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New approaches to blockade of $\alpha 4$ -integrins, proven therapeutic targets in chronic inflammation

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ARTICLE INFO

Article history:

Received 6 April 2006

Accepted 12 June 2006

Keywords:

Integrins

Chronic inflammation

Therapeutic targets

Cell migration

ABSTRACT

The recruitment of leukocytes into tissue is a pivotal step in inflammation. $\alpha 4$ -Integrins are adhesion receptors on circulating leukocytes that mediate attachment to the endothelium and facilitate their migration into the inflamed tissue. This multistep process is mediated by the interaction of $\alpha 4$ -integrins with their counter receptors VCAM-1 and MadCAM-1 that are expressed on endothelial cells. $\alpha 4$ -Integrins act as both adhesive and signaling receptors. Paxillin, a signaling adaptor molecule, binds directly to the $\alpha 4$ cytoplasmic tail and its binding is important for cell migration. Blocking the adhesive functions of $\alpha 4$ -integrins has been shown to be an effective therapeutic approach in the treatment of autoimmune diseases, but also carries the risk of defects in development, hematopoiesis and immune surveillance. Interfering with $\alpha 4$ signaling by inhibiting the $\alpha 4$ –paxillin interaction decreases $\alpha 4$ -mediated cell migration and adhesion to VCAM-1 and MadCAM under shear flow. These in vitro effects are accompanied by a selective impairment of leukocyte migration into inflammatory sites when the $\alpha 4$ –paxillin interaction is blocked in vivo. Thus, blockade of $\alpha 4$ -integrin signaling may offer a novel strategy for interfering with the functions of these receptors in pathological events while sparing important physiological functions.

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1. Introduction

Autoimmune diseases are characterized by an inappropriate response of the immune system against self which leads to inflammation-induced dysfunction and ultimately to the destruction of the affected tissue. In rheumatoid arthritis

for example, the immune system attacks the synovium [1] while in inflammatory bowel disease (Crohn's disease) the intestinal mucosa is affected [2–4]. In multiple sclerosis T cells, B cells, macrophages and microglia mount a concerted attack against the myelin sheath surrounding the nerve fibers in the brain and spinal cord [5–8], whereas in type 1 diabetes mellitus

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doi:10.1016/j.bcp.2006.06.014

destruction of the insulin producing β -cells of the pancreatic islets is mediated largely by T lymphocytes [9–11].

Although the exact causes of most chronic inflammatory diseases are unclear, leukocyte accumulation in the affected tissues or organs contributes to the pathogenesis of the disease [12,13]. The recruitment of leukocytes from the blood into the tissue at sites of inflammation is regulated by sequential engagement of adhesion and signaling molecules on leukocytes and endothelial cells such as $\alpha 4$ -integrins and their ligands [14,15]. In this review we discuss recent findings on the role of $\alpha 4$ -integrins in chronic inflammatory diseases and the impact of anti $\alpha 4$ -integrin therapy to treat these disorders. Furthermore, we describe the importance of $\alpha 4$ -integrin signaling in the immune response and thus in autoimmune diseases and highlight the possible usefulness of $\alpha 4$ -integrin signaling as a therapeutic target.

2. $\alpha 4$ -Integrins in adhesion and migration: function blocking antagonists

Integrins are cell surface receptors, which mediate cell adhesion and migration and regulate cell growth and survival. They are heterodimers consisting of α and β subunits. Each subunit contains an extracellular domain involved in ligand binding, a single transmembrane domain, and a cytoplasmic domain, which regulates integrin function. Integrins function as bi-directional signaling molecules [12,16], and binding to their ligands results in intracellular signals and conversely, cellular signaling events can modulate the affinity of integrins for extracellular ligands.

The $\alpha 4$ -integrins, $\alpha 4\beta 1$ (very late antigen-4: VLA-4) and $\alpha 4\beta 7$ are most prominent on mononuclear leukocytes, but can also be expressed on neutrophils [17]. $\alpha 4\beta 1$ mediates cells adhesion to vascular cell adhesion molecule-1 (VCAM-1) and to an alternatively spliced form of the extracellular matrix protein fibronectin (FN) [18–21]. $\alpha 4\beta 7$ is important in lymphocyte homing to mucosal tissue by adhering to the gut homing receptor mucosa addressin cell adhesion molecule (MadCAM) [22] and it also binds to VCAM-1 and FN [23,24].

$\alpha 4$ -Integrins are essential for embryogenesis, hematopoiesis, lymphocyte homing and the recruitment of leukocytes to sites of inflammation [14,21]. $\alpha 4$ -Integrins are involved in the pathogenesis of chronic inflammatory diseases such as rheumatoid arthritis [25], diabetes type 1 [26,27], inflammatory bowel disease [28–31] and multiple sclerosis. Migration of circulating leukocytes from the blood into sites of inflammation is a multistep event that involves sequential leukocyte–endothelial interactions. This process includes initial tethering to and rolling along the vascular endothelial surface, leukocyte stimulation, primarily of integrin molecules, firm adhesion and spreading to the endothelium, and finally migration across the endothelium (diapedesis) [21,32–34]. $\alpha 4$ -Integrins and their endothelial counter receptors have a unique role in this multistep cascade because they are the only molecules known to mediate both rolling (when the integrins are in a low-affinity state) and arrest (when they are in a high-affinity state) [35,36].

Because of the important role of $\alpha 4$ -integrins in cell trafficking during inflammatory processes and in autoimmune diseases they may be useful as targets in the treatment

of these disorders. A multitude of papers have been published during the last decade describing monoclonal antibodies or small molecules that are directed against $\alpha 4$ -integrins or their endothelial ligands (reviewed by [37,38]).

Monoclonal antibodies directed against $\alpha 4$ -integrins or their cell adhesion molecule ligands have been shown to be effective modulators in animal models for autoimmune diseases such as asthma [39], rheumatoid arthritis [40–43], inflammatory bowel disease [44] or diabetes type 1 [45].

Early studies provided first evidence for the importance of anti- $\alpha 4$ antibodies in inflammatory bowel disease. Administration of HP1/2, an anti- $\alpha 4$ antibody that inhibits $\alpha 4$ binding to VCAM-1 and FN [46] to the cotton-top Tamarin, a primate that develops spontaneous acute and chronic colitis that resembles ulcerative colitis, resulted in significant attenuation of inflammation [31]. Further studies on the effect of antibodies against $\alpha 4$ -integrin, $\alpha 4\beta 7$ integrin or its ligand MadCAM-1 in animal models of colitis report reduced T cell mediated intestinal inflammation and abrogated symptoms of colitis [28–31]. The promising result of these pre-clinical studies in animals led to human trials using humanized $\alpha 4$ -integrin antibodies. LDP-02 (MLN02), a $\alpha 4\beta 7$ blocking antibody was successfully used in a phase I/II clinical trial of ulcerative colitis and Crohn's disease [47,48].

Efficacy of antibodies directed against $\alpha 4$ -integrin was also studied in models for autoimmune encephalomyelitis (EAE), an autoimmune disorder with similarities to multiple sclerosis. In Lewis rats, the antibody HP1/2 completely prevented the development of paralysis in 75% of the treated animals. In those that developed the disease, paralysis was delayed and its severity was reduced [49]. Another antibody, AN100226m, was studied in a guinea pig model of EAE and administration prevented leukocyte infiltration and suppressed clinical and pathological features of EAE [50]. The humanized version of this antibody, natalizumab [51–53], has been successful in the treatment of multiple sclerosis and Crohn's disease in humans [54,55]. However, the mechanisms by which natalizumab exerts its beneficial effects are poorly understood. It is known though that it binds to $\alpha 4$ and thereby inhibits the interaction between $\alpha 4\beta 1$ and VCAM-1 and between $\alpha 4\beta 7$ and MadCAM-1 [56–58]. It has been suggested, that by inhibiting the interaction of $\alpha 4\beta 1$ and VCAM, natalizumab blocks leukocyte trafficking across the blood–brain barrier and thereby moderates inflammation within multiple sclerosis lesions. In Crohn's disease, the major players of the inflammatory process are neutrophils. Since $\alpha 4$ -integrin expression is very low on circulating neutrophils [21], it is believed, that in Crohn's disease natalizumab functions by inhibiting T lymphocytes that induce cytokines and chemokines needed to sustain neutrophil recruitment [59].

To date, approximately 8000 patients have received natalizumab for the treatment of multiple sclerosis or Crohn's disease. However, the occurrence of three cases of progressive multifocal leucoencephalopathy (PML) and their association with anti- $\alpha 4$ therapy [60–62] led to suspension of natalizumab from sales and clinical trials in February 2005 [63,64]. Clinical trials have been revived in February 2006 and in June 2006 the FDA approved an application for resumed marketing of natalizumab with a special restricted distribution program [65]. Nevertheless, it is possible that in some patients long-term $\alpha 4$ -integrin

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