

Alpha E beta 7

P J Kilshaw

Abstract

α E β 7 is a member of the integrin family and is expressed almost exclusively by cells of the T lymphocyte lineage in mucosal tissues. Expression is induced by transforming growth factor β in the mucosal microenvironment. Genetic elements that control transcription are under investigation and may prove valuable for directing the expression of transgenes in mucosal T cells. The only known ligand for α E β 7 is E-cadherin, which is expressed on epithelial cells. In this article, molecular aspects of ligand recognition by α E β 7 in relation to recent structural data on cadherin domains are reviewed. Expression of α E β 7 is often increased in inflammatory diseases, particularly where T cells infiltrate epithelial tissues. The function of α E β 7 is not yet fully understood, but it is likely to be important in retention of T cells in mucosal tissues and may also have a role in cell signalling and communication between lymphocytes and epithelial surfaces.

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The integrin α E β 7 (CD103) is expressed mainly by cells of the T lymphocyte lineage within mucosal tissues.^{1,2} This is a strikingly narrow pattern of expression compared with that of other integrins. Lymphocytes expressing α E β 7 are abundant in the gut and comprise a major part of the total T cell complement of the body. The integrin is present on T cells within or closely juxtaposed to epithelia and it is expressed at very high levels on all intraepithelial lymphocytes (IELs) in gut villi and on about 50% of T cells in the lamina propria. It is also found on mucosal dendritic antigen presenting cells, bronchoalveolar lavage T cells, and activated mucosal mast cells.³⁻⁵ Expression is induced and maintained by transforming growth factor β (TGF- β),⁶ and ligation of β 1 integrins has been reported to costimulate expression.⁴

Only two integrins use the β 7 subunit and each is particularly important in the mucosal immune system. The sister molecule to α E β 7, α 4 β 7, is the homing receptor that directs lymphocytes to the gut mucosa and Peyer's patches.⁷ Its principal ligand is the mucosal vascular addressin MAdCAM-1 (mucosal addressin cell adhesion molecule) on mucosal endothelial cells. In contrast, α E β 7 does not recognise MAdCAM-1 and neither does it have a role in lymphocyte homing.⁸ Expression

of the α E subunit is believed to be induced by TGF- β , produced mainly by epithelial cells, after T cells have migrated to mucosal tissues.

The gene for the human α E subunit is on chromosome 17 and contains 31 exons spanning more than 75 kb (PJ Kilshaw, 1999, unpublished data). The 5' upstream proximal promoter contains numerous copies of the TGF- β response element,⁹ which binds Smad transcription factors. Nevertheless, the proximal promoter alone does not determine T cell specificity and TGF- β responsiveness. Experiments are in progress to identify additional enhancer elements elsewhere in the gene. The β 7 gene, which is far more widely transcribed in lymphoid tissues,¹⁰ has two functional TGF- β response regions in the promoter.¹¹ Transcription induced by TGF- β depends on tyrosine phosphorylation of putative transcription factors that bind to these regions.¹¹

The ligand for α E β 7 is E-cadherin

Experiments in the mouse and human established that the ligand for this integrin is expressed exclusively by epithelial cells and that it is E-cadherin.¹²⁻¹⁵ Thus, α E β 7 caused adhesion of mucosal T cells to cultured gut epithelial cells in vitro.^{12,13} Importantly, spontaneous or lectin induced cytotoxic effector function of IELs against epithelial cell targets could be inhibited by blocking the integrin-cadherin interaction.^{13,16} So far, no other ligand for α E β 7 has been identified.

E-cadherin is a calcium dependent, homophilic cell adhesion molecule expressed by epithelial cells. It plays a vital role in embryonic development and in the polarisation of epithelial cells.^{17,18} It is concentrated in adherens junctions between epithelial cells and is detectable also at the basolateral membrane. E-cadherin comprises five extracellular domains, each made up of ~110 amino acids arranged as seven β sheets in an immunoglobulin (Ig) fold.¹⁹ Nine calcium atoms are bound in the interdomain junctions and these are important for maintaining the rod-like conformation and functional activity of the molecule.²⁰ Adjacent E-cadherin molecules on the cell surface can dimerise in parallel, and this is thought to be a prerequisite for homophilic adhesive interactions between E-cadherin molecules on opposing cells.^{21,22}

Structural requirements for recognition of E-cadherin by α E β 7

Extracellular domains 1 and 2 of E-cadherin are required for recognition by α E β 7.²³ Alanine point mutations of six acidic residues within domain 1 (fig 1) revealed an essential integrin recognition motif in a highly flexible quasi helix connecting β strands B and C. The mutation Glu 31/Ala in this loop prevented binding to

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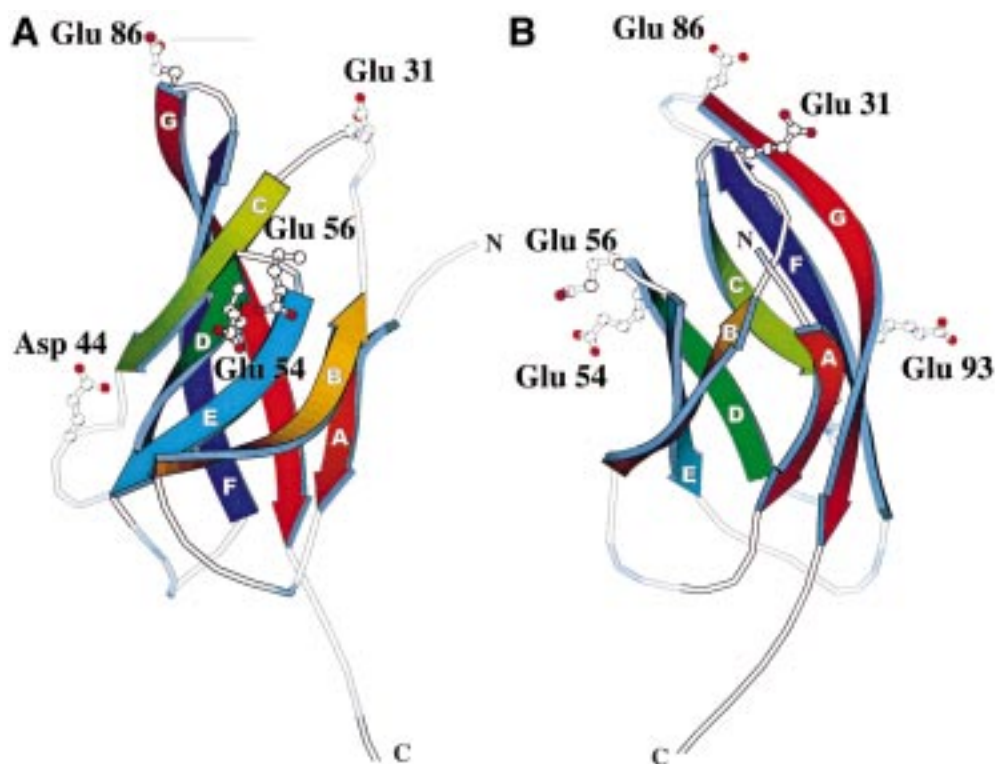


Figure 1 Model of E-cadherin domain 1 showing the positions of six acidic amino acids that were mutated to alanine; (A) and (B) differ by 90° in the vertical axis. Only the mutation at Glu31 inhibited recognition by α E β 7.

α E β 7.²³ The location of the integrin binding site in E-cadherin differs from that of other integrin ligands of the Ig superfamily, such as intercellular adhesion molecule 1 (ICAM-1), ICAM-2, ICAM-3, vascular cell adhesion molecule 1 (VCAM-1), and MAdCAM-1, in which the CD region on the CFG face of domain 1 is important for recognition by integrins.^{24, 25} In E-cadherin, the BC loop is distant from both the CFG surface, which is required for homophilic adhesion, and the AB face, which is involved in strand dimerisation.^{20, 21} A cyclic peptide mimicking the BC loop failed to inhibit integrin binding,²³ indicating that additional contact sites may be required. Other members of the cadherin family do not contain the BC recognition motif and show little or no adhesion to α E β 7. Human, but not mouse, P-cadherin contains aspartic acid rather than glutamic acid in the crucial position of the BC loop and supports very weak adhesion to α E β 7.²⁶

Domain 2 of E-cadherin is essential for the engagement of α E β 7 but its precise role is not understood. This domain might provide additional contact sites for the integrin. Another possibility is that α E β 7 recognises E-cadherin only as a strand dimer. In this case, domain 2 would be required for lateral dimerisation.^{21, 27, 28} Dimerisation could provide the rigidity necessary for integrin binding; alternatively, two separate sites on the integrin could engage the two cadherin molecules. Two models for dimer formation have been proposed, based on *x* ray crystallography. One directly involves calcium in the junction between domains 1 and 2,²¹ the other requires the mutual intercalation of tryptophan residues

in the first domains of adjacent cadherin molecules.²⁰ Each model is supported by experimental evidence. Calcium is required for dimerisation of recombinant E-cadherin domains 1 and 2 in solution,²⁷ but is not necessary for dimer formation on the cell surface²⁹ or for adhesion between α E β 7 and the E-cadherin-Fc fusion protein.²⁶ In either model, the integrin recognition motifs of the two E-cadherin molecules are in close apposition (fig 2), so it is enticing to speculate that both loops could be engaged simultaneously by one integrin molecule. The stoichiometry of the interaction has not yet been investigated. Regardless of whether or not dimerisation is necessary for binding to α E β 7, it is clear that the C-terminal region of the cytoplasmic domain that links E-cadherin to the cytoskeleton is not required for recognition by the integrin.²³ The role of this region in regulating lateral dimerisation and clustering is complex and not yet fully resolved.^{30, 31}

In common with six other integrin α subunits (α 1, α 2, α L, α M, α X, and α D), α E contains an I domain.³² This structure forms a "Rossmann" fold incorporating a metal ion dependent adhesion site, which is thought to contribute a major part of the ligand binding activity of the integrin molecule.³³ Recombinant I domains of α 1, α 2, α M, and α L subunits exhibit divalent cation dependent ligand binding activity in isolation from the rest of the molecule.³⁴⁻³⁷ This has not yet been demonstrated for α E, but the I domain is clearly important for ligand recognition because an antibody that blocks α E β 7 function (M290) recognises an epitope in this region (PJ Kilshaw, 1999, unpublished data).

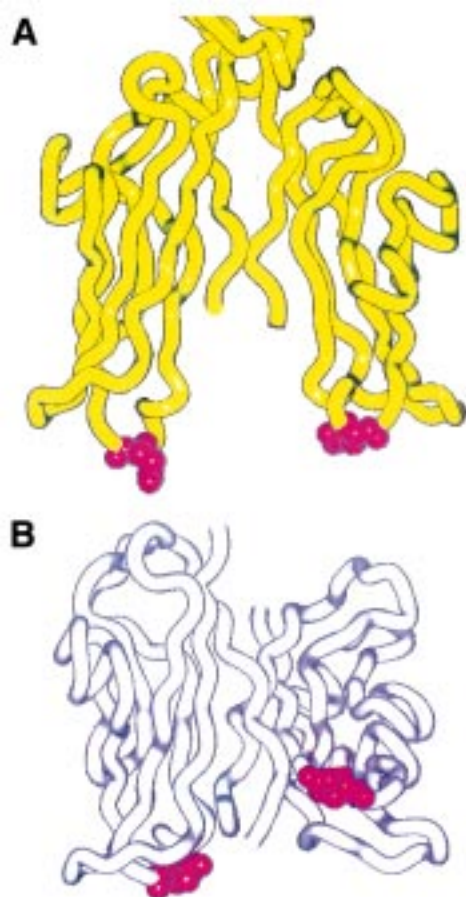


Figure 2 Two interpretations of E-cadherin domain 1 in dimeric form. (A) Calcium dependent dimer according to the model of Nagar et al.²¹ (B) Tryptophan dependent dimer based on the the model of Shapiro et al for N-cadherin.²⁰ In each case Glu 31 is shown in magenta.

α E β 7 in disease

In Crohn's disease, the expression of α E β 7 on IELs in the ileum is reduced. This change is seen in both inflamed and non-inflamed regions, and might be an early sign of incipient disease.³⁸ Conversely, in mouse models of colitis, such as that induced by injection of CD4⁺ CD45RB^{hi} cells into severe combined immunodeficient (SCID) mice, the T cells that infiltrate the epithelium are α E β 7 positive.³⁹ In Sjogren's syndrome, a T cell mediated autoimmune disease of salivary and lacrimal glands, the effector CD8⁺ T cells that are found in close association with the acinar and ductal epithelium express α E β 7.⁴⁰⁻⁴¹ Increased expression of α E β 7 is also seen on cultured peripheral blood T cells in systemic lupus erythematosus with epithelial involvement,⁴² and in cutaneous T cell lymphomas.⁴³ In normal lung, most CD8⁺ T cells and a few CD4⁺ cells in bronchoalveolar lavage fluid are α E β 7 positive.⁴ The expression of α E β 7, particularly on CD4⁺ cells, increases dramatically in certain types of pulmonary inflammation, such as sarcoidosis, hypersensitivity pneumonitis, and idiopathic pulmonary fibrosis.⁴ This integrin may also be relevant in allotransplantation because CD8⁺ cytotoxic T lymphocytes (CTLs) found in close apposition to the tubular epithelium of renal allografts undergoing chronic rejection

express α E β 7 (JA Kirby, 1999, unpublished data). Moreover, about 50% of the CTLs generated in vitro in response to allogeneic renal epithelial cells express α E β 7, a feature that biases their effector function towards epithelial target cells as opposed to lymphocytic targets.⁴⁴ α E β 7 has also been detected in the inflamed synovium and it is notable that its ligand, E-cadherin, is strongly expressed by synovocytes.⁴⁵ It is sometimes assumed that α E β 7⁺ T cells that infiltrate non-mucosal organs are gut derived. In most instances a more plausible explanation is that integrin expression is induced in situ by the influence of TGF- β in the local microenvironment.

So far, the importance of α E β 7 in animal models of inflammatory disease has been assessed in only one study.^{45a} A blocking antibody, M290, to the α E subunit was shown to prevent or ameliorate immunisation induced colitis in interleukin 2 deficient mice. The effect was attributed to reduced retention of CD4⁺ T cells in the mucosa. In addition to a role in tissue retention, α E β 7 might also contribute directly to T cell mediated damage of epithelial cells. In this case, inhibition of the interaction between α E β 7 and E-cadherin could be beneficial. This strategy would be especially appropriate in circumstances in which α E β 7 provides the dominant adhesion pathway between the T cell and its target—for example, when ICAM-1 is absent from the epithelium or is inaccessible or expressed at low levels, such as in inflamed gut.⁴⁶⁻⁴⁷

The function of α E β 7: facts and speculations

It has been widely assumed that α E β 7 serves to locate and retain T cells at epithelial surfaces by engaging E-cadherin on the basolateral surface of epithelial cells. Although the assumption may be correct, this adhesion pathway is not a prerequisite for penetration of lymphocytes into epithelia. T cells that infiltrate the gut epithelium in graft versus host disease lack α E β 7.¹ Furthermore, IELs are abundant in regions of inflamed gut epithelium in which E-cadherin is lacking as a result of genetic manipulation.⁴⁸ Ablation of α E β 7 function in vivo either with antibodies or by knockout technology has, so far, failed to give an adequate picture of its function in healthy or antigen challenged mice, although it is notable that IELs in the gut of α E^{-/-} mice are somewhat reduced in number (C M Parker, 1998, unpublished data). In common with other integrins, the adhesive function of α E β 7 is regulated by modulating affinity or avidity.⁴⁹ Treatment of lymphocytes with phorbol ester or ligation of the T cell receptor complex increases the adhesive capacity of α E β 7 and the addition of manganese ions increases affinity.²⁶ Recently, the cytoplasmic tails of both α E and β 7 have been shown to associate with the WD repeat protein WAIT-1, which is thought to play a part in regulating adhesion, although the mechanism is not understood.⁵⁰ The functional state of α E β 7 on IELs in the normal gut is unclear and it is possible that engagement of

E-cadherin on the epithelial cell occurs only after the T cell has been stimulated by antigen.

Both E-cadherin and $\alpha E\beta 7$ take part in cell signalling. Crosslinking the integrin costimulates the proliferative response and cytotoxic function of IELs.^{13–51} E-cadherin, in addition to its role as a cell adhesion molecule, has profound effects on the morphological and genetic regulation of epithelial cells. Impaired function of E-cadherin resulting from point mutations or reduced expression is associated with dysplasia, genetic instability, and progression to neoplasia.^{52–54} β -Catenin may provide the connection between adhesion and gene transcription. This protein links the cytoplasmic domain of E-cadherin to the cytoskeleton in adherens junctions. In this way, cell adhesion can influence the cytoplasmic pool of free, unassociated β -catenin. This pool is also regulated by the Wnt signalling pathway.⁵⁵ Free β -catenin is transported to the nucleus, where it activates transcription factors that act upon genes involved in oncogenic progression. The engagement of E-cadherin by $\alpha E\beta 7$ on T cells patrolling the epithelium would be expected to perturb E-cadherin homotypic adhesion and may affect the interaction of the cytoplasmic domain with β -catenin or other proteins associated with this signalling pathway. By this means, $\alpha E\beta 7$ could influence gene transcription in epithelial cells.

The role of $\alpha E\beta 7$ as an adhesion molecule is only partly understood. Its importance in disease and its potential role as a conduit for the transfer of information between lymphocytes, epithelial cells, and the external environment invites further exploration.

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