider reaching inhibitory potential, much like the broader range of SHIP-1 (73, 74). This phenomenon is not unique to FcαRI, similar inhibitory activity has been observed in the case of FcγRIIa (75). Stimulation with IVIG or $F(ab')_2$ anti-FcγRIIa resulted in inhibitory signaling by FcγRIIa independent of FcγRIIb. Low level ITAM phosphorylation reportedly leads to a transient Syk recruitment followed by a stable SHP-1 recruitment.

We suggest that low avidity ligand stimulation of ITAM receptors in general leads to biased generation of inhibitory signals due to ITAM monophosphorylation. In addition to FcR, observations have been made for T cell receptors (76) and B cell receptors (71) all leading to inhibitory signaling. Syk recruitment to ITAMs requires engagement of two ITAM cis phosphotyrosines with the two SH2 domains of the kinase (77–79). Furthermore, as we have shown, ITAM monophosphorylation is both necessary and sufficient to activate SHIP and Dok inhibitory signaling (71). Accordingly in the case of FcγRIIb only one tyrosine was required of ITAMi activity (75). As discussed below, ITAMi signaling by Fc receptors could be of clinical utility. It is also worth noting that while the examples above are all mediated by SHP-1, in other systems such as DAP12 mediated regulation of the LPS response it has been shown that ITAMs can recruit SHIP-1 in a Dok2 dependent manner, and thereby inhibit the PI3K pathway (80, 81).

Practical application of inhibitory Fc receptor signaling: IVIG

Intravenous IgG (IVIG) has well described anti-inflammatory activity. It is likely that several mechanisms are at play. FcγRIIb has been reported to be indispensable for this IVIG anti-inflammatory signaling (82). A relative small fraction of IgG with sialic acid bound to its core Fc glycans is thought to interact with DC-SIGN on myeloid regulatory cells leading to cytokine production that causes upregulation of FcγRIIb, decreasing the threshold for activation of anti-inflammatory activity (83). However, other studies have suggested that

FcγRIIb can be dispensable for the IVIG effect and that ITAMi signaling of FcγRIII can mediate anti-inflammatory effects in a SHP-1 mediated manner (84, 85). Finally, as described above, IVIG can reportedly function though FcγRIIa via ITAMi activity and SHP-1 activation. The potential for use of IVIG to treat arthritis was validated by showing treatment-associated ITAMi-like activity in infiltrating cells from synovial fluid of RA patients (75).

Concluding remarks

It's complicated, but in the context of stimulation by ligands of differing avidity, ITAMs and ITIMs seem to have enormous potential to tune biological responses. Appropriate surrogates of ligands that activate inhibitory signaling may have great utility in the clinic.

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