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Leukocyte Beta2-Integrins; Genes and Disease

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Abstract

Integrins are heterodimeric transmembrane receptors that mediate cell-cell and cell-extracellular matrix interactions. Beta2-integrins are expressed exclusively in leukocytes and mediate many important functions in the immune system. Beta2-integrin genes are important in the pathologies of several diseases and genetic syndromes. These include Leukocyte Adhesion Deficiency (LAD) and Systemic Lupus Erythematosus (SLE), disorders which lie at opposite ends of the spectrum of immunological diseases. In LAD-I and LAD-III syndromes, beta2-integrin expression or function is reduced or absent. In SLE, genetic variants of the *ITGAM* gene, which encodes for the alpha M/CD11b chain of the beta2-integrin Mac-1,are associated with SLE development. In this mini review we summarise current knowledge regarding the involvement of beta2-integrins in LAD and SLE. Interestingly, dysfunctional beta2-integrins have been linked to both disorders, shedding light on the diverse roles of these receptors in the immune system.

Keywords: Beta2-integrins; Leukocyte adhesion deficiency; Systemic lupus erythematosus; ITGAM

Beta2-Integrins and Their Roles in the Immune System

Members of the beta2-integrin family are expressed exclusively on leukocytes. The beta2-integrin family has four members, sharing a common beta-chain (the beta2- or CD18 integrin), but with different alpha chains (CD11a/CD11b/CD11c/CD11d) that convey the ligand specificity and function of each integrin subtype [1]. Beta2-integrins mediate cell adhesion and signalling in immune cells (Figure 1) and are of pivotal importance for immune system function *in vivo*.

LFA-1 (CD11a/CD18; alphaLbeta2-integrin) is expressed on all leukocytes andbinds to members of the ICAM (intercellular adhesion molecule) family. LFA-1 mediates the firm adhesion of leukocytes to endothelial cells surrounding blood vessels, which is necessary for leukocyte extravasation at inflammatory sites. Selectin binding and inflammatory signals (such as chemokines) stimulate the increase in LFA-1 affinity necessary for firm adhesion to ICAM-ligands. LFA-1 expressed on T cells also binds to ICAM -1 on antigen presenting cells at the immune synapse, thereby strengthening the interaction between the cells and optimising subsequent signalling and T-cell activation [1,2].

In contrast to LFA-1, which is found on all leukocytes, Mac-1 (CD11b/CD18; alphaMbeta2-integrin) is mainly expressed on myeloid cells (such as neutrophils, monocytes, macrophages and myeloid dendritic cells). Mac-1binds to a wide variety of ligands including ICAM-1 and complement component iC3b; Mac-1 is also called complement receptor 3(CR3). Through binding to iC3b, the Mac-1 integrin mediates phagocytosis of complement opsonised bodies, including pathogens, apoptotic cells and immune complexes [3]. Mac-1 binding to ICAM-1 is important for neutrophil extravasation at inflammatory sites [4]. Recently, it has become apparent that Mac-1 is also an important negative regulator of leukocyte function. For example, Mac-1 restricts dendritic cell (DC) maturation and function [5] and DC-induced T cell activation [6]. Mac-1 also plays a role in oral tolerance by restricting Th17 cell differentiation [7]. In macrophages, Mac-1 has been reported to restrict Toll-like receptor (TLR) signalling. In these cells, Mac-1 induces Src/Syk signalling, which results in degradation of TLR signalling adaptors MyD88 and TRIF [8]. In addition, Mac-1 has also been implicated in limitingmacrophage inflammatory responses through the induction of signalling inhibitors such as SOCS3 and A20, as well as the anti-inflammatory cytokine IL-10 [9]. Thus, Mac-1 has an important role in limiting pro-inflammatory responses in addition to its critical roles as a complement receptor and in extravasation.

Complement receptor 4 (CR4; CD11c/CD18) is very similar to Mac-1, and these two beta2-integrin family members appears to have overlapping functions. Like Mac-1, CD11c/CD18 also binds iC3b and mediates phagocytosis of iC3b-coated particles, and immune complex clearance. This receptor also binds fibrinogen and ICAM ligands and may play a role in leukocyte adhesion and migration [10]. It appears to be necessary for protection from systemic *Candida-albicans* infections [11].

Relatively little known is known about CD11d/CD18 (alphaMbeta2), the fourth and most recently discovered beta2-integrin, though a few recent studies have shed some light onto the potential functions of this integrin [12,13].

Leukocyte Adhesion Deficiency (LAD)

A loss of beta2-integrin expression or function is associated with the genetic syndrome Leukocyte Adhesion Deficiency (LAD). LAD is a group of primary immunodeficiency disorders characterised by persistent infections caused by an inability of immune cells to adhere to the endothelium and migrate to infected tissue [14]. LAD can be divided into three different subtypes (LAD-I-III), depending on the causative mutation(s) [15].

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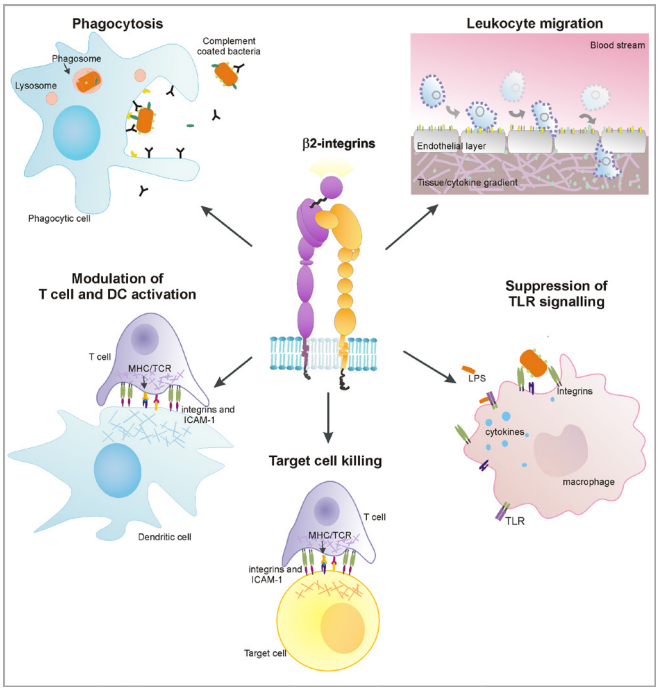

Figure 1: Beta2-integrin functions in the immune system. Beta2-integrins are critical to many functions inthe immune system. Complement receptors 3 and 4 (Mac-1 and CD11c/CD18) mediate phagocytosis of complement opsonized particles, and are important for theclearance of immune complexes and apoptotic cells. Binding of beta2-integrins on T cells to ICAM-1 on dendritic cells strengthens thecell-cell interaction and contributes to T cell activation. Beta2-integrin outside-in signalling in macrophages dampens TLR signalling and inflammatory cytokine production. The binding of leukocyte integrins to ICAM ligands expressed on endothelial cells arrests leukocytes at sites of inflammation and precedes extravasation into surrounding tissue.

LAD-I

LAD-I can be caused by somatic mutations in the promoter region of the beta2-integrin gene resulting in reduced or no expression of beta2-integrin protein. Alternatively, mutations within the coding region of the beta2-integrin gene give rise to a truncated or non-functional beta2-integrin subunit. Over 200 separate mutations have been identified that result in reduced expression of the beta2-integrin protein. The severity of the disorder varies depending on the level of remaining beta2-integrins on the cell surface [16].

Since beta2-integrins are crucial for leukocyte function, particularly for leukocyte migration into sites of infection, LAD-I patients suffer from recurrent bacterial infections, fungal infections, delayed wound healing, leucocytosis and periodontitis. Because neutrophils don't express high levels of other integrin subfamilies that could compensate for the lack of expression of beta2-integrin, their migration into sites of infection and functions are particularly affected by this disorder.

Beta2-integrin knockout mice display splenomegaly, increased circulating neutrophil numbers and are susceptible to infections. The phenotype of these mice resembles that of human LAD-I patients, and they have been useful for the elucidation of beta2-integrin function in different immune cells and immune processes *in vivo* [17-20]. The phenotype of leukocytes in LAD-I and beta2-integrin knockout mice reveal the crucial importance of beta2-integrins (probably LFA-1 in particular) in mediating firm adhesion of neutrophils to endothelial cells under shear flow conditions, and therefore in immune defence against bacteria and fungi in particular [21].

LAD-II

LAD-II is much rarer than LAD-I and is caused by defects in fucosylation of oligosaccharides including PSGL-1 and other selectin ligands [22-24]. The binding of P- and E-selectin expressed on endothelial cells to leukocyte PSGL-1, CD44 and ESL-1 signals to activate the beta2-integrins LFA-1 and Mac-1.This promotes tethering/rolling and arrest of leukocytes prior to extravasation at sites of infection [2]. The gene for GDP-fucose specific transporter (SLC35C1) is mutated in LAD-II, affecting either its function and/or its subcellular localisation [23]. SLC35C1 knockout mice presented with a condition similar to that of LAD-II patients, with symptoms including severe growth retardation, elevated postnatal mortality, dilation of lung alveoli and hypocellular lymph nodes [25,26].

LAD-III

More recently, a LAD-I variant syndrome now called LAD-III was identified. In this disorder, the patients display similar symptoms to patients with LAD-I, but also present with a Glanzmann-type bleeding disorder and in some cases also with osteopetrosis [27-30]. The causative mutations were found to occur in the FERMT3 gene that encodes kindlin-3, introducing premature stop codons resulting in a non-functioning protein [31-36]. Kindlin-3 is one of three orthologs found in humans and has been shown to bind to and regulate beta1-, beta2- and beta3-integrin functions [37]. The generation of kindlin-3 knockout mice were of pivotal importance in the elucidation of the molecular defect in LAD-III, and have also aided the understanding of how kindlin-3 regulates integrins in different cell types [37]. However, much remains to be discovered about the roles of this fundamental integrin regulator in different immune cell types and in immune functions *in vivo*, as kindlin-3 knockout mice also suffer from the bleeding disorder found in human LAD-III and as a result die soon after birth.

Because several classes of integrins are affected by kindlin-3 deficiency, the symptoms of LAD-III are more complex than those of LAD-I. As kindlin-3 regulates beta3-integrin-mediated adhesion in platelets, LAD-III patients suffer from a bleeding disorder [31,32]. The osteopetrosis is related to deficient osteoclast-mediated bone resorption, which is regulated by several integrin subclasses and their signalling in these cells [34]. Also, deficiencies in T cell adhesion and activation, NK cell activation and erythrocyte shape have been described in LAD-III patients [38,39].

Kindlin-3 shares some properties with the well-characterized integrin activator talin. Like talin, kindlin-3 contains a FERM motif (FERM stands for 4.1, ezrin, radixin, moesin), and appears to be critical for integrin adhesion, through its binding to the integrin beta-chain cytoplasmic tail. However, kindling binds to a site distinct from that of talin. The talin binding site lies at a membrane proximal NXXY motif whereas kindlin-3 binds at the membrane-distal NXXY/F motif in the integrin beta-chain cytoplasmic domain [40,41]. At present, it is unclear whether the binding of either protein excludes or indeed promotes that of the other [2,42]. Certainly both are required for beta2-integrin-mediated adhesion and arrest of leukocytes on endothelium under conditions of shear flow [43]. Kindlin-3 is also important for outside-in signalling through integrins, perhaps by stabilising the adhesive contacts required, for example, under shear flow conditions [44]. There is little doubt that there will be much research activity in

this field in the coming years, leading to an increased understanding of the role and regulation of leukocyte beta2-integrins *in vitro*, *in vivo* and in genetic disorders.

SLE and Mac-1

Interestingly, beta2-integrins have also been linked to a disorder at the other end of the immunological disease spectrum. Systemic Lupus Erythematosus (SLE) is a type III hypersensitivity (immune complex-mediated) disorder prevalent in women of child bearing age [45]. It is a clinically heterogeneous disease, affecting many organs in the body such as the skin, heart, lungs, liver, kidneys, joints and central nervous system [46]. This disorder has a strong genetic component, and it is more common and more severe in non-European populations. Reduced "waste disposal" has been proposed as a disease mechanism in lupus. Inefficient phagocytosis by macrophages/neutrophils may lead to an accumulation of apoptotic cells and fragments ("cellular waste"), which may be taken up by immune cells, such as dendritic cells, and lead them to present nuclear antigens to T cells. This may in turn contribute to B cell activation and production of autoantibodies against nuclear antigens, which lies at the heart of the formation and accumulation of immune complexes in this disease [47].

Recently, several genome wide association studies have found an association between SLE susceptibility and the ITGAM-ITGAX gene region (encoding for CD11b and CD11c integrin chains, respectively) [48,49]. Further, the single nucleotide polymorphism (SNP) rs1143679 has been robustly associated with SLE development in several studies [50]. It has also been found to influence the risk of renal disease, discoid rash and immunological manifestations in SLE patients [51,52]. The rs1143679 SNP occurs within the CD11b coding region and encodes a histidine instead of an arginine at position 77 of the CD11b polypeptide. Amino acid77 lies in the beta-propeller domain proximal to the ligand binding domain in the extracellular region of Mac-1.

The substitution of R77 withH77 was not predicted to affect ligand binding and indeed, studies have shown that the affinity for ligand of H77-Mac-1 appears to be unchanged [53,54]. Also, surface expression of the variant form is normal. However, it was demonstrated that H77-Mac-1 integrin-mediated functions are altered as compared to the normal (non-disease associated) R77-Mac-1. In particular, H77-Mac-1 displays reduced ability to mediate phagocytosis of iC3b-coated particles [53,54]. More recently, a study comparing Mac-1-mediated phagocytosis in cells from healthy donors expressing either R/H, H/H and R/R variants of Mac-1observed reduced phagocytosis in cells isolated from the R/H and H/H subjects, although the effect was fairly small [55]. Experiments from our laboratory appear to corroborate this observation. We report here that R/H heterozygous macrophages display slightly reduced Mac-1 mediated phagocytosis (Figure 2), though the difference was not statistically significant. Although the effect is modest, the deficiency in phagocytosis may contribute to SLE development through prolonged inflammation, or may relate to inefficient clearance of apoptotic cells and/or immune complexes, thereby fuelling the disease.

The ability of the H77-Mac-1 integrin to dampen inflammatory cytokine production has also been examined. TLR7/8- or Mac-1-stimulated cytokine production in freshly isolated polymorphonuclear leukocytes was unchanged between the genotypes [55]. However, iC3b-binding to R77-Mac-1 prior to stimulation of TLR7/8 led to a reduction in production of inflammatory cytokines IL-1beta, IL-6 and TNF-alpha in monocytes. This effect was reduced in the H77 homozygous monocytes [54]. In other words, the H77-variant of Mac-1 is not as capable as the R77-variant in suppressing cytokine production in monocytes.

The effect of the H77 mutation on integrin-mediated adhesion and function is not confined to iC3b binding and phagocytosis. Adhesion of H77-Mac-1 transfected cells to ICAM-1 was also severely reduced, especially under conditions of shear flow (mimicking the conditions in blood vessels) [53]. Additionally, H77-Mac-1 homozygous monocyte adhesion to ICAM-1was also slightly reduced, although the presence of LFA-1 in these cells may have masked somewhat the effect of the H77-Mac-1 in these assays [54]. In contrast, R/H heterozygous macrophage adhesion to ICAM-1 is relatively normal (Figure 2), although the effect of this variant on human primary monocyte/neutrophil adhesion to ICAM-1 under shear flow conditions has not been examined.

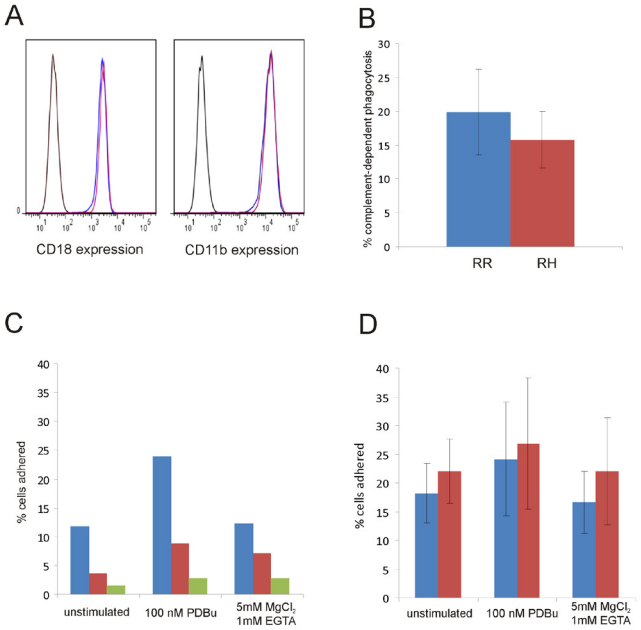

Figure 2: Phagocytosis and adhesion of monocyte derived macrophages from individuals homozygous (77R/R) or heterozygous (77R/H) for the Mac-1 alleles. Monocytes from buffy coats (obtained from the Scottish National Blood Transfusion Service, Ninewells Hospital) were isolated and cultured in Macrophage specific serum free media (Life technologies) with 10ng/ml GM-CSF (Peprotech) for 6 days prior to experiments, resulting in differentiation of monocytes to macrophages, as analysed by flow cytometry for macrophage markers ($CD14^{high}$, $CD11b^{high}$)(not shown). A-Cell surface expression of CD11b and CD18 was examined by flow cytometry using CD11b and CD18 specific antibodies (Biolegend) and was similar in 77R/H heterozygous cells (red) and 77RR cells (blue). Isotype control is shown in black. B-Phagocytosis of iC3b-coated fluorescent beads.Monocyte-derived macrophages from individuals homozygous (77R/R, n=17) or heterozygous (77R/H, n=5) were challenged with fluorescent beads coated with iC3b or with IgM alone [56] for 20 min prior to washing and analysis by flow cytometry. The percentage of cells with increased fluorescence due to bead phagocytosis was measured, and that solely due to Complement -mediated phagocytosis was calculated by subtracting the percentage phagocytosis of IgM coated beads from that of iC3b coated beads. C-Monocyte –derived macrophages were analysed in static adhesion assays [57] on plates coated with 6 µg/ml human ICAM-1 (R and D systems)as described previously [57]. Prior to adhesion cells were incubated with control IgG (blue), anti-CD11b (red) or anti-CD18 (green) to estimate the separate contributions of beta2-family integrins to cell-adhesion, and then stimulated with PdBuor magnesium to activate integrins. D-Adhesion of 77R/H heterozygous macrophages (red) and 77R/R macrophages (blue) to ICAM-1was examined as above using monocyte-derived macrophages from individuals homozygous (77R/R, n=18) or heterozygous (77R/H, n=6) for the Mac-1 allele. No significant differences in adhesion were observed.

Notably, any effects of the H77 variation on functions mediated through Mac-1 binding to ICAM-1 have yet to be examined in *ex vivo* human leukocytes. Mac-1 has been shown to inhibit several immunological processes through its binding to ICAM-1 or through its effect on signalling, as described earlier, and several of these processes may impact on SLE development.The prominent hypothesis is that signal transduction through the integrin is compromised in the H77-Mac-1 variant. However, the exact molecular mechanism involved and the signalling pathways affected by this mutation have not been elucidated, and studies in this area are eagerly awaited.This hypothesis would predict that all possible functions of Mac-1 would be potentially compromised. Therefore, although the main contributory effect of the H77 variant on SLE may be through reduced Mac-1-mediated phagocytic uptake (influencing clearance of immune complexes and apoptotic cells), it remains to be seen if other, ICAM-1-dependent processes also contribute to the pathology.

Conclusions and Future Prospects

A study of the molecular and immunological mechanisms in genetic disorders where beta2-integrin expression or function is affected has shed light on the roles of these complicated receptors in the immune system. Beta2-integrins are crucial for the recruitment of leukocytes into sites of infection or inflammation. Because of this, they are of fundamental importance for the generation of, in particular, the early innate immune response to bacteria and fungi, as demonstrated in human LAD-I and LAD-III syndromes. However, beta2-integrins, especially Mac-1, are also important phagocytic receptors, and a deficiency in Mac-1-mediated phagocytosis may explain why a genetic variant of Mac-1 is associated with SLE. Mac-1 also restricts myeloid cell signalling and cytokine production, thereby restricting inflammatory responses *in vivo*. These processes may also be affected by the non-functional variant of Mac-1, and therefore be important for SLE development. Dysfunctional or absent beta2-integrins therefore contribute to immune disease at both ends of the disease spectrum, in immunodeficiency and hypersensitivity. Further elucidation of the molecular mechanisms involved in regulation of these receptors is pivotal for our understanding of the immune system as a whole, and may aid in the development of novel therapeutics to immunological diseases.

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