The low affinity receptor for IgG, FcγRIIIA, is a multimeric receptor composed of the ligand binding subunit FcγRIIIAβ (CD16) in association with the signal-transducing subunits ζ or γ. Previous studies suggested that the cytoplasmic tail of FcγRIIIAα was not required for FcγRIIIAα-ζ association or signaling by FcγRIIIA. However, in these studies, the truncated FcγRIIIA chains still expressed the four most membrane-proximal amino acids of the cytoplasmic tail (amino acids 290–233). By successive truncations from the C terminus of FcγRIIIAα, we have studied the role played by the membrane-proximal amino acids of the cytoplasmic tail of FcγRIIIAα in (i) FcγRIIIA expression, (ii) FcγRIIIAα-ζ association, and (iii) signal transduction. We provide evidence that this region is not required for FcγRIIIA expression or FcγRIIIAα-ζ association. However, signaling by FcγRIIIA is strictly dependent on the membrane-proximal amino acids in the cytoplasmic tail of FcγRIIIAα. Thus, total deletion of the cytoplasmic tail of FcγRIIIAα results in a severely impaired tyrosine phosphorylation of phospholipase C-γ1, zap, and syk and rise in intracellular free Ca2+ following receptor ligation with specific anti-CD16 monoclonal antibody or Ig-anti-Ig complexes, suggesting that FcγRIIIAα-ζ association per se is not sufficient to establish the signal function of FcγRIIIA. In conclusion, the present findings demonstrate that the most membrane-proximal amino acids of the FcγRIIIAα cytoplasmic tail play a critical role in ligand-induced signal transduction by the FcγRIIIAα-ζ complex.

Binding of antibodies to effector cells by Fc receptors (FcR) provide an important link in the cooperation between the innate and the adaptive immune systems. Natural killer (NK) cells are cytotoxic for target cells coated with IgG antibodies. This property is referred to as antibody-dependent cellular cytotoxicity and is mediated through binding to target-bound IgG by the low affinity FcR for IgG expressed at the NK cell surface. Two distinct forms of the human low affinity FcR for IgG, FcγRIIIA and FcγRIIB, have been identified. FcγRIIIA, which is found on NK cells and macrophages, is a transmembrane protein complex, whereas the form expressed on neutrophils, FcγRIIB, is anchored to the outer plasma membrane by a glycosylphosphatidylinositol moiety (1). FcγRIIIA, the T cell receptor (TCR), and the B cell receptor (BCR) have many structural and functional features in common. Like TCR and BCR complexes, FcγRIIIA exist as multimeric receptor complexes composed of the ligand-binding FcγRIIIAα (CD16) chain noncovalently associated with several disulfide-linked subunits (2–5). The associated chains are defined as a family of disulfide-linked dimers (6), which are closely related and can substitute for each other (7, 8). They can be found as a ζ homodimer (2, 3), a γ homodimer, originally described as a component of the high affinity FcR for IgE (4), or as a γζ heterodimer (9). In addition, all of these dimers can form part of the TCR complex (8, 10) and cell surface expression of both FcγRIIIAα and the TCR is dependent on corexpression of the ζ or the γ chains (4, 11–13). It is not entirely clear how the FcγRIIIAα-ζ association takes place.

In addition to structural similarities, there are significant similarities between the signaling pathways coupled to FcγRIIIA, the TCR, and the BCR, respectively. Thus, ligation of each of these receptors induces tyrosine phosphorylation of several substrates including phospholipase C-γ1 (PLC-γ1) (14–17), and a rise in intracellular free Ca2+ (Ca2+)i (18, 19). The precise pathway by which receptor engagement initiates these events is not fully known, although src family kinases, the zap/syk kinases, and the tyrosine-containing activation motif (TAM) in the cytoplasmic tail of the associated subunits, all play important roles (reviewed in Ref. 20). Previous studies suggested that the cytoplasmic tail of FcγRIIIAα might not be required for signaling by FcγRIIIA (21–23). In all of these studies, however, the truncated FcγRIIIAα chains still expressed the four most membrane-proximal amino acids of the cytoplasmic tail. Thus, it remained unknown whether the membrane-proximal amino acids in the cytoplasmic tail of FcγRIIIAα also play a role in signal transduction following FcγRIIIA ligation. Although chimeric receptor molecules containing the extracellular part of FcγRIIIAα and the cytoplasmic domain of subunits with TAM are effective signal transducers when cross-linked by extracellular ligands (24, 25), it is possible that the cytoplasmic tail of the ligand binding subunit in intact receptors plays a role in signaling, as recently demonstrated for the BCR (26). In this study, we show that signaling by FcγRIIIA following stimulation with specific anti-CD16 mAb or immune complexes...
is strictly dependent on the membrane-proximal amino acids in the cytoplasmic tail of FcRIIIAa. In contrast, this region is not required for FcRIIIA-α association and cell surface expression.

EXPERIMENTAL PROCEDURES

Cells and Antibodies—JG cells, a TCR cell surface negative variant of the human T cell line Jurkat that synthesizes no CD3γ (27) were cultured in RPMI 1640 medium supplemented with 2 × 10⁻⁵ units/liter penicillin (Leo Pharmaceutical Products, Ballerup, Denmark), 50 mg/liter streptomycin (Merck, Darmstadt, Germany), and 10% (v/v) fetal calf serum (Life Technologies, Paisley, UK) at 37 °C in 5% CO₂. The anti-FcRIIIA mAb 9G11 (28) and Gr1L, Leu-14, and 36B8 were from the St. Jude (St. Louis, St. Louis, The Netherlands), Becton Dickinson (Mountain View, CA), and Immunotech (Marseille, France), respectively. The hamster antimouse/human μ mAb was kindly donated by Dr. Ralph Kubo (Cytel Corp., San Diego, CA). The mouse anti-human TCR mAb F101.01 (IgGl) was produced and characterized in our own laboratory (28). Rabbit anti-mouse (RAM) Ig antibodies were obtained purified, fluorescein isothiocyanate-conjugated, and as Fab(ab)₂ fragments from Jackson ImmunoResearch Laboratories, Inc. (West Grove, PA). Mouse anti-phosphotyrosine 4G10, anti-PLC-γ of plasmids. The last possibility seems less likely as confirmed by complete DNA sequencing. Sequencing demonstrated one nucleotide mismatch at base position 559 as compared to the published sequence (1, 33). In all constructs, a guanosine instead of a cytosine was found at position 559 (resulting in a valine instead of a glutamine). The correct sequence was subsequently published as 5′-TGTTGACCATGGT-3′ (corresponding to base 819–793 including the isodosaic and 170° a stop codon corresponding to residue 232). FcRIIIA was cloned into the Smal site of pUC-18 (kindly donated by Dr. J. V. Ravetch) (1). The following upstream primer was used. Fc-WT-up: 5′-TGTCACCTCTAGATCCCGCCCGTCATTT-3′. This primer spoiled the internal BamHI site of FcRIIIA and introduced a XbaI site just 5′ to the FcRIIIAα sequence. The following downstream primers were used. Fc-WT-down: 5′-ATTACCCCCATGGGACCCGGGTCATTT-3′ (corresponding to base 819–793 including the Styl site and with introduction of a Smal site). Fc242: 5′-TTAAAAACGCTGCTTCACTCCTGTTTGTGA-3′ (corresponding to base 771–739 with introduction of a Styl site and with introduction of a Smal site). The polymerase chain reaction products were cut with XbaI and Styl and ligated into the 4.1 kilobase XbaI-Styl fragment of pBluescript βWT (29). From here the constructs were cut out with XbaI-BamHI and ligated into the expression vector pTmtFneo (32). Mutations were confirmed by complete DNA sequencing. Sequencing demonstrated one nucleotide mismatch at base position 559 as compared to the published sequence (1, 33). In all constructs, a guanosine instead of a thymidine was found at position 559 (resulting in a valine instead of a phenylalanine at amino acid position 176 in the extracellular domain). Accordingly, two independent samples of the original FcRIIIA-2 plasmid (kindly donated by Dr. J. V. Ravetch) were sequenced and in both samples the base at position 559 was found to be a guanosine and not a thymidine as previously published. These results indicated that position 559 in FcRIIIAa might be polymorphic in the population or that a variation had been introduced into position 559 as a result of propagation of the plasmids. The last possibility seems less likely as identical sequencing results were obtained from two independent plasmids. The constructs were transfected into JGN cells using the Bio-Rad Gene Pulsor at a setting of 270 V and 960 μF with 40 μg of plasmid per 2 × 10⁷ cells. After 3–4 weeks of selection, G418-resistant clones were expanded and maintained in medium without G418.

Flow Cytometric Analyses and Intracellular Calcium—FACS analyses were performed as described previously on a FACScan (Becton

2 J. V. Ravetch, personal communication.
interference in signaling by the TCR, these constructs were transfected into the TCR cell surface negative Jurkat variant JGN(27). G418-resistant clones were isolated and analyzed for cell surface expression of FcγRIIIAα. All of the truncated FcγRIIIAα chains were expressed at the surface of JGN with comparable intensity as determined by FACS analyses using CLB/FcRgran1, 3G8, or Leu-11c mAb (Fig. 1B).

**Fig. 1.** A, schematic representation of the amino acid sequences in the cytoplasmic tails of FcγRIIIAα expressed in the indicated cell lines. B, FACS histograms of cells incubated with PE-conjugated anti-CD16 mAb (Leu-11c) (black) and cells incubated with irrelevant isotype-matched PE-conjugated mAb (white). The cell line analyzed is given in each histogram. The abscissa represents the fluorescence intensity on a logarithmic scale and the ordinate the relative cell number on a linear scale.

A Role of the Cytoplasmic Tail of FcγRIIIAα in Signal Transduction

| Cell line | FcγRIIIAα cytoplasmic tail sequence |
|-----------|-----------------------------------|
| JGN-FcγWT | KTNIRSSTRD WKDHFKWRK DPQDK        |
| JGN-Fcγt242 | KTNIRSSTRD WK                  |
| JGN-Fcγt234 | KTI                      |
| JGN-Fcγt233 | KTN                     |
| JGN-Fcγt232 | K                        |
| JGN-Fcγt231 | K                        |
| JGN-Fcγt230 | K                        |

Association of the Truncated FcγRIIIAα with the ζ Subunit—Several studies have demonstrated the requirement of the ζ/γ subunits for signaling through FcγRIIIAα (21–23). It was therefore important to analyze whether the truncated FcγRIIIAα chains expressed at the cell surface were associated with the ζ chain. The ζ chain is poorly labeled by cell surface iodination; however, it should be possible to detect FcγRIIIAα-ζ association by coprecipitation-labeled FcγRIIIAα with anti-ζ mAb. Accordingly, cells were surface radioiodinated, lysed in 1% digitonin lysis buffer, and immunoprecipitated with anti-CD16 mAb CLB/FcRgran1, 3G8, or Leu-11c mAb (Fig. 1B).
A Role of the Cytoplasmic Tail of FcγRIIIAα in Signal Transduction

Receptor-induced Mobilization of Intracellular Calcium——The ability of FcγRIIIA containing truncated FcγRIIIAα chains to mediate a rise in [Ca\(^{2+}\)](i), following stimulation with the specific anti-CD16 mAb 3G8, was next studied. As shown in Fig. 3B, 3G8 induced a rapid but weak rise in [Ca\(^{2+}\)](i), in JGN cells transfected with FcγWT. This response was further potentiated following cross-linking with F(ab)\(_2\) fragments of RAM Ig (Fig. 3B). As expected, no detectable rise in [Ca\(^{2+}\)](i), was observed in the FcγRIIIA negative parent cell line, JGN (Fig. 3A). In contrast to JGN-FcγWT cells, none of the transfectants expressing truncated FcγRIIIAα chains showed a rise in [Ca\(^{2+}\)](i), following stimulation with 3G8 alone. Following optimal stimulation by cross-linking with RAM Ig, a rise in [Ca\(^{2+}\)](i), in JGN-Fcγt242 and JGN-Fcγt234 cells was seen equal to the one observed for JGN-FcγWT cells. However, further truncation resulted in an impaired rise in [Ca\(^{2+}\)](i) (Fig. 3) suggesting that the most membrane-proximal amino acids were required for an efficient rise in [Ca\(^{2+}\)](i). Indeed, cells expressing FcγRIIIAα lacking all of the amino acids of the cytoplasmic tail were nearly unable to respond to optimal stimulation (Fig. 3H). Similar results were obtained following stimulation of the transfectants with Ig-anti-Ig complexes. Whereas the rise in [Ca\(^{2+}\)](i), was comparable for JGN-Fcγt230, JGN-Fcγt242, and JGN-Fcγt234 cells, truncations from residue 233 to 230 resulted in a progressive weakening of the response following treatment with Ig-anti-Ig complexes (Fig. 4).

Receptor-induced Protein Tyrosine Phosphorylation——One of the earliest signaling events following FcγRIIIA ligation is tyrosine phosphorylation of several cytoplasmic substrates including the \(\zeta\) subunit (14). To analyze the role of the FcγRIIIAα tail in receptor-mediated protein tyrosine phosphorylation, JGN-FcγWT and JGN-Fcγt230 cells were treated with either cross-linked anti-CD16 mAb (3G8), Ig-anti-Ig complexes, or PBS for 2 min at 37 °C prior to lysisation and immunoprecipitation with anti-phosphotyrosine mAb 4G10 coupled to agarose beads. The precipitates were separated by 10% SDS-PAGE and analyzed in Western blotting with 4G10 (Fig. 5A). Treatment with cross-linked anti-CD16 mAb or Ig-anti-Ig complexes resulted in tyrosine phosphorylation of several proteins in both JGN-FcγWT and JGN-Fcγt230 cells. Although no significant qualitative differences were observed in the tyrosine-phosphorylated proteins from the two cell lines, significant quantitative differences were seen. Most strikingly, the \(\zeta\) chain and two unidentified proteins with a molecular mass of approximately 40 and 55–60 kDa became only weakly phosphorylated in JGN-Fcγt230 cells as compared with the corresponding proteins in JGN-FcγWT cells, suggesting that some of the tyrosine kinases activated by engagement of wild-type FcγRIIIAα were not as efficiently (or not at all) activated by engagement of FcγRIIIA containing the tail-less FcγRIIIAα chain.

As deletion of the cytoplasmic tail of FcγRIIIAα resulted in a severe impairment of the rise in [Ca\(^{2+}\)](i), following receptor engagement, it was of interest to analyze whether truncation of the cytoplasmic tail of FcγRIIIAα influenced tyrosine phosphorylation of PLC-\(\gamma\)1. Accordingly, PLC-\(\gamma\)1 was immunoprecipitated from JGN-FcγWT and JGN-Fcγt230 cells treated with cross-linked anti-CD16 mAb (3G8), Ig-anti-Ig complexes, or PBS for 2 min at 37 °C, and the immunoreactive material was analyzed in Western blotting with the anti-phosphotyrosine mAb 4G10 (Fig. 5B, upper panel). A tyrosine-phosphorylated protein with a molecular mass of 145–150 kDa was detected only in the PLC-\(\gamma\)1 immunoprecipitates from JGN-FcγWT cells treated with cross-linked anti-CD16 mAb or with Ig-anti-Ig complexes. Using anti-PLC-\(\gamma\)1 antibodies as blotting reagents, a single band was detected, at similar levels in all anti-PLC-\(\gamma\)1 immunoprecipitates, corresponding to a protein with a molecular mass identical to that of the phosphoprotein, confirming the identification of the tyrosine-phosphorylated protein with
PLC-γ, and excluding that the lack of its detection with the anti-phosphotyrosine mAb in the precipitates from JGN-FcγRIIIAa230 cells was due to its absence from these precipitates (Fig. 5B, lower panel).

These results strongly suggested that deletion of the cytoplasmic tail of FcγRIIIAα disturbed the coupling of the receptor
Fig. 5. A, total protein tyrosine phosphorylation. After incubation of JGN-FcγWT (lanes 1–3) and JGN-Fcγt230 (lanes 4–6) cells with the anti-CD16 mAb 3G8 plus F(ab)2 fragments of RAM Ig (lanes 1 and 4), F101.01 plus RAM Ig (lanes 2 and 5), or PBS (lanes 3 and 6), cells were lysed and the lysates were immunoprecipitated with anti-phosphotyrosine mAb. Immunoprecipitated proteins were electrophoresed on 10% SDS-PAGE under reducing conditions. Western blot analysis was performed using anti-phosphotyrosine mAb. The positions of the ζ chains and the molecular mass markers are indicated. B, tyrosine phosphorylation of PLC-γ1. After incubation of JGN-FcγWT (lanes 1–3) and JGN-Fcγt230 (lanes 4–6) cells with anti-CD16 mAb (3G8) plus F(ab)2 fragments of RAM Ig (lanes 1 and 4), F101.01 plus RAM Ig (lanes 2 and 5), or PBS (lanes 3 and 6), cells were lysed and the lysates were immunoprecipitated with anti-PLC-γ1 mAb. Immunoprecipitated proteins were electrophoresed on 8% SDS-PAGE. Western blot analysis was performed using, sequentially on the same blot, the anti-phosphotyrosine mAb 4G10 (upper panel) and anti-PLC-γ1 mAb (lower panel).

Fig. 6. Tyrosine phosphorylation of zap and syk. After incubation of JGN-FcγWT (lanes 1–3 and 7–9) and JGN-Fcγt230 (lanes 4–6 and 10–12), cells with anti-CD16 mAb plus F(ab)2 fragments of RAM Ig (lanes 1, 4, 7, and 10), F101.01 plus RAM Ig (lanes 2, 5, 8, and 11), or PBS (lanes 3, 6, 9, and 12), cells were lysed and the lysates were immunoprecipitated with anti-zap mAb (A) or anti-syk polyclonal antibodies (B). Immunoprecipitated proteins were electrophoresed on 10% SDS-PAGE under reducing conditions. Western blot analysis was performed using anti-phosphotyrosine mAb. The positions of zap (ZAP-70), syk, the ζ chains, and the molecular mass markers are indicated.

to protein tyrosine phosphorylation events involving the phosphorylation of ζ and PLC-γ1. Since the known components of FcγRIIIA lack intrinsic kinase activity, this indicated that the association and/or activation of non-receptor protein-tyrosine kinases involved in FcγRIIIA signaling is dependent on the cytoplasmic tail of FcγRIIIAα. It has been demonstrated that stimulation of FcγRIIIA induces an increased tyrosine phosphorylation of the non-receptor protein-tyrosine kinases zap...
and syk (16, 17). Accordingly, zap and syk were immunoprecipitated from JGN-FcγWT and JGN-Fcγt230 cells treated with cross-linked anti-CD16 mAb (3G8), Ig-anti-Ig complexes, or PBS for 2 min at 37 °C, and the immunoreactive material was analyzed in Western blotting with the anti-phosphotyrosine mAb 4G10 (Fig. 6). zap from JGN-FcγWT cells became strongly phosphorylated whereas zap from JGN-Fcγt230 cells became only weakly phosphorylated following stimulation with cross-linked anti-CD16 mAb or Ig-anti-Ig complexes (Fig. 6A). Likewise, syk from JGN-FcγWT cells became strongly phosphorylated whereas syk from JGN-Fcγt230 cells became only weakly phosphorylated following stimulation with cross-linked anti-CD16 mAb or Ig-anti-Ig complexes (Fig. 6B). In addition, phosphorylated ζ was clearly coprecipitated with syk in JGN-FcγWT cells following stimulation with cross-linked anti-CD16 mAb or Ig-anti-Ig complexes but was only weakly coprecipitated with syk from JGN-Fcγt230 cells following stimulation with cross-linked anti-CD16 mAb.


discussion

It has previously been shown that truncated FcγRIIIαs with only the four most membrane-proximal amino acids of the cytoplasmic tail left allows surface expression and signaling through FcγRIIIα (21–23). Our results are in agreement with these results. More importantly, we have extended these studies by demonstrating that further truncations of the cytoplasmic tail of FcγRIIIα still allow FcγRIIIα-ζ association and expression but severely affect the signaling capacity of FcγRIIIA. At first sight, our results might seem controversial as it has generally been believed that the short cytoplasmic tails of the Ig superfamily molecules allows a closer “nonphysiological” contact of their signaling domains with the membrane-bound IgM (mIgM). Point mutation of one of the three amino acids of the cytoplasmic tail of mIgM completely abolished antigen-induced signal-transduction by the BCR (26).

Several possibilities for the role of the membrane-proximal amino acids of the cytoplasmic tail of FcγRIIIα may be suggested. The cytoplasmic tail of FcγRIIIα may be directly involved in association with non-receptor protein-tyrosine kinases e.g. syk. syk is found in association with FcγRIIIα (17), FcεRI (36), the BCR (37), and the TCR (38). In B cells, syk may associate with the BCR by two different mechanisms: syk may be bound to the resting BCR via the transmembrane and cytoplasmic domain of mlg, and syk may be bound to the tyrosine-phosphorylated TAM of the Ig α and β chains of the activated BCR via its SH2 domains (39). Likewise, in T cells there is evidence that syk is constitutively bound to the resting TCR by a still unidentified mechanism (40) and that syk associates with the tyrosine-phosphorylated TAM of the ζ chain of the activated TCR via its SH2 domains (38). Therefore, it is possible that syk binds to FcγRIIIα via the transmembrane and membrane-proximal part of the FcγRIIIα chain. Alternatively, the transmembrane and membrane-proximal part of the FcγRIIIα chain might be indirectly involved in the association with syk or other protein-tyrosine kinases via a third unidentified molecule.

An alternative but not mutually exclusive explanation might be that the membrane-proximal part of the cytoplasmic tail of FcγRIIIα in response to ligand binding induces conformational changes in the ζ chain promoting optimal binding and/or function of the TAM-associated kinases. Thus, this model implies that the membrane-proximal part of the cytoplasmic tail of FcγRIIIα is involved in transfer of information from the ligand binding subunit to subunits involved in downstream signaling.

CD45 has been found to associate with FcγRIIIα at the cell surface (41). CD45 is a phosphotyrosine phosphatase that is crucial for the normal function of T and B cells and presumably other leukocytes as well (42–45). In the absence of CD45, the rapid TCR-triggered tyrosine phosphorylation of cellular proteins normally seen is severely reduced resulting in impaired activation of PLC and rise in [Ca2+]i (42–44). One mechanism by which CD45 seems to regulate these events is by regulating src family protein-tyrosine kinases including lck (reviewed in Ref. 46). A third role of the membrane-proximal part of the cytoplasmic tail of FcγRIIIα could be to contribute to the association between FcγRIIIα and CD45 and thereby indirectly to regulate lck.

The roles of the membrane-proximal part of the cytoplasmic tail of FcγRIIIα proposed above appear to be inconsistent with the finding that receptor chimeras containing the cytoplasmic tail of γ/δ (22–25, 47, 48), CD5ζ (49), and Ig-α (50) are effective signal transducers when cross-linked by mAb. It is, however, possible that cross-linking of such chimeric receptor molecules allows a closer “nonphysiological” contact of their cytoplasmic tails than cross-linking of the ligand binding subunits of intact receptors does. A closer contact of the TAM in chimeric receptors could facilitate activation of protein-tyrosine kinases constitutively bound to the TAM (51). Clearly, further studies are necessary to resolve the role of the cytoplasmic tail of FcγRIIIα in signal transduction.

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