Review

Integrins: Integrating the Biology and Therapy of Cell–Cell Interactions

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ABSTRACT

Purpose: Although the role of integrins has been described in a variety of diseases, these roles seem to be distinct. To date, no study has attempted to provide links to the various pathways by which such integrins can be involved in these diverse disease settings. The purpose of this review was to address this gap in our knowledge with the hypothesis that there is, in fact, a common pathway by which integrins may function.

Methods: This article provides an in-depth perspective on the discovery, development, and design of therapeutics that modulate cellular function by targeting integrin:ligand interactions by reviewing the literature on this subject; the review included the most recent results of clinical and subclinical studies. A MEDLINE search was conducted for articles pertaining to the various issues related to integrins, and the most relevant articles are discussed (ie, not only those published in journals with a higher impact factor).

Findings: It seems that the ligation of the integrins with their cognate ligands plays a major role in translating membrane dialogue into biological function. In addition, they also seem to play a major regulatory role that can enhance or inhibit biological function depending on the context within which such receptor:ligand interactions occur and the organ and tissues at which interactions occurs and is manipulated. Those studies that used statistical analyses have been included where appropriate.

Implications: Our findings show that anti-integrin treatment has the potential to become a valid coadjuvant in the treatment of several diseases including cancer, inflammatory diseases, HIv infection and cardiovascular diseases. (*Clin Ther*. 2017;▮:▮▮▮–▮▮▮)

Key words: integrins, lymphocyte homing, T-lymphocytes, IBD, HIV.

INTRODUCTION

Integrins have been shown to play a pivotal role in the activation and homing of a variety of hematopoietic cell lineages. Cells can make contact with each other as well as the extracellular matrix. The molecular mechanisms involved in homing have come under extensive scrutiny in recent years.[1] Integrins are dimeric molecules belonging to the immunoglobulin gene superfamily: there are 18 α- and 8 β-subunits that combine into 24 αβ combinations.[2] Of these, the integrins α4β1, α4β7, αEβ7, and αLβ2 have been implicated as receptors that contribute to leukocyte trafficking.

As is discussed later, integrins (which are sometimes called addressins) play a crucial role in tissue homing and consequent pathology. For example, alpha 4 beta 7 and cluster of differentiation (CD) 103 bind to mucosal addressin cell adhesion molecule-1 (MAdCAM-1), thus allowing lymphocyte migration to gut endothelium and a relative role in inflammatory bowel diseases (IBDs);

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Table I. Summary of key integrins.

Integrin	Alpha/Beta Subunits	CD	Ligand	Expression Patterns	Main Functions
LFA-1	Alpha L/beta 2	Cd11a/Cd18	ICAM-1-5, TLN, type I collagen	T cell, B cell, monocyte/ macrophage, NK cell, DC, neutrophil, eosinophil	T-cell migration
Alpha 1	Alpha 1 beta 2	CD49a/CD29	Collagen laminin	Lymphocytes, stem cells	Cell adhesion
Mac-1/CR3	Alpha M beta2 (Mac-1, CR3, CD11b/CD18)	Cd11b Cd18	ICAM-1, ICAM-2, ICAM-4, iC3b, fibrinogen, factor X, heparin, laminin, LPS	Monocyte/macrophage, DC, neutrophil	Adhesion, activation and phagocytosis of macro phage, monocyte, neutrophil, eosinophil
CR4	Alpha X beta 2 (p150/95, CR4, CD11c/CD18)	Cd11c CD18	C3bi, fibrinogen, collagen,	Monocyte/macrophage	Adhesion and phagocytosis of monocyte/macrophage and neutrophil, adhesion
P150, 95	Alpha D beta 2 CD11d/ CD18)	CD11d/CD18	ICAM-3, VCAM-1	Macrophage, eosinophil, T cell, NK cell	Adhesion and migration
CD103/alpha E	Alpha E beta 7 (HML-1, CD103/CD-)	D103	E-cadherin	T cell, NK cell, DC, macrophage	Adhesion and activation
	Alpha 4 beta1 (VLA-4, CD49d/CD29)	CD49d/CD29	VCAM-1, MAdCAM-1,	Lymphocytes	Homing of T and B cells
	Alpha 4 beta 7 (LPAM-1, (CD49d/Act-1)	CD49d	MAdCAM-1, VCAM-1	Lymphocytes, eosinophil macrophages	Adhesion activation and recruitment
	Alpha V beta 3	VD51/CD61	Vitronectin, ICAM-1, VCAM-1, PECAM-1, fibrinogen, fibronectin	Monocyte, macrophage, DC, neutrophil	Migration of monocyte, macrophage and neutrophil, phagocytosis
VLA-2,	α2β1	CD49b/CD29	Laminin, collagen	Epidermal keratinocytes	Kinase signaling
Alpha 5/VLA-5	α5β1	CD49e/CD29	Fibronectin receptor		

CD = cluster of differentiation; CR = complement receptor; DC = dendritic cell; ICAM = intracellular adhesion molecule; LFA-1 = lymphocyte function antigen-1; LPS = lipopolysaccharide; MAdCAM = mucosal addressin cell adhesion molecule; NK = natural killer; PECAM-1 = platelet endothelial cell adhesion molecule-1; VLA = very late antigen; VCAM-1 = vascular cell adhesion molecule 1.