Editorial

Complement receptor type 3 (CR3, CD11b/CD18, Mac-1, Mo1) is still a source of fascination and continued discovery even 13 yr after its initial biochemical and functional characterization (1). For readers who are not integrin aficionados, CR3 is a heterodimeric gp (gp165,95) that is expressed on the plasma membrane of mammalian PMNs, most mononuclear phagocytes, and natural killer (NK) cells. It is a member of the β2 integrin family that also includes lymphocyte function antigen-1 (LFA-1; CD11a/CD18) and protein 150,95 (p150,95; CD11c/CD18), each of which consists of unique (but homologous) α (CD11a, b, and c) subunits noncovalently associated with a common β (CD18) subunit. The first function attributed to CR3 was its ability to bind C (specifically the iC3b fragment of C3) which was demonstrated by the capacity of anti-CR3 mAb to block the binding of iC3b-opsonized particles to normal PMNs and the failure of these particles to bind to CR3-deficient PMNs. Whereas its iC3b binding activity seemed to justify CR3's designation as the C receptor type 3 (as distinguished from CR1 and CR2 which bind C3b and C3d, respectively), this moniker has proven to be inadequate to describe CR3's full range of functional properties. Indeed, subsequent investigations revealed that CR3 is involved in PMN homotypic aggregation (recognizing a still-to-be-determined cellular counter receptor), cellular adherence to activated endothelial cells (via ICAM-1), and cellular adhesion to such disparate proteins as fibrinogen and Factor X. Experiments using mutant/chimeric forms of CR3 (as expressed in transfectant cells) along with mAb blocking studies demonstrated that several of the adhesion functions of CR3 were attributed to an "I" domain within the CD11b (αm) subunit (2). Other experiments showed that CR3's binding activity is not constitutive but is induced by "inside-out signaling" (in response to a variety of soluble and particulate stimuli) that results in a conformational change facilitating receptor function. Conversely, CR3, when engaged by some ligands, transduces "outside-in" signals resulting in certain kinase-dependent cellular effector responses.

In addition to the I domain of CR3 (which is responsible for its recognition of iC3b, ICAM-1, and fibrinogen), CR3 also expresses a lectin-like domain with a capacity to bind certain complex polysaccharides including β-glucan. The specificity of CR3 for β-glucan sugars was demonstrated by Ross and coworkers in 1987 (3) when they showed that (*a*) PMN ingestion of yeast or yeast-derived β-glucan particles was blocked by anti-CR3 mAb or by fluid-phase iC3b; (*b*) the oxidative burst of PMNs in response to zymosan or β-glucan particles was blocked by anti-CR3 (or fluid phase iC3b) and was absent in PMNs deficient in CR3; and (*c*) CR3 from detergent-solubilized PMNs could be affinity-isolated by β-glucan–Sepharose. The discovery of a lectin domain on CR3 not only provided a unique recognition site for phagocyte attachment and phagocytosis of unopsonized yeast microorganisms, but also suggested a mechanism for a novel form of interreceptor cooperation. Specifically, recent experiments have demonstrated a lectin-carbohydrate linkage between CR3 and certain glycosylphosphatidylinositol (GPI)-anchored receptor glycoproteins (e.g., FcγRIIIb; the receptors for urokinase plasminogen activator and for endotoxin/endotoxin-binding protein) in which CR3 participates as a mechanotransducer of signals initiated by the binding of ligands to these GPI receptors (which lack transmembrane domains) (4).

As an important extension of their earlier characterization of the lectin domain of CR3, Ross and colleagues recently mapped its location to a region that is COOH-terminal to the I domain of the CD11b subunit, and further defined its sugar specificity to include polysaccharides that contain mannose and *N*-acetyl-D-glucosamine in addition to glucose (5). Moreover, as described in their report in this issue of *The Journal*, Větvička et al. (6) provide evidence that supports the role of the CR3 lectin domain in priming CR3-expressing PMNs and NK cells for cytotoxicity of iC3b-opsonized targets (erythrocytes and tumor cells) that are otherwise resistant to killing. Specifically, they show that a 10-kD soluble mannose-rich polysaccharide, SZP, as well as higher molecular mass β-glucans can induce a primed state of CR3 which promotes the subsequent lysis of iC3b-opsonized target cells that are bound via the I domain of CR3 (but which lack membrane polysaccharide ligands for the lectin domain). Polysaccharide priming of CR3 via the lectin domain occurs as a result of a magnesium- and tyrosine kinase–dependent conformation change in the adjacent I domain as detected by the expression of an activation epitope. The full activation of CR3 leading to killing therefore occurs as a two-step process that depends upon polysaccharide (either cell membrane–associated or soluble) binding to the lectin domain and the recognition of membrane-bound iC3b via the I domain. Microorganisms that express CR3-stimulating polysaccharides (e.g., yeast) and which bear opsonized iC3b are killed directly by CR3-expressing effector cells, whereas iC3b-opsonized tumor cells that lack stimulatory surface polysaccharides are resistant to CR3-dependent killing unless the effector cell is exposed to a soluble priming stimulus.

What is the clinical relevance of these observations? The results of previous investigations have demonstrated the capacity of β-glucans to activate neutrophils, mononuclear phagocytes, and NK cells to develop cytolytic activity for tumor target cells in vitro. Moreover, the outcome of several clinical studies (the majority performed in Japan) has suggested the efficacy of mushroom-derived soluble β-glucans such as lentinan and schizophyllan in promoting antitumor immunity in patients with gastrointestinal cancer. In certain controlled clinical trials, the increased survival of patients receiving these immunostimulatory β-glucans has been reported. Whereas the use of soluble β-glucans as therapeutic agents in cancer has not received widespread attention in the oncology community, the results of Větvička et al. (6) may provide a more rational basis for the design of preclinical and clinical trials targeted specifi-

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cally to human tumors that trigger surface complement opsonization.

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