MINI-REVIEW

Receptor-receptor interactions of complement receptor type 3 in neutrophil membranes

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Abstract: The leukocyte integrin CR3 (CD11b/CD18) is known to participate in a variety of cell functions. Recent studies have indicated that CR3 may communicate with other plasma membrane receptors to carry out several cell functions. In this review we discuss these potential receptor-receptor interactions of CR3 and present a unifying model of CR3's diverse functions. *J. Leukoc. Biol.* 54: 492-494; 1993.

Key Words: *Fc receptors • lectin-like interactions • target recognition • transmembrane signaling*

INTRODUCTION

Cell membrane-associated proteins can be operationally classified as integral, peripheral, and glycophospholipid linked [1]. Membrane proteins are assembled from similar or dissimilar subunits in a variety of ways to form receptors, channels, and enzymes. For example, antigen receptors of T and B cells are composed of at least seven and five protein subunits, respectively [e.g., 2-5]. Whether multimeric membrane complexes are involved in neutrophil or macrophage transmembrane signaling is unknown. In this review we discuss the emerging theme of receptor-receptor interactions in neutrophil membranes with particular emphasis on CR3 (CD11b/CD18) as a membrane transducer, especially for glycophospholipid-linked proteins.

CR3

CR3 (CD11b/CD18), a leukocyte integrin, participates in a broad spectrum of adherence-related leukocyte functions including cell adherence, cytolysis, phagocytosis, and chemotaxis [6, 7]. After SDS-PAGE, CR3 is found as a heterodimeric glycoprotein composed of 155- and 94-kd subunits [8]. Each subunit spans the membrane bilayer. CR3 interacts with the cytoskeleton and potentiates the release of cytoplasmic messengers [9-11]. CR3 is a pluripotent membrane recognition and triggering device. In addition to being the receptor for complement fragment iC3b [7], it recognizes zymosan [12], β-glucans [13], *Escherichia coli,* and lipopolysaccharide [14], *Leishmania* [15], and fibrinogen [16]. Carbohydrates expressed on CR3 are recognized by concanavalin A [17] and *E. coli* [18] lectins.

CR3-TO-Fcγ RECEPTOR INTERACTIONS

Several lines of evidence support the hypothesis that CR3 interacts with Fcγ receptors. Early studies showed that Fab fragments of anti-CR3 monoclonal antibody inhibit immunoglobulin G (IgG) dependent phagocytosis [8]. Furthermore, neutrophils from patients with leukocyte adhesion deficiency (LAD) express diminished IgG-dependent phagocytosis and cytolysis compared with controls [19, 20]. Phagocytosis and rosetting experiments have indicated that CR3 may interact with Fcγ receptors [21, 22]. Recent studies have indicated that CR3 and FcγRII (CDw32) cooperate in the generation of leukotriene B_4 [23]. When neutrophils adhere to immune complex-coated surfaces, molecular proximity between CR3, but not Fcγ receptors, and the cytoskeleton is triggered [11], providing physical evidence for the participation of CR3 in antibody-dependent functions. Further evidence for the interaction of these receptors comes from cocapping studies. We have shown that CR3 cocaps with FcγRIIIB (CD16) and that specific saccharides, which interact with CR3's lectin-like site [12], inhibit cocapping [24]. The same saccharides decrease immune complex-dependent transmembrane signaling and superoxide production [25], suggesting that the receptor-receptor interactions identified in the cocapping experiments participate in signal transduction and superoxide production. Furthermore, studies using transfected fibroblasts have shown that neither CR3 or FcγRIIIB is capable of independently triggering antibody-dependent phagocytosis, whereas cells coexpressing these receptors display antibody-dependent phagocytosis (Krauss, J.C., Poo, H., Xue, W., Mayo-Bond, L., Todd, R.F., Petty, H.R., manuscript submitted).

CR3 AS A MEMBRANE TRANSDUCER

The presence of membrane transducers for GPI-linked proteins has been variously postulated in the scientific literature [26]. We propose that CR3 is one such transducer. **Figure 1** shows a schematic summary of the potential extramembrane and intramembrane interactions of CR3. The extramembrane interactions, as described above, can be classified as protein dependent and carbohydrate dependent. CR3's carbohydrate-dependent recognition mechanisms include both interactions mediated by its lectin-like site and interactions of its saccharide chains with other lectins. In addition to its interactions with macromolecules outside the plane of the membrane, CR3 can communicate with other plasma membrane proteins. In the preceding paragraph we described various experiments that provide evidence for interactions between CR3 and FcγRIIIB and CR3 and FcγRII.

Abbreviations: fMLP, *N*-formylmethionyl-leucyl-phenylalanine; IgG, immunoglobulin G; LAD, leukocyte adhesion deficiency; uPaR, urokinase-type plasminogen activator receptor.

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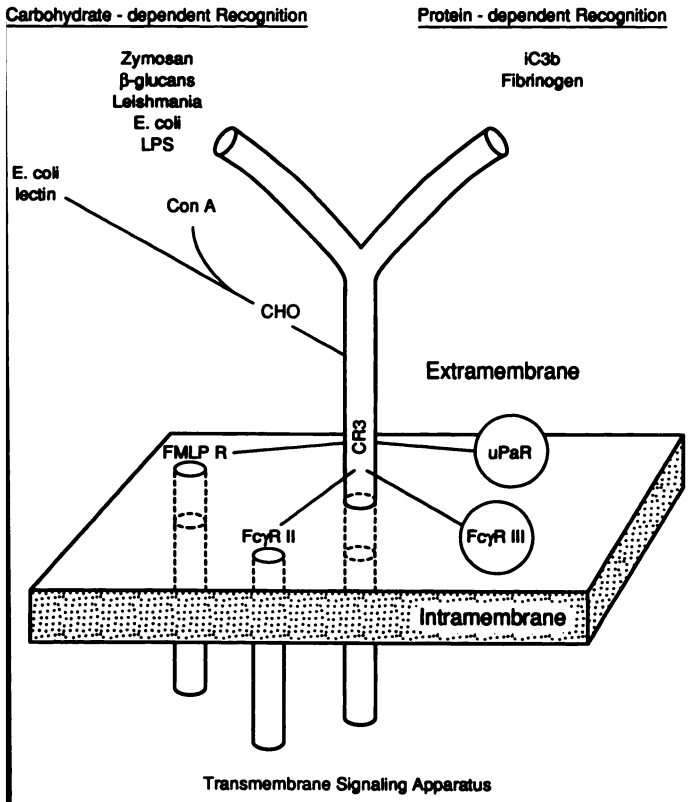

Fig. 1. A highly schematic illustration of potential extramembrane and intramembrane interactions of CR3. Extramembrane interactions are shown above and below the membrane. Interactions with external macromolecules are listed as carbohydrate or protein dependent. Potential intramembrane interactions with FcγRIIIB, FcγRII, uPaR, and fMLP receptors are shown.

These interactions may help to explain the co-up-regulation and co-down-regulation of these receptors [27, 28] and the interplay between the receptors (e.g., FcγRII-FcγRIIIB [29]) in cell membranes.

In addition to FcγRs, CR3 apparently interacts with other receptors. We have shown that the urokinase-type plasminogen activator receptor (uPaR), another heavily glycosylated GPI-linked protein, cocaps with CR3 [30]. Furthermore, Kew et al. [31] have provided evidence that FcγRIIIB communicates with the fMLP receptor. To integrate this work with our own, we have studied the surface distribution of fMLP receptors using a fluorescent analogue. These unpublished experiments have shown that ligated fMLP receptors cocap with CR3 and collect at sites of antibody-dependent binding and phagocytosis. This may eventually provide a better molecular rationale for the defective chemotaxis seen using LAD neutrophils.

CR3 COMMUNICATES WITH THE CYTOSKELETON

Neutrophil functions such as chemotaxis, phagocytosis, and adherence require the participation of cytoskeletal structures. Integrin molecules are known to be associated with the cytoskeleton [1]. A recent study has shown that integrins transmit mechanical signals to the cytoskeleton [32]. When CR3 binds iC3b, one of its potential ligands, its proximity to the cytoskeletal actin filaments is dramatically enhanced [33]. As mentioned earlier, immune complexes enhance CR3, but not FcγR, proximity to microfilaments [11]. This suggests that several receptors could affect transmembrane chemical signal transduction and mechanotransduction via CR3.

The cytoskeleton may also play a role in receptor-receptor interactions for transmembrane proteins. CR3 clustering [34] may be a reflection of their cytoskeletal attachments [33], although the detailed nature of CR3-CR3 interactions is unknown. It is also possible that other specific transmembrane proteins, such as the fMLP receptor, might be tethered to the cytoskeleton in a fashion that promotes interactions with CR3.

PROSPECTS

We are all familiar with the idea that extracellular ligands bind to membrane receptors, but perhaps less so with interactions between ostensibly separate receptors within a membrane. These interactions need not be static. Receptors probably display various affinities for one another that could be modulated by cytoplasmic messengers or ligation status. These interactions may be restricted to the reduced dimensionality of membranes, in analogy with the spontaneous formation of insulin heterotetrameric receptors in membranes but not in solution [1]. The effector recognition complex formed by CR3 and its several partners could generate a diversity of signals; for example, if each of the three transmembrane proteins mentioned above could generate one cytoplasmic signal, seven different cytoplasmic combinations can be obtained. In addition, CR3 could provide other membrane receptors, such as FcγRIIIB and uPaR, with a membrane mechanotransduction device to affect phagocytosis and locomotion, respectively. Receptor-receptor interactions of integrins have also been observed for T cells [35]. Further experiments will better define the nature of these membrane complexes and their role in the promotion of effector functions.

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