Integrin beta-2

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Integrins are heterodimeric transmembrane (TM) glycoproteins containing one each of α and β subunit, which are held together by non-covalent forces. Integrin β2 (CD18) is the β subunit for four heterodimers: αDβ2, αXβ2, αMβ2 and αLβ2. Integrin β2 family plays an essential role in leukocyte recruitment and activation during inflammation. Structurally, while most part of the αβ dimer is extracellular, both the subunits traverse the plasma membrane and terminate as short cytoplasmic domains. Each heterodimeric integrin exists on the cell surface mainly in an inactive (bent) form until they receive stimulating signals from other receptors (via inside-out signaling), and the end result of integrin activation is a shift in integrin conformation from a bent to an extended one. The binding of cytoplasmic proteins to α- and/or β-subunit carboxy-terminal tails is an essential part of the activation process, as these interactions stabilize the extended integrin conformation and provide connections to the cytoskeleton. The binding of extracellular ligand to the extended form of integrin (via outside-in signaling) triggers a large variety of signal transduction events that modulate cell behaviors such as adhesion, proliferation, survival or apoptosis, shape, polarity, motility, and differentiation, mostly through effects on the cytoskeleton. The receptors αMβ2 (Complement Receptor type 3, CR3) and αXβ2 (Complement Receptor type 4, CR4) are regarded to be the most important mediators for complement-driven phagocytosis.

KEYWORDS
CD18; Cell surface adhesion glycoprotein LFA-1/CR3/P150,959 beta subunit precursor; Cell surface adhesion glycoproteins LFA-1/CR3/p150,95 subunit beta; Complement receptor C3 beta-subunit; Complement receptor C3 subunit beta; Integrin beta chain, beta 2; Integrin beta-2; Integrin, beta 2 (complement component 3 receptor 3 and 4 subunit); ITGB2; LAD; LCAMB; Leukocyte cell adhesion molecule CD18; Leukocyte-associated antigens CD18/11A, CD18/11B, CD18/11C; LFA-1; MAC-1; MF17; MF17

IDENTIFIERS
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PROTEIN FUNCTION
Inflammation which occurs due to infection or tissue injury, controls a cascade of cellular and microvascular reactions that allow the removal of pathogens or cell debris, and finally give rise to wound healing, repair and homeostasis. The process of the inflammation includes recruitment (migration) of free-flowing immune cells such as polymorphonuclear neutrophils (PMN) and monocytes/macrophages to the site of infection (Simon and Green 2005; Nourshargh et al. 2005). The essential steps during leukocyte recruitment includes tethering and rolling, activation, firm adhesion, intraluminal crawling, and extravasation. Firm adhesion and crawling are largely mediated by β2-integrins (Kolaczkowska and Kubes 2013, Hajishengallis and Chavakis 2013). Signaling via adhesion molecules of the β2 integrin family plays an essential role for immune cell recruitment and activation during inflammation. An important function of these recruited leukocytes is the phagocytosis of complement opsonized particles mediated by integrin αMβ2 (Anderson and Springer 1987). Therefore, integrin β2-mediated leukocyte migration contributes crucially to the performance of the immune defense system.

Integrin structure: Integrins are noncovalently associated αβ heterodimeric cell surface glycoproteins. The known 18 α and 8 β subunits in humans generate 24 different heterodimeric receptors, each of which exhibits distinct ligand-binding specificities and tissue distribution (Takada et al. 2007; Hynes 2002). Both the α and β subunits are type I membrane proteins (single-pass transmembrane (TM) proteins, which have their N-terminus exposed to the extracellular or luminal space), with a large extracellular ligand-binding region (a.k.a ectodomain) and generally a short cytoplasmic tail that binds multiple cytoskeletal and adaptor/signaling proteins that regulate the affinity of integrin for extracellular ligands (Hynes 2002; Suzuki and Naitoh 1990; Anthis and Campbell 2011). The cytoplasmic region of the α subunit is composed of a β-propeller fold with seven blades (W1-W7), a Thigh domain, and two Calf domains (Calf-I and Calf-II) (Xiong et al. 2001; Zhu et al. 2009; Xie et al. 2010). Further, an I-(inserted or αA) domain (in β-propeller) is present in nine of the α subunits (Lee et al. 1995). The cytoplasmic region of the β subunit is composed of a plexin-semaphorin-integrin (PSI) domain, an I-like (or βA) domain, a hybrid domain, four integrin-epidermal growth factor (I-EGF1 to I-EGF4) folds and a β tail domain (βTD) (Xiong et al. 2001; Zhu et al. 2009; Xie et al. 2010; Tan et al. 2001; Shi et al. 2007; Shi et al. 2005; Zhu et al. 2008). The I-like domain is inserted into hybrid domain, which in turn is inserted into PSI domain. The two α-helical TM domains of a resting integrin adopt a ridge-in-groove packing (Zhu et al. 2009; Lau et al. 2009) and the association of the TM domains is specific (Vararrattanavech et al. 2008). The cytoplasmic tails of the β subunits (other than β4 and β8) contain one or two highly conserved NxxY/F motifs (x represents other amino acids) that can recognize a wide variety of signaling and cytoskeletal proteins (e.g. adaptor molecules such as ILK, DAB1, Dok-1 and FHL2) that connects integrins to the actin cytoskeleton or activate a range of signaling pathways. In contrast, apart from having a highly conserved juxtamembrane GFFKR motif, α cytoplasmic tails are divergent in their lengths and sequences.
Integrin β2 family genes and selectivity: The human CD18 gene, a.k.a ITGB2, is located on chromosome 21q22.3 and encodes a 95-kDa glycoprotein, Integrin β2 (Kishimoto et al. 1987). The human CD11 genes such as ITGAL, ITGAM, ITGAX and ITGAD are located on chromosome 16p11.2 and encode glycoproteins αL (CD11a, 180kDa), αM (CD11b, 160kDa), αX (CD11c, 150kDa) and αD (CD11d, 145 kDa), respectively (Tan 2012; Fu et al. 2012; Luo et al. 2007). Integrin β2, exclusively expressed on leukocytes, forms heterodimers with the above four α subunits and these heterodimers are signal transducer receptors involved in phagocytosis, degranulation and cell adhesions. Even though β2 integrin is common to all these heterodimers, differences in divergent α tails confer structural variations between these integrins. For example, αLβ2 and αMβ2 integrins show distinct chemokine-induced activation kinetics (Weber et al. 1999), sites for the docking of specific cytosolic molecules such as selective recruitment of the Src kinase Hck to αMβ2 but not αLβ2 (Tang et al. 2006), and specific association of CD45 cytoplasmic domain with αL (Geng et al. 2005). See ‘Interactions with Ligands and Other Proteins’ section for further details.

Leukocyte migration/adhesion: The movement of leukocytes from the bloodstream to the tissue occurs in several distinct steps as explained above. The β2 integrin family of adhesion molecules plays a central role in firm adhesion and subsequent crawling on the endothelium, during which leukocytes seek an appropriate site for diapedesis through endothelial junctions (Grönholm et al. 2011; Gahmberg et al. 1999). See ‘Interactions with Ligands and Other Proteins’ section for further details.

Phagocytosis: Phagocytosis is a physiological process by which specialized cells (e.g. macrophages) recognize, bind and internalize materials such as cell debris, microbes, necrotic/apoptotic cells through the use of phagocytic receptors such as Fcγ receptors (utilizes membrane pseudopods), scavenger receptors (mediates binding to modified lipoprotein particles) or integrins (utilizes membrane ruffle mechanism). Integrin activation through bidirectional (inside-out and outside-in) signaling leads to the interaction between particle and integrin which results in an actin-driven uptake of the particle. Activated integrins link actin dynamics to extracellular components that involves cytoskeletal remodeling and cell-shape changes during phagocytosis. However, integrin signaling is also exploited by a variety of pathogen for entry into host cells (Dupuy and Caron 2008). See ‘Interactions with Ligands and Other Proteins’ section for further details.

REGULATION OF ACTIVITY
Integrins lack enzymatic (intrinsic) activity and the interactions between the membrane proximal regions of α and β are crucial for maintaining integrins in resting state (Chua et al. 2011). Integrins use classical bidirectional (a.k.a inside-out and outside-in) signaling and non-classical signaling processes (integrin clustering and membrane ruffling) to integrate the intracellular and extracellular environments (Lim and Hotchin 2012). Inside-out signaling refers to intracellular signaling events that result in a higher-affinity state of the ectodomain of integrin for its cognate ligands. Regulatory events that mediate inside-out signaling converge on the cytoplastic tails of the α and β chains, which transduce signals to their ectodomains (Dustin et al. 2004).

Intracellular signaling pathways, which regulate the interactions of integrins with their ligands, affect a wide variety of biological functions. Integrin activation is usually initiated by integrin β subunit cytoplasmic tail (Calderwood et al. 1999) through the recruitment of cytosolic proteins and many of these interactions are modulated by tail phosphorylation (Gahmberg et al. 2009; Fagerholm et al. 2004; Liu et al. 2000). Signaling molecules implicated in inside-out signaling through αLβ2 include talin, Vav1, PKD1, several adaptor proteins (SLP-76, ADAP, and SKAP-55), the Ras family GTPase Rap1, and two of its effectors, RAPL and RIAM (Ménasché et al. 2007). Apart from talin, kindlin-3 was shown to bind to, and activate Integrin β2 and that a direct interaction of kindlin with the β subunit cytoplasmic tail is required, but not sufficient, for integrin activation (Moser et al. 2009). Integrin-linked kinase (ILK) interacts with the cytoplasmic domains of integrin β2 (also β1 and β3) (Hannigan et al. 1997; Hannigan et al. 1996; Delcommenne et al. 1998) which acts as a proximal receptor kinase that regulates integrin-mediated signal transduction. Spleen tyrosine kinase (Syk) is constitutively associated with the cytoplasmic tail of β2 integrin (Willeke et al. 2003; Woodside et al. 2002). Syk is known to be phosphorylated and activated upon β2 integrin mediated adhesion (Mósai et al. 2002; Willeke et al. 2003). Syk and Zap-70 (Zeta-chain-associated protein kinase) are non-receptor cytoplasmic tyrosine kinases with two Src homology (SH)2-domains, a kinase domain and two interdomains (A and B). Syk and Zap-70 transmit signals from the immune receptors (B-Cell receptor and T-Cell receptor), CD74, Fc Receptor and integrins (Mósai et al. 2002; Turner et al. 2000). The inside-out activation leads to an increase in the binding affinity of integrin ectodomains for their extracellular ligands (known as ‘outside-in’ activation) (Calderwood et al. 1999; Tadokoro et al. 2003; Li et al. 2007; Wegener et al. 2007; Lim et al. 2007; Garcia-Alvarez et al. 2003; Calderwood 2004). Outside-in signaling is analogous to signaling by conventional receptors and is defined as stimulation of intracellular signaling pathways as a consequence of ligation of αLβ2 with any of its extracellular ligands, such as intracellular adhesion molecule 1 (ICAM-1). Guanine nucleotide exchange factors Cytohesin-1 and Cytohesin-3, activated by PI(3,4,5)P3, bind β2 integrin which leads to an increase cell adhesion through an affinity-independent processes, such as integrin clustering, rather than integrin activation (Calderwood 2004). Cytohesin-1 interacts with the cytoplasmic domains of the integrin β-chain common to all β2 integrins such as αLβ2 and αMβ2 and regulates cell adhesion (Geiger et al. 2000; Hyduk and Cybulsky 2011; El Azreq et al. 2011).

αMβ2 also mediates events (classified as non-classical) such as integrin clustering and membrane ruffling in a ligand independent fashion in macrophages following treatment with phorbol 12-myristate 13-acetate (PMA) or lipopolysaccharide (LPS) (Patel and Harrison 2008; Williams and Ridley 2000). The bacterial endotoxin LPS is a potent stimulator of monocyte/macroage activation and induces adhesion of monocytes while PMA is used in monocyte differentiation. The integrin clustering (in phagocytic function) occurs through the cytoplasmic tails which is different from the extracellular clustering (promotes differentiation to macrophage) of monocyte integrins. The association of Rack1 to integrin β2 (coimmunoprecipitated with αLβ2) in vivo (Liliental and Chang 1998) requires a treatment with PMA which promotes cell spreading and adhesion. These findings suggest that Rack1 may link protein kinase C directly to integrin β2 and participate in the regulation of integrin functions (Liliental and Chang 1998).
Bacteria derived fMLP (N-formyl-Met-Leu-Phe, also known as fMLF) induces chemotactic migration and it activates αMβ2 or αLβ2 in human neutrophils through vasodilator stimulated protein (VASP) (Deevi et al. 2010) and cytohesin-1 (El Azreq et al. 2011). Both VASP and cytohesin-1 function as ‘negative regulators’ of inside-out function of αMβ2 (El Azreq et al. 2011). fMLP, activates Rap1 and inside-out signaling of β2 integrins (Deevi et al. 2010), triggers phosphorylation of VASP on S239 and, thereby, controls membrane recruitment of C3G (a guanine nucleotide exchange factor for Rap1), which is required for activation of Rap1 and antibacterial (β2 integrin-dependent) functions of neutrophils.

**INTERACTIONS**

Integrins are heterodimeric (αβ) type I membrane receptors which have their N-terminus exposed to the extracellular space with a large extracellular ligand-binding region and a short cytoplasmic tail that binds multiple cytoskeletal adaptor or signaling proteins that regulate the affinity of integrin for extracellular ligands. The adhesion of integrins to the extracellular matrix is regulated by binding of the cytoskeletal protein talin to the cytoplasmic tail of the β-integrin subunit. Activation is initiated by tail separation and propagation of conformational changes to the outside of the cell. Rap1, a small GTPase, controls activation of integrin (αMβ2) in a talin-dependent manner (Lim et al. 2010). Ligand interaction with activated β2 integrins takes place via an inserted I-domain in the α subunit (Shimaoka et al. 2003; Shimaoka et al. 2005). Integrin αL domains interact with β2 in the following orders of affinity: ICAM-1 > ICAM-2 > ICAM-3 (Guernonprez et al. 2001). Leukocyte integrins αLβ2, αMβ2 and αXβ2 act as collagen receptors and the α domains favor different collagen subtypes and also differ in their requirements for activation (Lahti et al. 2013).

αLβ2 (CD11a/CD18; Leucocyte Function-associated Antigen-1, LFA-1): αLβ2, a leukocyte-restricted integrin, is essential for the adhesion, migration, proliferation of leukocytes, immune synapse formation, and NK cell cytotoxicity (Kinishi 2007; Smith et al. 2007; Bryceson et al. 2006; Bhunia et al. 2009). Ectopic expression of talin head domain induces αLβ2 activation possibly via association of talin head domain with the membrane proximal NPXF motif in the β2 tail (Li et al. 2003; Kim et al. 2003). Another actin-binding protein – actinin binds to the membrane proximal sequence of the β2 tail (Tohyama et al. 1993; Stanley et al. 2008). Interestingly, the binding of filamin to triplet Thr motif of the β2 tail has an inhibitory effect on αLβ2-mediated T cell adhesion (Takala et al. 2008) (Bhunia et al. 2009). RAPL (regulator of adhesion and cell polarization enriched in lymphoid tissues) associates with Rap1-GTP, and the activating effect of this complex on αLβ2 requires the membrane proximal Lys1097 and Lys1099 in the αL tail (Tohyama et al. 2003). Collectively, a multifaceted (positive and negative) regulatory network of molecules at the cytoplasmic face of the αLβ2 allows fine-tuning of αLβ2 activity in cells under different contexts such as physiological conditions, and in different regions of a polarized and migrating cell (Chua et al. 2013). Studies in mice have led to identification of developmental endothelial locus-1 (Del-1) as an endogenous antagonist of LFA-1 (Choi et al. 2008) and it inhibits transmigration to inflamed tissues (Eskan et al. 2012).

Integrin αLβ2 interacts with ICAM1-4. ICAM-1 is an inducible molecule that is up-regulated by inflammatory cytokines on endothelium, leukocytes, and multiple other cell types, whereas ICAM-3 is constitutively expressed on leukocytes and absent from endothelium and most other cell types under normal conditions (Springer 1990; Fawcett et al. 1992). ICAM-1/αLβ2 interaction is essential for T-cell activation as well as for migration of T-cells to target tissues (Anderson and Siahahan 2003). CD47, also called Integrin Associated Protein (IAP), has been demonstrated to associate with β2 integrins. The interaction between Jurkat T-cell β2 integrins and CD47 were detected by fluorescence lifetime imaging microscopy (Azcutia et al. 2013) and that CD47 is necessary for induction of αLβ2 high affinity conformations that bind to their ligand ICAM-1. ICAM-1, as a member of super-IgG family, consists of five IgG-like domains (D1–D5) and binds to αMβ2 via D3 domain (Diamond et al. 1991) and αLβ2 via D1 domain (Staunton et al. 1991), respectively. Cytohesin-1 interacts with the intracellular portion of the integrin β2 chain (Kolanus et al. 1996). Co-localization of CD82 antigen or Cytohesin-1 with αLβ2 at an adhesion foci results in enhanced interaction between αLβ2 and ICAM-1 during T cell-T cell and T cell-APC interactions (Shibagaki et al. 1999; Kolanus et al. 1996). Except αLβ2, all other β2 Integrins binds to Fibrin.

αMβ2 (CD11b/CD18; Complement Receptor type 3, CR3; Macrophage-1 antigen, Mac-1; the iC3b receptor): αMβ2, a leukocyte restricted integrin, mediates leukocyte migration, adhesion, phagocytosis, degradation and the maintenance of immune tolerance. The receptor αMβ2 is regarded to be the most important mediator for complement-driven phagocytosis. Signaling via αMβ2 predominantly occur, in polymorphonuclear neutrophils (PMN), upon ligand binding and may have a unique role in neutrophil migration (Walzog et al. 1996; Yan et al. 1997; Ross and Lambri 1982). Integrin αMβ2 binds ligands such as intercellular adhesion molecule -1 (ICAM-1) on inflamed endothelial cells, the complement C3 (fragments such as iC3b), fibrinogen and fibrin, collagens and coagulation factor X (Plow et al. 2000; Walzog et al. 1995). Being expressed on phagocytes, it interacts with iC3b opsonized pathogen (Bajic et al. 2013). Complement C3 deposition on the bacterial surface and αMβ2 on the macrophage surface play important roles in the uptake of the highly virulent Franciscella tularensis subsp. Tularensis, an infectious facultative intracellular pathogen (Schulert and Allen 2006; Clemens et al. 2005; Clay et al. 2008). Complement receptors, particularly αMβ2, have long been postulated to allow for safe passage for intracellular pathogens (Wright and Silverstein 1983). There is an increasing evidence for signaling crosstalk between complement receptors and TLRs (Hajishengallis and Lambris 2010; Hajishengallis and Lambris 2011; Ivashkiv 2009). For example, TLR2 is able to trans-activate αMβ2 through inside-out signaling including the activation of Rac1, PI3K and cytohesin-1 (Harokopakis et al. 2005; Sendide et al. 2005). Integrin β2 signaling can also negatively regulate TLR responses (Ivashkiv 2009; Wang et al. 2010). Specifically, αMβ2 can inhibit TLR4 signaling by promoting the degradation of MyD88 and TRIF (Han et al. 2010).

Integrin αMβ2’s function is dependent on the activation of outside-in and inside-out two way signals (Abram and Lowell 2009). Signaling via αMβ2 plays an important role in regulating production of interleukin-12 (IL-12), a key mediator of cell-mediated immunity (Marth and Kelsall 1997). In addition, engagement of αMβ2 has been shown to down-regulate IL-12 production (Marth and Kelsall 1997) and avoid initiation of the oxidative burst in macrophages following phagocytosis of apoptotic cells (Kim et al. 2005). Known key players during...
inside-out activation of αMβ2 include Rap1, talin1 and CamKII. CamKII phosphorylation of S756, allows Rap1 and talin to be recruited to β2 and consequently activate αMβ2 (Lim et al. 2011). Ceramide, a constituent of atherogenic lipoproteins, binds with CD14 (membrane anchored) and induces clustering of CD14 with co-receptors in lipid rafts (Ceramide recruits αMβ2 and CD36 to the proximity of CD14). CD14 lacks a transmembrane signaling domain and signals through TLR4 or TLR2 and plays a major role in the inflammatory response of monocytes to LPS (Pfeiffer et al. 2001).

Integrin αMβ2 is a known ligand of RAGE (Advanced glycosylation end-product-specific receptor) protein. RAGE and αMβ2 have been shown by Ma et al. 2012 to interact with C1q, both individually (αMβ2/RAGE and RAGE/C1q complexes) and together as a complex (αMβ2/RAGE/C1q complex) (Ma et al. 2012). The outcome of C1q interaction with these proteins, is enhanced phagocytosis. The tri-complex of αMβ2/RAGE/C1q shows more efficient phagocytosis than C1q/RAGE or RAGE/αMβ2. RIAM (Rap1-interacting adaptor molecule), in contrast to the previous study (Lim et al. 2010), regulates the recruitment of talin (via Rap1) to αMβ2 in complement-mediated phagocytosis in human myeloid cell lines (HL-60 and THP-1) and macrophages derived from primary monocytes (Lee et al. 2009; Medrano-Fernandez et al. 2013).

Integrin αMβ2 interacts with fimbriae of Porphyromonas gingivalis (P. gingivalis) (Hajishengallis et al. 2007). P. gingivalis (Harokopakis et al. 2005) and Mycobacterium bovis BCG (Sendide et al. 2005) can activate αMβ2 through inside-out signaling via TLR2 to facilitate bacterial uptake. CyaA (Bordetella pertussis) uses the αMβ2 as a cell receptor and CyaA intoxication leads to increased intracellular cAMP level and cell death (Guerronprez et al. 2001). RrgA on pneumococcal pili 1 promotes nonopsonic αMβ2-dependent uptake of S. pneumoniae by murine and human macrophages. RrgA-αMβ2-mediated phagocytosis promotes systemic pneumococcal spread from local sites (Orskog et al. 2012). Complement iC3b covalently bound to the gonococcus serves as a primary ligand for αMβ2 adherence. However, gonococcal porin and pilil also bound to the I-domain of αMβ2 in non-opsonic manner. αMβ2-mediated endocytosis serves as a primary mechanism by which N. gonorrhoeae elicits membrane ruffling and cellular invasion of primary, human, cervical epithelial cells and this data suggest that gonococcal adherence to αMβ2 occurs in a co-operative manner, which requires gonococcal iC3b-opsionization, porin and pilil (Edwards et al. 2002; Jones et al. 2008). CD14 cooperates with αMβ2 to mediate phagocytosis of Borrelia burgdorferi. Complement enhances phagocytosis of B. burgdorferi in a C3-dependent manner (Hawley et al. 2013). αM interacts with leukocidin A/B (LukAB), which is produced by S. aureus upon encountering neutrophils and is both necessary and sufficient for S. aureus to kill human neutrophils, macrophages and dendritic cells (DuMont et al. 2011, DuMont et al. 2013a). The α subunit of the αMβ2 integrin acts as a cellular receptor for LukAB (DuMont et al. 2013b).

αXβ2 (CD11c/CD18; p150,95; Complement Receptor type 4, CR4): Integrin αXβ2 is a receptor for iC3b, C3dg, and C3d fragments of complement C3 (Myones et al. 1988, Vik and Fearon 1985; Chen et al. 2012; Micklem and Sim 1985) and was shown to bind with apparently equal affinity (Vik and Fearon 1985). Integrin αXβ2 also shares some functional properties with αMβ2 as an adhesion surface molecule. Both αMβ2 (Wright and Jong 1986) and αXβ2 bind bacterial LPS and β-glucans and promote phagocytosis of unopsonized bacteria and yeast. A large number of intracellular proteins have been found to interact with the cytosolic tails (CTs) of this integrin linking αXβ2 to the cytoskeleton (Chua et al. 2012).

αβ2 (CD11d/CD18): Integrin αβ2 is a multiligand macrophage receptor with recognition specificity identical to that of the major myeloid cell-specific integrin αMβ2. Integrin αβ2 is capable of supporting cell adhesion to various extra cellular matrix (ECM) proteins, including fibronectin, vitronectin, fibrinogen, CCN1 (Cyr61) and others. αβ2, selectively binds ICAM-3 and VCAM-1 and does not appear to bind ICAM-1 (Van der Vieren et al. 1995; Van der Vieren et al. 1999; Grayson et al. 1998). The αD I-domain is responsible for the binding function and that the mechanism whereby αD I-domain recognizes its ligands is similar to that utilized by αMβ2.

CMAP, a complement database, documents the biochemical methods used to identify these interactions (Yang et al. 2013).

PHENOTYPES
Leukocyte emigration, from the bloodstream to tissue to sites of inflammation, is a dynamic process and involve multiple steps in an adhesion cascade. Various adhesion molecules are expressed on both resting and stimulated endothelial cells and leukocytes (Nagendran et al. 2012; Muller 2003). Leukocyte adhesion and tethering defects involve β2 integrins and selectin ligands (Bunting et al. 2002). Selectins are found on both leukocytes and endothelial cells and primarily mediate cellular margination and rolling. Defects in a number of these adhesion molecules result in recognized clinical syndromes called Leukocyte Adhesion Deficiency (LAD) syndrome in which leukocytes (particularly neutrophils) cannot leave the vasculature to migrate normally into tissues under conditions of inflammation or infection. Affected individuals display blood neutrophilia, suffer from recurrent infections, and invariably develop aggressive periodontitis leading to premature loss of primary and permanent teeth (Bowen et al. 1982; Anderson and Springer 1987; Arnaut 1990; Shaw et al. 2001; Wright et al. 1995; Etzioni 1999).

LAD I, in which the β2-integrin family is deficient or defective.

LAD II, in which the fucosylated carbohydrate ligands for selectins are absent.

LAD III, in which the activation of β integrins (β1, β2, and β3) are defective (Karokos et al. 2010; Plow et al. 2009; Jurk et al. 2010). LAD III is mainly due to mutations in fermitin family member 3 (FERMT3, aka KIND3). All LAD III patients have premature stop codons or nonsense mutations in both alleles of their FERMT3 gene (Malinin et al. 2009; Manevich-Mendelson et al. 2009; Kuipers et al. 2009; Svensson et al. 2009; Kuipers et al. 1997). Kindlin-3 is a cytoplasmic protein that acts cooperatively with talin-1 in activating β1, β2, and β3 integrins. LAD III is characterized by bleeding disorders and defective recruitment of leukocytes into sites of infection.

MAJOR SITES OF EXPRESSION
αLβ2 (CD11a/CD18, LFA-1): Integrin αLβ2 is the only integrin expressed on all leukocyte lineages.

αMβ2 (CD11b/CD18, CR3; Mac-1): Expressed on
polymorphonuclear leukocytes (mainly, neutrophils), mononuclear phagocytes (dendritic cells, monocytes and macrophages), lymphocytes (mainly, natural killer (NK) and γδ T-cells) and microglia.

αXβ2 (CD11c/CD18, CR4): Expressed on mononuclear phagocytes (dendritic cells, monocytes and macrophages), polymorphonuclear leukocytes (mainly, neutrophils), activated B lymphocytes and natural killer (NK) cells.

αDβ2 (CD11d/CD18): Expressed on macrophages and eosinophils.

**SPLICE VARIANTS**

Integrin β2 is a 95-kDa glycoprotein, encoded by the ITGB2 gene and is located on chromosome 21q22.3 (Kishimoto et al. 1987). Human ITGB2 spans approximately 40 kb of DNA and contains 16 exons (Weitzman et al. 1991). Two transcript variants encoding the same protein have been identified.

**REGULATION OF CONCENTRATION**

The expression of the leukocyte integrins is cell-specific and is coordinately regulated during leukocyte differentiation through transcriptional and post-transcriptional mechanisms (Miller et al. 1986; Noti et al. 2001; Noti and Reinemann 1995; Back et al. 1992). The promoters for the CD11a-d (Pahl et al. 1992; Nueda et al. 1993; López-Rodriguez et al. 1995; Cornwell et al. 1993; Noti et al. 1992; López-Cabrera et al. 1993; Agura et al. 1992; Hickstein et al. 1992) and CD18 (Rosmarin et al. 1992; Agura et al. 1992) genes lack classical TATA boxes but instead appear to be controlled by initiator elements positioned within 100 bp of their ATG translational start codons. Cis elements are found within 500 bp upstream of the ATG site, some of which control cell-specific expression.

**ANTIBODIES**

Monoclonal antibodies (mAbs) directed against the CD18 (β2): blocking IB4 (Bednar et al. 1996) and an activating KIM-127. KIM127 is a widely used mAb that recognizes a β2 subunit epitope (on epidermal growth factor (EGF)-like domain 2) that is cryptic on bent αLβ2, but exposed when the integrin extends (Beglova et al. 2002; Kamata et al. 2002; Chen et al. 2010). Efalizumab is a monoclonal antibody, which is specific for αLβ2 to treat psoriasis. Anti-integrin β2 mAb MEM-48 is available from Sigma.
### Table 1: Functional States

| STATE DESCRIPTION | LOCATION | REFERENCES |
|-------------------|----------|------------|
| β2 (CD18)         | plasma membrane | Dyer MD et al. |
| αLβ2/CD47         | integrin complex | Calderwood DA et al. 2003 |
| αLβ2/CD45         | integrin complex | Calderwood DA et al. 2003 |
| αLβ2 (LFA-1, CD11a/18) | integrin complex | Fagerholm S et al. 2002 |
| αXβ2/LPS (E. coli) | integrin complex | Hannigan GE et al. 1997; Delcommenne M et al. 1998 |
| αXβ2/ICAM-1       | integrin complex | Willeke T et al. 2003; Woodside DG et al. 2002; Miura Y et al. 2000 |
| αXβ2/Fibrinogen    | integrin complex | Dyer MD et al. |
| αXβ2/FUT4 (CR4/CD15) | integrin complex | Yakuhenko VP et al. 2006 |
| αXβ2/CD23         | integrin complex | Armaout MA et al. 1988; Sándor N et al. 2013 |
| αXβ2/CD59         | integrin complex | Ross GD et al.; Leconet-Henchoz S et al. 1995 |
| αMβ2/Collagen     | integrin complex | Ross GD et al. |
| αMβ2/Fibrinogen    | alphaM-beta2 integrin complex | Ross GD et al. |
| αMβ2/ELANE        | alphaM-beta2 integrin complex | Ross GD et al. |
| αMβ2/Heparan sulfate | alphaM-beta2 integrin complex | Ross GD et al. |
| αMβ2/RH           | alphaM-beta2 integrin complex | Ross GD et al. |
| αMβ2/FX           | alphaM-beta2 integrin complex | Ross GD et al. |
| αMβ2/B-glucan     | alphaM-beta2 integrin complex | Ross GD et al.; Proynat-Seauve O et al. 2004; Sehgal G et al. 1993; Zhou M et al. 1993 |
| αMβ2/BN-LN-8      | alphaM-beta2 integrin complex | Ross GD et al. |
| αMβ2/GP1bo        | alphaM-beta2 integrin complex | Ross GD et al. |
| αMβ2/uPAR-GPI     | alphaM-beta2 integrin complex | Ross GD et al.; Xue W et al. 1994 |
| αMβ2/uPAR-GPI/UPA | alphaM-beta2 integrin complex | Ross GD et al.; Xue W et al. 1994 |
| αMβ2/FcyRIIa (CR3/CD32) | alphaM-beta2 integrin complex | Ross GD et al.; Preynat-Seauve O et al. 2004; Sehgal G et al. 1993; Zhou M et al. 1993 |
| αMβ2/FcyRIIB (CR3/CD16) | alphaM-beta2 integrin complex | Ross GD et al.; Preynat-Seauve O et al. 2004; Sehgal G et al. 1993; Zhou M et al. 1993 |
| αMβ2/HP           | alphaM-beta2 integrin complex | El-Ghmati SM et al. 2002 |
| αMβ2/PR-3         | alphaM-beta2 integrin complex | Gordon DL et al. 1987 |
| αMβ2/C3b          | alphaM-beta2 integrin complex | Diamond MS et al. 1993; Ross GD et al. |
| αMβ2/ICAM [1,2,4] | alphaM-beta2 integrin complex | Ross GD et al.; Preynat-Seauve O et al. 2004; Sehgal G et al. 1993; Zhou M et al. 1993 |
| αMβ2/Talin-1      | alphaM-beta2 integrin complex | Ross GD et al.; Preynat-Seauve O et al. 2004; Sehgal G et al. 1993; Zhou M et al. 1993 |
| αMβ2/Kindlin-3    | alphaM-beta2 integrin complex | Ross GD et al.; Preynat-Seauve O et al. 2004; Sehgal G et al. 1993; Zhou M et al. 1993 |
| αMβ2/FUT4 (CR3/CD15) | alphaM-beta2 integrin complex | Ross GD et al.; Preynat-Seauve O et al. 2004; Sehgal G et al. 1993; Zhou M et al. 1993 |
| αMβ2/RAGE         | alphaM-beta2 integrin complex | Ma W et al. |
| αMβ2/RAGE/C1q     | alphaM-beta2 integrin complex | Ma W et al. |
| αMβ2/CYR61 (CCN1) | alphaM-beta2 integrin complex | Schober JM et al. 2002; Schober JM et al. 2003 |
| αMβ2/CCN2         | alphaM-beta2 integrin complex | Schober JM et al. 2002; Schober JM et al. 2003 |
| αMβ2/MPO          | alphaM-beta2 integrin complex | El Kebir D et al. 2008; Johansson MW et al. 1997; Lau D et al. 2005 |
| αMβ2/PLG          | alphaM-beta2 integrin complex | Lishko VK et al. 2004 |
| αMβ2/CyaA (B.pertussis) | alphaM-beta2 integrin complex | Gueronprez P et al. 2001 |
| αMβ2/App1 (C. neoformans) | alphaM-beta2 integrin complex | Stano P et al. 2009 |
| αMβ2/Rga (S. pneumoniae) | alphaM-beta2 integrin complex | Orskog S et al. |
| αMβ2/LPS (E.coli) | alphaM-beta2 integrin complex | Ross GD et al.; Preynat-Seauve O et al. 2004; Sehgal G et al. 1993; Zhou M et al. 1993 |
| αXβ2 (CR4, CD11c/18) | alphaX-beta2 integrin complex | Shelley CS et al. 2002; Leconet-Henchoz S et al. 1995 |
| αXβ2/CD23         | alphaX-beta2 integrin complex | Leconet-Henchoz S et al. 1995 |
| αXβ2/FUT4 (CR4/CD15) | alphaX-beta2 integrin complex | Skubitz KM and Snook RW 1997 |
| αXβ2/Fibrinogen    | alphaX-beta2 integrin complex | Skubitz KM and Snook RW 1997 |
| αXβ2/C3b          | alphaX-beta2 integrin complex | Mclellan KJ and Sim RB 1985; Chen X et al. 2012 |
| αXβ2/ICAM-1       | alphaX-beta2 integrin complex | Inglis RR and Golenbock DT 1995 |
| αXβ2/LPS (E. coli) | alphaX-beta2 integrin complex | Inglis RR and Golenbock DT 1995 |
| αLβ2 (LFA-1, CD11a/18) | alphaL-beta2 integrin complex | Geng X et al. 2005 |
| αLβ2/CD45         | alphaL-beta2 integrin complex | Geng X et al. 2005 |
| αLβ2/CD47         | alphaL-beta2 integrin complex | Azcutia V et al. 2013 |
| αLβ2/CD82     | alphaL-beta2 integrin complex | Shibagaki N et al. 1999 |
|--------------|-------------------------------|------------------------|
| αLβ2/Cytohesin-1 | alphaL-beta2 integrin complex | Kolanus W et al. 1996; Geiger C et al. 2000 |
| αLβ2/ICAM[1-4]  | alphaL-beta2 integrin complex | Edwards CP et al. 1998; Hermand P et al. 2000; Huang C and Springer TA 1995; Li N et al. 2013; Mizuno T et al. 1997; Shimaoka M et al. 2001 |
| αLβ2/RanBPM    | alphaL-beta2 integrin complex | Denti S et al. 2004 |
| αLβ2/DNAM-1    | alphaL-beta2 integrin complex | Shibuya K et al. 1999 |
| αLβ2/JAB1      | alphaL-beta2 integrin complex | Bianchi E et al. 2000; Kinoshita SM et al. |
| αLβ2/FUT4      | alphaL-beta2 integrin complex | Skubitz KM and Snook RW 1987 |
| αLβ2/ESM-1     | alphaL-beta2 integrin complex | Béchard D et al. 2001 |
| αLβ2/Rack1     | alphaL-beta2 integrin complex | Liliental J and Chang DD 1998 |
| αLβ2/VacA (H. pylori) | alphaL-beta2 integrin complex | Cover TL et al. 2008; Sewald X et al. 2008 |
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SUPPLEMENTARY

Supplementary information is available online.

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This molecule exists in 66 states, has 66 transitions between these states and has 0 enzyme functions. (Please zoom in the pdf file to view details.)