The B cell antigen receptor complex contains heterodimers of Ig-α and Ig-β. The cytoplasmic tails of each of these chains contain two conserved tyrosines, phosphorylation of which initiates the signal transduction cascades activated by the receptor complex. Although the cytoplasmic domains of Ig-α and Ig-β have been expressed individually and demonstrated to be competent signal transduction units, we postulated that within the context of a heterodimer, Ig-α and Ig-β could have new, complementary or even synergistic functions. Therefore we developed a system to compare the signal transducing capacities of dimers of Ig-α/Ig-α, Ig-β/Ig-β, or Ig-α/Ig-β. This was done by fusing the extracellular and transmembrane domains of either human platelet-derived growth factor receptor (PDGFR) α or β to the cytoplasmic tail of either Ig-α or Ig-β. Three cell lines expressing PDGFRβ/Ig-α, PDGFRβ/Ig-β, or PDGFRα/Ig-β together with PDGFRβ/Ig-α were established in the murine B cell line A20 II A 16. While aggregation of each dimer by itself could induce the tyrosine phosphorylation of cellular substrates, only aggregation of the heterodimer induced the phosphorylation of substrates similar in range and intensity to that induced by the endogenous B cell antigen receptor complex. Interestingly, Ig-β remarkably enhanced the rapidity (T_max decreased from 5 to 1 min) and intensity (greater than 10-fold enhancement) of Ig-α phosphorylation. Conversely, the phosphorylation of Ig-β was reduced to undetectable levels when co-aggregated with Ig-α. The enhancement of Ig-α phosphorylation by Ig-β correlated with a lowering of the stimulation threshold for tyrosine kinase activation.

A B cell's response to antigen, whether it be proliferation, differentiation, anergy, or deletion, is dependent upon recognition of that antigen by the B cell antigen receptor (BCR)1 (1–3). The receptor is a multimeric complex consisting of the antigen-recognition substructure, membrane-bound immunoglobulin in non-covalently associated with heterodimer(s) of Ig-α and Ig-β (4–6). Present evidence indicates that the cytoplasmic tails of Ig-α and β (7) translate antigen engagement into cytoplasmic signaling events that initiate cellular responses (8–12). Most proximally in the signaling cascade, one or more tyrosine kinases, including Syk and members of the Src family, are activated (13–15). These in turn activate a variety of pathways whose constituents include Ras, phosphatidylinositol 3-kinase, and phospholipase C (1). Embedded within the cytoplasmic tails of both Ig-α and β is a sequence common to other multichain immune recognition receptor (MIRR) subunits including CD3ε, CD3γ, TCRζ, FcγRIIIγ, and FcεRIγ, termed the immunoreceptor tyrosine-based activation motif (ITAM) (16, 17). The motif contains two tyrosines, both of which are critical for initiating tyrosine kinase activation (10, 18). Phosphorylation of these tyrosines facilitates the recruitment and activation of tyrosine kinases which contain SH2 domains, such as Syk and Fyn (19–22). Substrates for these kinases may also be recruited (22). The presence of the ITAM in all MIRR chains involved in signal transduction has led some to suggest that apparently heterologous chains such as CD3ε and TCRζ are functionally redundant and the presence of multiple ITAMs within each MIRR serve to increase the strength of signal which can be generated via the receptor. Evidence for this assertion has been obtained in studies of both the B and T cell antigen receptors (8, 12, 23, 24). In contrast, we and others have provided evidence indicating that each heterologous ITAM containing chain has a distinct function (10, 11, 19, 25, 26).

Many of the above studies utilized chimeras in which irrelevant extracellular and transmembrane domains were fused to the single cytoplasmic domain under study (18, 27, 28). Although this approach has yielded considerable insight into ITAM-containing chains, it assumes that functions observed in the isolated circumstance of a single chimera are reflective of the function of that cytoplasmic domain within the intact receptor complex. This might not be true since most ITAM-containing chains, such as Ig-α and Ig-β, are expressed on cell surfaces as heterodimers (29–32). Therefore, we postulated that within the context of a heterodimer, Ig-α and Ig-β would have new, complementary or even synergistic functions, not predicted from studies of single chain chimeras.

As demonstrated in this report, Ig-α and β have new and unpredicted functions in the context of a heterodimer. Using a novel chimera system, which allowed us to form either hetero- or homodimers of the cytoplasmic domains of Ig-α and Ig-β, we observed that when Ig-β is ligated independently it is able to activate tyrosine kinases. However, when co-aggregated with Ig-α, Ig-β appears to remarkably enhance Ig-α phosphorylation. This in turn correlates with an increase in the range and intensity of cellular substrates phosphorylated by the heterodimer and a lowering of the stimulation threshold for tyrosine kinase activation.

**Cooperativity and Segregation of Function within the Ig-α/β Heterodimer of the B Cell Antigen Receptor Complex**

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**Materials and Methods**

Construction of PDGFR/Ig-α/β Chimeras—The construction and expression of the chimeras has been described in detail elsewhere.2

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2 B. J. Eisfelder and M. R. Clark, submitted for publication.
Briefly, cDNAs encoding the PDGFRα and β chains (gift of A. Kazlauskas, National Jewish Center, Denver, CO) were mutagenized to introduce BamHI and EcoRI sites immediately after that portion of each cDNA which encodes the transmembrane domain. The introduction of these sites facilitated the insertion of cDNA fragments encoding the cytoplasmic domains of Ig-α and Ig-β (25). These fragments were assembled with an EcoRI/XhoI-flanked cDNA fragment containing multiple stop codons in pSK (Stratagene, La Jolla, CA), which were then subcloned into the expression vector pCB6/immTk (gift of H. Singh, University of Chicago, Chicago, IL) which contains a neomycin resistance gene, an IgM enhancer and a thymidine kinase promoter. The cDNAs encoding the chimera constructs PDGFRβ/Ig-α and PDGFRβ/Ig-β were transfected either separately or together into A20 IIA1.6 (33) by electroporation. The chimeric receptors were identified by selection with G-418 and stained with anti-PDGFRα and anti-PDGFRβ antibodies (Genzyme, Cambridge, MA) then FITC-conjugated anti-IgG (Zymed, San Francisco, CA). They were analyzed by flow cytometry (FACScan, Becton Dickinson, Bedford, MA).

Reagents—Polyclonal anti-Ig-α and anti-Ig-β antibodies were made by immunizing rabbits (HTI Bioproducts, Ramona, CA) with glutathione S-transferase fusion proteins containing the cytoplasmic domains of murine Ig-α or Ig-β (25). The serum of rabbits immunized with the Ig-α fusion protein was purified over a column (CNBr-activated Sepharose, Pharmacia Biotech Inc.) coupled to a peptide corresponding to the murine Ig-α cytoplasmic tail ITAM (amino acid residues 177-196) (34), whereas the polyclonal anti-Ig-β antibody was purified over a column containing the immunizing Ig-β fusion protein. The anti-phosphotyrosine monoclonal antibodies FB2 and Ab2 were obtained from ATCC (Rockville, MD) and Oncogene Sciences (Uniondale, NY), respectively.

Cell Growth and Stimulation—For most experiments, cells were grown in Iscove’s modified Dulbecco’s medium (Sigma) supplemented with 10% fetal calf serum (HyClone, Logan UT), 2 mM glutamine, 100 units/ml penicillin, and 100 μg/ml streptomycin at 37°C in 7.5% CO2. For the experiments described in Fig. 6, cells were serum-starved (0.5% fetal calf serum) for 18 h before initiation of each experiment. For all the stimulation experiments described, aliquots of 10^6 cells were suspended in 300 μl of Iscove’s modified Dulbecco’s medium and incubated at 37°C for 5 min. To stimulate cells via the endogenous BCR, cells were incubated with anti-IgG1 antibody and then with rabbit anti-mouse IgG1 antibodies (Amersham Corp., Arlington Heights, IL) or goat anti-mouse IgG1 antibodies (Jackson Immunoresearch, West Grove, PA) at 15 μg/ml for 5 min, followed by anti-PDGFRβ antibody (5 μg/ml), anti-Ig-α antibody (5 μg/ml) or a combination (Jackson Immunoresearch, West Grove, PA) at 15 μg/ml for 5 min. Anti-IgM antibodies (25 μg/ml) were added to the stimulating antigen receptor to induce tyrosine phosphorylation. Finally, at least one protein of 120–130 kDa was identified in co-immunoprecipitations, the latter presumably being a result of co-ligation of the Ig-α and Ig-β chains by the IgM enhancer in the expression vector used in this study. Antiphosphotyrosine, anti-Ig-α, and anti-Ig-β antibodies (Fig. 1C).

RESULTS

Construction, Expression, and Stimulation of PDGFR Chimeras—To examine if Ig-α and Ig-β may function together to initiate pathways of cellular activation, we designed a system using the human PDGFRs, which allowed us to form either homo- or heterodimers of Ig-α and β. Two forms of PDGFR exist, α and β, each of which is recognized by specific monoclonal antibodies. Furthermore, although distinct, each has an equal affinity for the naturally occurring ligand, PDGF-BB (35). Therefore, each chain can be expressed independently, yet made to form homodimers or predominantly heterodimers on singly or doubly transfected cells, respectively, by the addition of PDGF-BB. These dimers, which are representative of the resting complex (PDGF-BB does not induce tyrosine kinase activation; data not shown), can then be activated by specific antibodies (Fig. 1A).

We engineered cDNAs encoding for molecules in which either the cytoplasmic domains of Ig-α or Ig-β were fused to the extracellular and transmembrane domains of either PDGFRα or β (Figs. 1B). These cDNAs were expressed singly or in combination in A20 IIA1.6, a B cell lymphoma that lacks FcyRII, to yield three cell lines expressing approximately equal levels of each chimera (β/β/βα (expressing PDGFRβ/β/βα), β/β/ββ and α/β/ββ/βα (Figs. 1C and 3)).

The Cytoplasmic Domains of Both Ig-α and Ig-β Are Needed to Induce the Efficient Tyrosine Phosphorylation of Cellular Proteins—We first asked if the cytoplasmic tails of Ig-α or Ig-β alone, or the two chains together, were capable of inducing the tyrosine phosphorylation of cellular proteins in a manner similar to that induced via the endogenous BCR. Chimeras were stimulated by sequential incubation with PDGF-BB, followed by anti-PDGFRβ antibody and rabbit anti-mouse IgG1. In parallel samples, the endogenous BCR on each transfectant was stimulated with polyclonal antibodies to IgG. After stimulation, cells were lysed and phosphorylase immunoprecipitates (with FB2) from each lysate were resolved by SDS-PAGE and analyzed by blotting with anti-phosphotyrosine antibodies (Ab2). As shown in Fig. 2, stimulation of the BCR on wild type and transfected cells induced a similar spectrum and intensity of tyrosine phosphorylation. In contrast, only in α/β/ββ/ββ cells did stimulation of chimeras induce tyrosine phosphorylation that was similar in distribution and intensity to that induced by the endogenous antigen receptor. In β/β/βα or β/β/ββ cells, stimulation of the chimeras could only induce the strong tyrosine phosphorylation of a subset of proteins. In related experiments, truncated co-expressed versions of each chimera which lacked cytoplasmic domains, PDGFRαβ− and PDGFRβ−, were incapable of inducing any detectable tyrosine phosphorylation. However, differences were observed in the induction via the chimeras in α/β/ββ/ββ cells and by the endogenous BCR. Stimulation of α/β/ββ/βα failed to induce the tyrosine phosphorylation of proteins of 32 and 40 kDa. Subsequent immunoblotting revealed that the 32-kDa protein was Ig-α (data not shown). The 40-kDa protein appears to be a novel molecule which is associated with the endogenous Ig-α/β heterodimer. These observations suggest that the chimeras do not utilize the BCR, or associated structures, to initiate tyrosine phosphorylation. Finally, at least one protein of 120–130 kDa was phosphorylated strongly in α/β/ββ/βα-weakly in β/β/βα and β/β/ββ, but not at all by stimulation of the BCR. Since the chimeras are predicted to have molecular masses of approximately this size, we examined if this protein was a chimeric molecule.

Stimulation of Chimeric Heterodimers Induces the Tyrosine Phosphorylation of PDGFRβ/β/βα But Not PDGFRαβ−—The wild type A20 IIA1.6 and α/β/ββ/ββ cells were treated with PDGF-BB and then stimulated with anti-receptor antibodies as above. Anti-phosphotyrosine, anti-Ig-α, or anti-Ig-β immunoprecipitates were resolved by SDS-PAGE and probed with antibodies of the same specificity in various combinations. Immunoblotting of the α/βα and Ig-β immunoprecipitates with the same antibodies confirmed that α/βα/ββ/ββα cells, but not wild type cells, expressed PDGFRβ/βα (135 kDa) and PDGFRα/ββ/ββ (125 kDa) (Fig. 3). Although both chimeras were expressed in readily detectable amounts, only PDGFRβ/βα was observed to be phosphorylated following stimulation. The phosphorylation of PDGFRβ/βα was detected in both α/βα and Ig-β immunoprecipitations, the latter presumably being a result of co-ligation.3

3 Y. J. Lee and M. R. Clark, manuscript in preparation.
were then aggregated with anti-PDGFR antibodies, followed by goat anti-mouse antibodies. Omission of PDGF-BB before stimulating doubled transfection cells led to the aggregation of PDGFR chimeras. Homodimers or predominately heterodimers were formed on singly transfected cells. To stain for surface IgG, PDGFR of A20 IIA1.6 cells expressing PDGFR chimeras. Expression of either Igα or Igβ on wild type, β/1g-α, β/1g-β, and α/1g-β/1g-α cells. To stain for surface IgG, 2 × 10^6 cells/sample from each cell line were incubated with FITC-conjugated anti-IgG at 4°C. For chimera staining, 2 × 10^6 cells/sample from each cell line were incubated with anti-PDGFRα or anti-PDGFRβ antibodies and subsequently FITC-conjugated anti-IgG1 at 4°C. Also shown is staining of each cell line without primary antibody. As demonstrated by immunoprecipitation and immunoblotting, cells with equal staining intensity were stimulated through the endogenous receptor or through the chimeras. Heterodimers were precipitated from lysates of stimulated cells. No tyrosine phosphoproteins were precipitated through the chimeras as in Fig. 2. Lysates from these cells were immunoprecipitated with FB2, anti-Ig-α, or anti-Ig-β antibodies. Immunoprecipitates were resolved by 7.5% SDS-PAGE, transferred to nylon membrane, and then probed with the anti-phosphotyrosine antibody Ab2.

**Fig. 2.** The pattern of total protein phosphorylation in wild type (WT), β/1g-α, β/1g-β, and α/1g-β/1g-α cells upon stimulation through endogenous receptor or through the chimeras. 10 × 10^6 cells/sample of each cell line were left unstimulated (us) or were stimulated through the endogenous receptor (ig) or through the chimeras (Ch). Cells were then lysed in 1% Nonidet P-40 lysis buffer and cell lysates were immunoprecipitated with anti-phosphotyrosine antibodies (FB2). Immunoprecipitates were resolved by 10% SDS-PAGE, transferred to nylon membrane, and then probed with the anti-phosphotyrosine antibody Ab2.

**Fig. 3.** Only Ig-α was phosphorylated upon stimulation through the chimeras in α/1g-β/1g-α. 10 × 10^6 cells/sample of the wild type (WT) or α/1g-β/1g-α cells were either left unstimulated or were stimulated through the chimeras as in Fig. 2. Lysates from these cells were immunoprecipitated with FB2, anti-Ig-α, or anti-Ig-β antibodies. Immunoprecipitates were resolved by 7.5% SDS-PAGE, transferred to nylon membrane, and then probed with Ab2, anti-Ig-α, or anti-Ig-β antibodies.
(Fig. 4) Ig-β phosphorylation was extinguished to undetectable levels in α/Ig-β/β/Ig-α. 10 x 10^6 cells/sample of β/Ig-α, β/Ig-β and α/Ig-β/β/Ig-α were stimulated through the chimeras as before and then lysed at different time points after stimulation. Cell lysates were immunoprecipitated with a combination of anti-Ig-α and anti-Ig-β antibodies. Immunoprecipitates were resolved by 7.5% SDS-PAGE, transferred to nylon membrane, and blotted with Ab2 (upper panel). The immunoblot was then stripped and reprobed with a combination of anti-Ig-α and anti-Ig-β antibodies (lower panel).

PDGF-BB ligand and anti-PDGFRβ antibody followed by rabbit anti-mouse IgG1, for 1, 2, or 5 min. A representative experiment is shown in Fig. 4 (n = 4). In the β/α/β cell line, stimulation of the chimera induced its own phosphorylation, which was maximal at 2 min and transient (Fig. 4, upper panel). In contrast, phosphorylation of PDGFRα/Ig-β was not detected in α/Ig-β//β/Ig-α cells, even though more PDGFRα/Ig-β protein was immunoprecipitated (Fig. 4, lower panel). These results suggest that when expressed in isolation, Ig-β can be phosphorylated. However, when ligated in the presence of Ig-α, its own phosphorylation is inhibited. These observations are in accordance with the minimal inducible tyrosine phosphorylation of Ig-β observed following BCR ligation in A20 (Fig. 5C).

Ig-β Enhances the Phosphorylation of Ig-α—In Figs. 3 and 4, it is apparent that only PDGFRβ/Ig-α is tyrosine-phosphorylated following chimeric stimulation and its phosphorylation is strong only when co-ligated with PDGFR/Ig-β. To examine this further, we compared the inductive tyrosine phosphorylation of PDGFRβ/Ig-α when expressed alone (β/Ig-α) or with PDGFRα/Ig-β (α/Ig-β//β/Ig-α). The cell lines β/Ig-α and α/Ig-β//β/Ig-α were stimulated via the chimeras, lysed, and then immunoprecipitated with a combination of anti-Ig-α and anti-Ig-β antibodies. Shown in Fig. 5 are the results of a representative experiment (n = 3). Immunoprecipitates were resolved by SDS-PAGE, and after transfer to membrane, probed first with Ab2 (Fig. 5A, upper panel), then stripped and reprobed with a combination of anti-Ig-α and Ig-β antibodies (lower panel). There were remarkable differences in both the degree and kinetics of PDGFRβ/Ig-α phosphorylation with and without PDGFR/Ig-β co-ligation. In the absence of PDGFR/Ig-β, the tyrosine phosphorylation of PDGFRβ/Ig-α was weak at 1 min, increased to a maximum at 5 min, and was essentially absent at 30 min. In contrast, in the presence of PDGFR/Ig-β, PDGFRβ/Ig-α phosphorylation was maximal at 1 min and thereafter decreased, being almost undetectable at 30 min. To analyze this data further, we desensitometrically quantitated the immunoreactivity of each sample with Ab2 and anti-Ig-α antibodies and then plotted the ratio of these values as a function of time. As seen in Fig. 5B, co-ligation of PDGFR/Ig-β enhanced the phosphorylation of PDGFRβ/Ig-α approximately 12-fold at 1 min. This intensity and rapidity of tyrosine phosphorylation is similar to what is observed for endogenous Ig-α following ligation of the BCR (Fig. 5C).

It is possible that the observed differences in Ig-α phosphorylation with and without co-cross-linking Ig-β were due to differences intrinsic to those cells in which both chains were expressed. To address this possibility, we examined if the degree of phosphorylation of PDGFRβ/Ig-α was influenced by PDGFRα/Ig-β co-cross-linking on the same cell line. Therefore, we studied α/Ig-β//β/Ig-α cells under two different stimulating conditions. First, following the stimulating protocol described above, which includes PDGF-BB, heterodimers were formed and then aggregates in α/Ig-β//β/Ig-α. In parallel, cells were

![Fig. 4](http://www.jbc.org/)

![Fig. 5](http://www.jbc.org/)
stimulated without PDGF-BB, where only PDGFRβ/Ig-α would have been aggregated. As predicted, the degree of PDGFRβ/Ig-α phosphorylation was remarkably enhanced when heterodimers were first formed with PDGF-BB. The results from a representative experiment are shown in Fig. 6 (n = 3).

Co-aggregation of PDGFRβ/Ig-α and PDGFRα/Ig-β lowered the threshold for tyrosine kinase activation—Given the remarkable enhancement of Ig-α phosphorylation by Ig-β, we postulated that the heterodimeric complex would be more efficient in its ability to activate tyrosine kinases than a homodimeric complex. Therefore, we compared the stimulation threshold for the induction of tyrosine phosphorylation in α/Ig-β/β/Ig-α and β/Ig-α by titrating out the primary stimulating antibody. Cells were otherwise stimulated and analyzed as in Fig. 2. As can be seen in Fig. 7, stimulating both transfectants with high concentrations of primary stimulating antibody induced the tyrosine phosphorylation of cellular proteins. However, the tyrosine phosphorylation of cellular proteins in β/Ig-α diminished significantly after the 1st 4-fold dilution of anti-PDGFRβ antibody. In contrast to α/Ig-β/Ig-α, the tyrosine phosphorylation was still detected after two dilutions of anti-PDGFRβ antibody. Similar results were obtained when β/Ig-β was compared to α/Ig-β/Ig-β/Ig-α (data not shown). These results suggest that the heterodimeric structure of the BCR complex facilitates B cell responses to low doses of antigen.

DISCUSSION

Herein we report that the ITAM-containing subunits within an immune recognition receptor complex can cooperate to efficiently initiate signal transduction cascades. Using a system that allowed us to compare the signal transduction capacities and physical properties of homo- and heterodimers of Ig-α and Ig-β, we observed that the Ig-α/β heterodimer induced the phosphorylation of a wider range of substrates at a lower threshold of stimulation than either homodimer. This synergy correlated with the ability of Ig-β to enhance the tyrosine phosphorylation of Ig-α by more than 10-fold. Conversely, in the presence of Ig-α, Ig-β phosphorylation was extinguished to undetectable levels. These data suggest that one of the major functions of Ig-β is to enhance the phosphorylation and, therefore, the signal transducing capability of Ig-α. Furthermore, these data suggest that significant “cross-talk” or cross-modulation occurs between the subunits of the B cell antigen receptor.

Our results reveal a new level of complexity in the function of the BCR. Previous studies utilizing either fusion proteins, peptides or chimeras, have sought to characterize the functional capacities of individual cytoplasmic domains of the BCR complex (18, 19, 27, 28). This reductionist approach assumes that each ITAM-containing domain is an isolated signaling unit whose capacities can simply be added to those of other domains to form an accurate picture of the whole receptor complex. Our data suggest that this assumption is not entirely valid. Rather, we would argue that while the study of each individual subunit reveals what it can do, it is only in the context of other receptor structures that one can elucidate what that subunit does do.

We have recently obtained data directly demonstrating that the coordinate activities of Ig-α and Ig-β is of biological significance. We have established clones of WEHI 231, an immature B cell sensitive to apoptosis, expressing similar combinations of the chimeras described here. When the chimeras in these transfectants were stimulated, we observed that the induction of apoptosis required the cytoplasmic tails of both Ig-α and Ig-β. In those experiments, as in the experiments described in this report, only the heterodimerized chimeras induced tyrosine kinase activation efficiently.

Phosphorylation of the ITAM tyrosines within the BCR cytoplasmic domains is a necessary and early event in the initi-
ation of tyrosine kinase activation. Previously, we and others have demonstrated that members of the Src family of tyrosine kinases are constitutively associated with the resting receptor complex and that it is probably these kinases which mediate the phosphorylation of Ig-\(\alpha\) and thereby initiate signaling by recruiting and activating SH2 domain containing secondary effectors (2, 13, 19, 36). Which effectors are recruited by the receptor complex would be determined, in part, by which of the four tyrosines (34, 37) in the cytoplasmic domain of Ig-\(\alpha\) are phosphorylated upon receptor engagement (38). From our data it is not clear if Ig-\(\beta\) merely enhances the phosphorylation at previously modified tyrosines or directs the phosphorylation of new sites. This distinction is of potential significance because if Ig-\(\beta\) directs the phosphorylation of Ig-\(\alpha\), the spectrum of substrates activated by the receptor complex would be altered.

One of the mechanisms by which Ig-\(\beta\) could augment Ig-\(\alpha\) phosphorylation would be to recruit novel kinases to the receptor complex. Previously, we found that phosphoproteins of 40 and 42 kDa bind in vitro to the cytoplasmic domain of Ig-\(\beta\) via a phosphotyrosine-independent QTAT sequence embedded within the Ig-\(\beta\) ITAM (19). Recently, we have demonstrated that similar molecules are inducibly tyrosine-phosphorylated by BCR engagement and are associated with the native Ig-\(\alpha/\beta\) heterodimer. Alternatively, it is possible that kinases are constitutively associated with Ig-\(\beta\) because their SH2 domains bind a small subpopulation of phosphorylated Ig-\(\beta\) tails. While we did not observe any phosphorylation of Ig-\(\beta\) in our heterodimeric chimeras, there was a low level of Ig-\(\beta\) phosphorylation in the native BCR, which minimally increased following receptor engagement (Fig. 5C). It is possible that such phosphorylation of PDGFR\(\alpha/\beta\) occurred at a level too low to detect.

Another possibility is that Ig-\(\beta\) recruits SH2 domain-containing proteins, other than kinases, which bind to and protect Ig-\(\alpha\) tyrosines from dephosphorylation. This is a plausible alternative since the tyrosine phosphatase CD45 is associated with the receptor complex and its function is necessary for BCR-mediated signal transduction.

Previously, models of antigen receptor-mediated signal transduction have assumed that each ITAM-containing chain's functionwithin the multimeric whole. In the particular case of the BCR and tyrosine kinase activation, Ig-\(\beta\)’s function appears to be to facilitate the phosphorylation of Ig-\(\alpha\), which in turn allows the efficient activation of tyrosine kinases and possibly the recruitment of their substrates. The proof of this model will require an understanding of the mechanisms whereby Ig-\(\beta\) enhances Ig-\(\alpha\) phosphorylation.

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