Integrin αEβ7: Molecular Features and Functional Significance in the Immune System

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Abstract

Alpha E beta 7 (αEβ7) is an α-I domain-containing integrin that is highly expressed by a variety of leukocyte populations at mucosal sites including intraepithelial T cells, dendritic cells, mast cells, and T regulatory cells (Treg). Expression depends largely or solely on transforming growth factor beta (TGF-β) isoforms. The best characterized ligand for αEβ7 is E-cadherin on epithelial cells, though there is evidence of a second ligand in the human system. An exposed acidic residue on the distal aspect of E-cadherin domain 1 interacts with the MIDAS site in the αE α-I domain. By binding to E-cadherin, αEβ7 contributes to mucosal specific retention of leukocytes within epithelia. Studies on αE knockout mice have identified an additional important function for this integrin in allograft rejection and have also indicated that it may have a role in immunoregulation. Recent studies point to a multifaceted role for αEβ7 in regulating both innate and acquired immune responses to foreign antigen.

Keywords

Integrins · Intraepithelial T cells · Regulatory T cells · Dendritic cells · Mast cells · TGFβ

7.1 Introduction

Integrin αEβ7 is, in many respects, an unusual integrin. The αE subunit (CD103) has unique structural features (Fig. 7.1) and is the only α-I domain-containing integrin chain that pairs with β7. Beta 7, however, can pair with α4 as well as αE. Both heterodimers are expressed exclusively by leukocytes and have special significance for the mucosal immune system. Alpha 4 beta 7 is the principal mucosal homing receptor for

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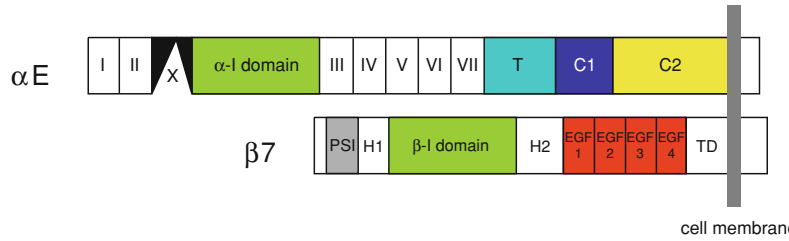

Fig. 7.1 Domain structure of integrin αEβ7. The seven blades of the β-propeller domain of αE are labeled I to VII; the thigh domain, T; the calf-1 and –2 domains, C1 and C2. The extra X-domain, not found in any other integrin chain and containing a post-translational cleavage site, is marked X. In β7, the plexin/semaphorin/integrin domain is labeled PSI; the two components of the hybrid domain, H1 and H2; and the β-tail domain, TD. Note that this figure does not illustrate the relative orientation of the different domains

leukocytes [11] whereas αEβ7 appears to play a role in retention of these cells within or near epithelia. In this review we shall discuss the tissue distribution and induction of αE and present a molecular perspective on the interaction between αEβ7 and its principal ligand, E-cadherin. The complex organization of the αE gene locus will be described. Finally, we aim to present current views of αEβ7 function.

Recent studies indicate that αEβ7 plays an important role in determining the localization of dendritic cell subsets, and therefore indirectly impacts all immune responses, both innate and adaptive. In fact, studies of the αE expressing subset of dendritic cells now dominate the literature on this subject. Of 94 αE integrin references published in 2013, 61 were about αEβ7 expressing dendritic cells. By contrast, in calendar year 2003, there were only 25 references to αE integrin, and none of these were about dendritic cells. The field initially focused on the role of αEβ7 in promoting the functional activities of mucosal T cells, then shifted to a focus to the functional relevance of αE on Tregs then to the current focus on the relevance of αE expression by dendritic cell subsets. The emphasis on the αE expressing subset of dendritic cells is warranted as it is now clear that dendritic cells initiate essentially all immune responses—both innate and adaptive—and thereby play a critical role in defining the nature and character of the immune response. Thus, αEβ7 likely controls these critical processes.

7.2 Tissue and Cellular Distribution

Integrin αEβ7 was originally discovered in the rat, human and mouse by screening panels of monoclonal antibodies for cell surface features that were distinctive for intestinal intraepithelial lymphocytes (IEL) [15, 16, 47]. The original mAbs to αEβ7, RGL-1, HML-1, and M290 (reactive in rat, man and mouse respectively) were subsequently shown to identify a novel integrin alpha chain now known as αE (CD103) [14, 49, 50, 54, 70, 76, 78, 89, 92, 115]. A fourth antibody, MRC-OX62, raised against rat lymphatic dendritic cells was later shown also to recognize αEβ7 [7, 8]. Thus, a distinguishing feature of αEβ7 is that it is expressed most prominently and abundantly in the gut, particularly on T cells in the epithelium [8, 15, 16, 25, 47, 49, 50]. At first, it seemed a foregone conclusion that αEβ7 functioned to retain T cells at mucosal sites, but recent studies reveal a more complex situation. In other compartments of the immune system and among other lymphoid/myeloid cell lineages expression is found on sub-populations which express αEβ7 at lower levels that are, nevertheless, functionally important. In particular, while αEβ7 is expressed by diverse leukocyte subsets, it is now clear that it defines a subset of dendritic cells, and thereby can have a global impact on immune responses.

αEβ7$^+$ T cells are usually found in locations where active TGF-β isoforms are abundant. Expression of αEβ7 on T cells is usually skewed towards the CD8 subset [16, 25, 47], a phenomenon that is readily seen in mixed T cell cultures stimulated with mitogen in the presence of TGF-βisoforms [9, 80, 87]. In the gut, almost all IEL and about half the T lymphocyte population in the lamina propria express αEβ7 [16, 25, 47]. Similarly, the integrin is present on T cells in or near other epithelial surfaces, including those of the lung [80] and genital tract [22, 77]. In lymphoid tissues, including Peyer's patches and mesenteric lymph nodes and in peripheral blood the percentage of αEβ7$^+$ T cells and their level of expression of αEβ7 is generally low [2, 16, 50].

Although αEβ7 was formerly considered to be a mucosal T cell marker, the molecule is also found on other cell lineages. Most studies on the distribution of αEβ7 have failed to detect the molecule on tissue macrophages, but there is an exception in which a proportion of macrophages in lung, liver and lymph node sinuses is reported to have stained positively with mAb HML-1 [100]. An interesting observation was also made that mucosal-type mast cells generated in vitro from bone marrow precursors by culturing in the presence of stem cell factor, IL-3, IL-9 and TGF-β expressed αEβ7 strongly [92, 111]. The presence of the integrin on mucosal mast cells in vivo is strongly supported by circumstantial evidence, but the functional significance and in vivo relevance of such expression remains to be demonstrated.

Significant subsets of dendritic antigen-presenting cells (DC) in the gut mucosa, the mesenteric lymph nodes and the epithelium of the airways of rats and mice are αEβ7$^+$ [7, 8, 46, 65, 73] but in lymph nodes which have no mucosal involvement the proportion is considerably smaller [46] and in the spleen αEβ7 expression is confined to the small subset of CD8$^+$ DC [69]. In man, expression of αEβ7 by mucosal dendritic cells has been less extensively documented but αEβ7$^+$ DC are present in the dome epithelium of Peyer's patches and in the lamina propria [25, 108]. In contrast, Langerhans-type DC generated in vitro from hematopoietic stem cells in the presence of TGF-β and other cytokines do not express the integrin [79].

Detailed scrutiny of B cell subsets for expression of αEβ7 has revealed a complex picture. Early studies showed that the integrin was expressed by few if any B cells in the gut mucosa or elsewhere. However, Csencsits et al. [23] identified a population of αEβ7$^+$ B220$^+$ cells in the intestinal mucosa following intranasal immunisation of mice with cholera toxin. That cells of B lymphocyte lineage can, in certain circumstances, express αEβ7 is supported by the detection of a small population CD19$^+$ αE$^+$ B cells in peripheral blood [40] and also by much earlier observations that αEβ7 expression is a diagnostic marker for hairy cell leukemias [70–72].

Studies of αEβ7 expression during thymic ontogeny in the mouse have shown that 3–5 % of cells express the integrin and that it is represented in both TCRαβ and γδ lineages, particularly in the late developmental stages [2, 59]. The integrin is present on about half the population of thymic precursors of dendritic epidermal T cells (DETC) and on all mature cells of this subset [59]. In humans, αEβ7 was found to be expressed by a major subpopulation of single positive CD8$^+$ human thymocytes and a smaller proportion of less mature double negative cells [56, 67]. Recent studies implicate Runx 3 in controlling αEβ7 expression during thymocyte development [33, 112], and indicate that CXCR3 and αEβ7 both are expressed by the CD8$^+$ single positive thymocyte subset [4], and that Treg likely derive from Foxp3$^+$ double positive (CD8$^+$CD4$^+$) cells that lack αEβ7 expression [75]. It has also been reported that most, if not all, naïve CD8$^+$ that have recently emigrated from the thymus into the circulation express αEβ7 [67]. Thus, the frequency of αEβ7$^+$ CD8 T cells in the blood with a naïve phenotype appears to be a useful indicator of thymopoiesis. Maintenance of αEβ7 expression by this cell population, and also by splenic and blood CD8$^+$ T cells, has been reported to depend on lymphotoxin alpha (LTα) [31]. However, the possibility was not excluded that LTα

induces expression of the αE subunit by an indirect effect on TGF-β processing. Single positive thymocytes expressing αEβ7 may migrate to the small intestine via a sphingosine 1-phosphate (S1P) dependent process [55].

The study of T regulatory (Treg) cells (formerly known as suppressor T cells) has undergone a renaissance and their importance in immune homeostasis and in the prevention of autoimmune diseases and allograft rejection is clear. In vivo models of suppression of autoimmunity involving adoptive cell transfer and in vitro studies on suppression of lymphocyte proliferation by spleen or lymph node T cell subpopulations have shown that Treg cells reside within a population that is $CD4^+$ $CD25^+$ $CD45RB^{low}$ [17, 64]. Four studies have shown that αEβ7 is expressed by 20–30 % of this T cell subset [32, 60, 68, 117]. Similarly, regulatory $CD8^+$ T cells generated by co-culture of intestinal epithelial cells and peripheral T cells were shown to express αEβ7 [1].

7.3 Induction of αEβ7

It is long been recognized that transcription of the αE subunit is regulated by transforming growth factor beta (TGF-β) [49, 50, 76, 85, 92]. Such induction is commonly attributed to the TGF-β1 isoform but all isoforms of TGF-β (also mouse TGF-β2, and -β3 for example) exhibit this property (GAH unpublished data); it has not yet been established which of the TGF-β isoforms contribute to αEβ7 induction in vivo. Recent studies point to a key role for membrane bound TGF-β in this process [113, 114], but a complete understanding of this important interaction is muddled by our poor understanding of how TGF-β isoforms are processed to their active forms in the particular cells used in these experiments. It has been reported that ligation of β1 integrins can act synergistically with TGF-β in αE induction [80], and that activation of naïve human $CD8^+$ T cells with anti-CD3 in the presence of IL-4 can also increase αEβ7 expression [99], though it is unclear if these apparent inducers operate through the indirect action of TGF-β isoforms.

It is widely held that αEβ7 expressed by T cells located in the vicinity of epithelia is induced locally by TGF-β isoforms produced mainly by epithelial cells. This view is supported by the observation that T cells stimulated in vitro by co-culture with allogeneic kidney epithelial cells, or T cells that migrate into epithelial monolayers, are induced to express αEβ7 and that expression is blocked by anti-TGF-β antibody [34, 90]. The results of a study of mucosal T cell memory by Kim et al. [51] are also consistent with the idea that αEβ7 is upregulated locally. Ovalbumin-specific transgenic $CD8^+$ T cells were adoptively transferred to recipients that were then infected with recombinant vesicular stomatitis virus expressing ovalbumin (VSV-OVA). Analysis of donor-type memory cells in various lymphoid compartments indicated that αEβ7 was strongly upregulated on IEL over the 5 week study period.

The notion that αEβ7 expression is mainly, if not solely, TGF-β-dependent is supported by a study showing that in transgenic mice which express the negative regulator of TGF-β isoform signalling, Smad7, under an *Lck* promoter, 50 % of intraepithelial T cells in the gut no longer express αE [96]. Expression of the integrin by the remaining cells probably reflects insufficient expression of the transgene in this population but leaves open the possibility that an alternative signaling pathway could be responsible for αE expression in these circumstances. Using a T cell line, Robinson et al. showed that TGF-β induces αE transcription de novo within 30 min [85]. The speed of induction suggests that synthesis of signaling intermediaries or new transcription factors was probably not required. These authors also looked for transcription control elements in the promoter region of the human αE gene using deletion analysis to examine 4 kb of genomic sequence upstream of the transcription start site. Although the promoter functioned well in reporter assays, it bestowed neither cell lineage specificity nor TGF-β responsiveness. Thus, transcription control mechanisms for αE are

likely to be considerably more complex than those of most other integrin α-chain genes, whereas lineage specificity is determined by the proximal promoter in other integrins.

7.4 Gene Structure

Past studies established the complexity at the locus of the integrin αE gene, *Itgae*. Schön et al. [88] generated a partial map of murine *Itgae*, and subsequently the human genome sequencing project provided more complete information on human *Itgae* [37]. Human *Itgae* contains 31 exons spanning approximately 85 kb (Fig. 7.2). Comparison with the genes encoding the closely related αM and αX integrin proteins [21, 27, 74] reveals a highly conserved gene structure. All the introns are located in similar positions and have the same phase in the three genes, although *Itgae* contains an extra exon (exon 6) that encodes the X domain not present in other integrins (see Fig. 7.1). The α-I domain is encoded by exons 7–10. Human *Itgae* is found at chromosome 17p13.3 rather than in the αL/αM/αX/αD integrin cluster at chromosome 16p11 [21, 110], and is syntenic with that of murine *Itgae* on chromosome 11 [88]. Robinson et al. [85] analyzed the transcription start site of human *Itgae*, and identified two start sites 51 and 44 bp upstream of the start codon, and a third possible initiation site around position ~90 bp. Interestingly, another gene, *Gsg2*, that encodes the mitotic protein kinase Haspin is found on the opposite strand within an intron of *Itgae* Fig. 7.2. The Haspin promoter appears also to drive expression of a truncated and alternatively spliced *Itgae* transcript that is widely expressed and could function as a non-coding RNA [37].

The human β7 gene, *Itgb7*, comprises 14 exons spanning approximately 10 kb and maps to chromosome 12q13.13 [5, 42], syntenic with murine β7 on chromosome 15 [116]. The intron-exon structure of *Itgb7* is more similar to that of the β1 and β2 genes than the β3, β5 and β6 genes, consistent with a similar sub-grouping derived from analyses of sequence homology [42].

7.5 Ligand Binding

Expression of αEβ7 by T cells closely juxtaposed to epithelial surfaces suggested that this integrin might bind a counter-receptor on the surface of epithelial cells. In 1993 three groups reported that a ligand for αEβ7 was present on epithelial cell lines [12, 81, 82]. The epithelial ligand was later identified as the homophilic adhesion molecule E-cadherin [13, 39, 44], and mutagenesis studies combined with crystal structure determination and molecular modeling led to a detailed model for αEβ7 binding to E-cadherin in which the MIDAS motif within the α-I domain of αE makes direct contact with an acidic residue at the tip of domain 1 in E-cadherin (Fig. 7.3) [38, 41, 45, 98]. These findings strengthened the concept that αEβ7 retains leukocytes in epithelial tissues by binding to E-cadherin on epithelial cells.

E-cadherin expression is found on most epithelial cells, but is not limited to this population. Recent studies suggest that E-cadherin can act at the level of dendritic cells to impact immune responses. For example, Siddequi et al. [91] observed that monocyte-derived inflammatory DCs express E-cadherin, and that these promote intestinal inflammation. Similarly, Uchida et al. [102] reported that E-cadherin and αEβ7 on DETC regulate their activation threshold through binding to E-cadherin on keratinocytes. Van den Bossch et al. [104, 105] detailed the regulation and function of the E-cadherin/catenin complex in cells of the monocyte-macrophage lineage and DCs, and found that E-cadherin is expressed by alternatively activated macrophages. Thus, αEβ7 expressing cells potentially interact with and regulate diverse leukocyte populations, but the extent to which this occurs in vivo has yet to be established.

E-cadherin is the only well-defined counter-receptor of αEβ7, but there is preliminary evidence for at least one further ligand on keratinocyte cell lines and intestinal lamina propria endothelial cells that lack E-cadherin expression [10, 41, 93].

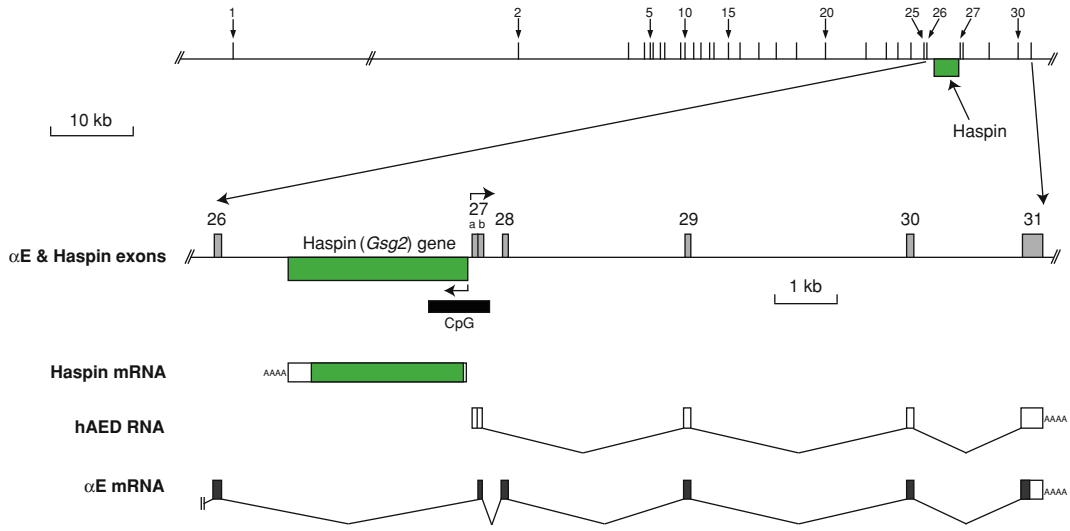

Fig. 7.2 Outline structure of the αE genomic locus. The *top line* shows the intron-exon structure of the integrin αE (*Itgae*) and Haspin (*Gsg2*) genes. On the *second line*, the 3′ region of the αE gene containing the Haspin gene is shown in more detail. Intronic regions are shown as *horizontal lines* and exons as *boxes*. *Bent arrows* represent transcription start sites, and the *thick black line* indicates the location of a CpG island. The *three lower lines* show the three transcribed products of this genomic region, including the Alpha-E derived mRNA, hAED. In each case, *boxes* represent exonic portions of RNA, *thin lines* indicate introns, *dark shading* indicates protein coding regions, and AAAA indicates a poly(A) tail

7.6 Function

7.6.1 Effector and Memory T Cells

It is now clear that αE controls the accumulation of effector and memory T cells (resident memory T cells, T_{rm}) in non-lymphoid tissues and thereby may promote their capacity to eliminate invading pathogens. Alpha-E expression marks T_{rm} cells in a variety of tissues [63, 107] (25), and there is good evidence that such expression promotes their local persistence, particularly for intraepithelial $CD8^+$ T cells in the intestinal and vaginal mucosa, where binding to E-cadherin may be critical [88, 107]. Moreover, it is not clear that αEβ7 expressing T cells present at all sites are exclusively memory T cells, in that many are present in naïve mice prior to specific antigen exposure. The underlying mechanisms regulating αEβ7 expression by T_{rm} remain poorly defined but are likely similar to those described above for other αEβ7 expressing cells. These include induction of αEβ7 and downregulation of the chemokine receptor CCR7 with a dominant role for local TGF-β activity in the process. Suvas et al. have shown that systemic and mucosal infection both are effective in generating mucosal $\alpha E\beta 7^+$ T_{rm} responses [95]. Yu et al. [113] have also reported that human $CD1c^+$ DCs express cell surface TGF-β and thereby drive the generation of αEβ7 expressing cytotoxic lymphocytes (CTL).

7.6.2 Allografts

A number of studies have examined whether αEβ7 on T cells could play a role in allograft rejection. Hadley et al. [35, 36] reported that up to 63 % of T cells infiltrating renal allografts undergoing a late rejection crisis expressed αEβ7 and that the cells were localized mainly in the tubular epithelium. Similar findings were reported by Robertson et al. [83, 84] who observed a correlation between the prevalence of

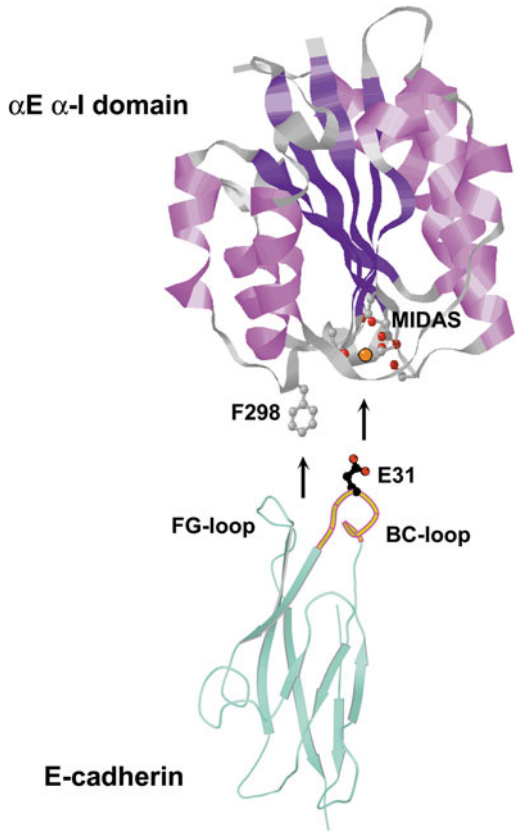

Fig. 7.3 A model of the αEβ7 integrin α-I domain docked onto E-cadherin domain 1. Residue E31 in the BC-loop of E-cadherin is predicted to coordinate the MIDAS magnesium ion in the α-I domain and F298 of αE is predicted to project into a hydrophobic pocket between the BC and FG loops of E-cadherin. For details see ref [38]. Reproduced with permission from Agace WW, Higgins JMG, Sadasivan B, Brenner MB, Parker CM. Curr. Opin. Cell Biol. 2000; 12:563–568 (Copyright 2000, Elsevier Science)

αEβ7$^+$ cells in the tubular epithelium, the severity of tubulitis and the levels of TGF-β in the epithelium. Earlier studies established that αEβ7 was induced on CD8$^+$ T cells co-cultured with renal epithelial cells [34] and that αEβ7 provided accessory function for cytotoxic lysis of target epithelial cells [86]. This evidence supports the view that αEβ7 is induced on infiltrating CD8$^+$ cells by TGF-β produced locally in the allograft and causes the cells to accumulate in the graft epithelium by adhesion to E-cadherin expressed by tubular epithelial cells. The integrin/ligand interaction would then provide accessory function for cytotoxic lysis or cytokine production. This interaction may be especially important in rejection when other integrin/ligand interactions, principally αLβ2 (LFA-1)/ICAM-1, are unavailable. This view is strongly supported by the observation that αE null/null mice are unable to reject pancreatic islet allografts [26, 48]. Although CD8$^+$ cells accumulate around the graft they do not come into intimate contact with islet cells, which are known to express E-cadherin but not ICAM-1. This view is further supported by the observation that T cells from αE null/null mice do not elicit gut graft-versus-host disease (GVHD) on transfer to wildtype allogenic recipients [24]. Zhou et al. [118] confirmed these findings in a rat GVHD model, and further observed that the skin epidermis in rats during GVHD is infiltrated by an equal number of CD4$^+$ T cells and CD8$^+$ T cells expressing αEβ7. Collazo et al. [19] reported that expression of SH2 domain–containing inositol 5-phosphatase (SHIP) is required for robust expansion of donor αEβ7$^+$ CD4$^+$ T cells during graft-versus-host and host-versus-graft responses by CD4$^+$ T cell and limits their immunoregulatory capacity. These observations on the role of αEβ7 in allograft rejection and GVHD identify a potential opportunity for therapeutic intervention using inhibitors specific for this integrin.

Separation of deleterious GVHD pathology from beneficial graft-versus-leukemia (GVL) responses following bone marrow transplantation (BMT) remains a major challenge in the treatment of hematologic malignancies by allogeneic hematopoietic cell transplantation (HCT). Liu et al. [62] used αE null/null mice to show that αEβ7 expression by CD8$^+$ T cells is required for the former but not the latter process, identifying αEβ7 blockade as an improved strategy for GVHD prophylaxis. Li et al. [61] showed that preconditioning of host mice with anti-CD3 mAb also separates GVHD and GVL effects, and does so by reducing the number of αEβ7 expressing dendritic cells in the mesenteric lymph nodes.

7.6.3 Tumor Immunology

Le Floc'h et al. [29, 57, 58] reported that αEβ7 expression by $CD8^+$ CTL clones in tumors can be induced by TGF-β expression within the tumor. These studies also showed that αEβ7 can participate in formation of the immunological synapse between the CTL and the tumor target, and that interaction with E-cadherin expressed by the tumor target is required for polarization and subsequent release of cytotoxic granules. Subsequent studies showed that interaction of αEβ7 with E-cadherin, but not αLβ2 with ICAM-1, acts at the level of the immunologic synapse formed between tumor-infiltrating lymphocytes and tumor cells to promote CCR5-dependent retention of CTL [30], that interaction of αEβ7 with E-cadherin promotes the phosphorylation of the ERK1/2 kinases and Phospholipase C-γ1 (PLC-γ1), which is sufficient to induce the polarization of cytolytic granules [57], and that interaction between CTL and epithelial tumor cells is regulated by αE expression at the immune synapse which can profoundly influence effector functions of CD8 T cells [29]. Thus, αEβ7 potentially plays a role in tumor elimination through interaction with E-cadherin. These findings raise the exciting possibility that the characteristic loss of E-cadherin expression and gain in invasiveness by metastatic epithelial tumors exhibited by many neoplastic epithelial cells [97] might, in part, reflect CTL selection. That said, the frequency of tumor-reactive CTL clones that express αEβ7 remains a matter of speculation. Nonetheless, together, these studies provide novel insight onto the role of αEβ7 in CTL function. Also, of relevance to the field of tumor immunotherapy, Trinite et al. [101] reported that immature ($CD4^-$ αE$β7^+$) rat dendritic cells can induce rapid caspase-independent apoptosis-like cell death and subsequent phagocytosis of tumor targets. Both of these sets of findings have spurred interest in the development of novel immunotherapeutic strategies to combat cancer.

7.6.4 T Regulatory Cells

The role of αEβ7 in Treg function is controversial and highly dependent on the model employed. However, there is evidence that αEβ7 plays an important role in promoting both the function and localization of Treg cells, and even that αEβ7 marks Tregs with the most potent immunosuppressive properties. McHugh et al. [68] and Lehmann et al. [60] both reported that that the αE$β7^+$ population was more efficient at suppressing anti-CD3 stimulated proliferation of $CD4^+$ CD25-cells than the αEβ7-subset. TGF-β plays a role in the development and function of Treg cells, and the presence of αEβ7 on the surface of a major subpopulation of Treg cells argues, at least, that these cells have recently been exposed to TGF-β. However, such expression may be misleading and it remains to be determined if a direct role of αEβ7 on Treg is always relevant. As described below, αEβ7 expressing dendritic cell subsets can also control the suppressive function of Tregs.

More recently, Suffia et al. [94] have shown that αEβ7 plays an essential role in retention of Treg and control of Leishmania major infection, and that targeted disruption of the αE gene renders mice susceptible to Leishmania infection, a result that could be reversed by transfer of αEβ7 expressing Tregs from wild type mice. In contrast, the Powrie group has reported that targeted disruption of αE has no effect on the suppressive capacity of Tregs in a mouse model of colitis [3]. Rather, expression of αEβ7 by dendritic cells was found to be necessary for Treg function (see below). Van et al. [106] showed that CD47 controls the in vivo proliferation and homeostasis of the αEβ7 expressing subset of peripheral Tregs. There is also evidence that αEβ7 expressing CD8 T cells can be suppressive. For example, Uss et al. provided evidence that αE$β7^+$ CD8 T cells can be potently immunosuppressive in vitro [103], effectively functioning as T regs.

7.6.5 Dendritic Cells

While the precise function of each dendritic cell (DC) subset remains to be clearly defined, it is clear that expression of αEβ7 allows DCs to control the balance of effector responses to foreign antigens. Annaker et al. reported that αEβ7 expression by DCs is required for the induction of Tregs to suppress intestinal bowel disease [3]. In this model, αEβ7$^-$ DCs promoted mainly effector cytokine IFN-γ production by the responding T cells whereas αEβ7$^+$ DCs enhanced immune protection by inducing the gut homing receptor CCR9 on responding T cells. These data indicated that αEβ7 can control the balance of effector vs regulatory T cell activity in the intestine. Indeed, Coombes et al. have shown that mucosal αEβ7$^+$ DC induce Foxp3$^+$ Treg by a TGF-β and retinoic acid-dependent pathway [20]. Subsequent studies confirmed that retinoic acid is centrally involved in regulating this pathway [53], and that human αEβ7$^+$ DC share this ability to induce T reg [108]. Choi et al. [18] reported that DC are dominant in normal aortic intima and, in contrast to macrophages which promote atherosclerosis, the αEβ7$^+$ DC subset was associated with protection from atherosclerosis. Weiner et al. reviewed the existing literature on oral tolerance and also concluded that αEβ7$^+$ DCs induce T regs [109].

There is also evidence that αEβ7$^+$ DC subsets can indirectly *promote* immune responses. For example, αEβ7$^+$ DC appear adept at generating gut-tropic effector CD8 T cells [43]. Recent studies provide further insight into the antigen-presenting qualities of αEβ7$^+$ dendritic cells. Bedoui et al. [6] reported that αEβ7$^+$ DCs in non-lymphoid tissues are specialized in the cross-presentation of cell-associated antigens and are essential for inducing proliferation of CD8 T cells, a finding that appears consistent with recent work in human DC [108].

7.6.6 Innate Immune Responses

McCarty et al. [66] reported that circulating Vδ2 T cells display enhanced gut-homing potential upon microbial activation and populate the human intestinal mucosa, generating functionally distinct αEβ7$^+$ and αEβ7$^-$ subsets that promoted inflammation by colonic αβ T cells. Further evidence that αEβ7 functions in innate immune responses is provided by the findings of Kinnebrew et al. [52] who reported that αEβ7$^+$ CD11b (αMβ2)$^+$ DCs in the lamina propria, in addition to promoting long-term tolerance to ingested antigens, also rapidly produce IL-23 in response to detection of flagellin in the lamina propria. Flores-Langarica et al. [28] showed that systemic flagellin immunization can induce mucosal immune responses.

7.7 Conclusions

Integrin αEβ7 has proved to be enigmatic and tantalising. Considerable efforts to define its true significance in vivo have met with mixed fortunes. Whilst this integrin undoubtedly contributes to mucosal specific retention of diverse leukocyte subpopulations there are valid grounds in the future to seek deeper significance in its signaling capacity, especially in relation to cross-talk with the epithelium. Studies of αE knockout mice have clearly identified an important role for this integrin in allograft rejection and also have provided a glimpse of its possible significance in immunoregulation. Resonance with the finding that αEβ7 is expressed by major leukocyte subsets is striking and the functional relationships between these observations provide fertile ground for further investigation. It is evident, for example, that while αEβ7 expressing mouse dendritic cells are important, the molecular function of αEβ7 in this context, and on T_{rm} in the brain, is less clear. The role of αEβ7 on similar cells in humans also invites further study. TGF-β signaling to both the αEβ7 expressing leukocyte and its target (if any), and the significance of cell surface-bound TGF-β, merit further attention. In mice, the αE integrin gene locus is sandwiched between the Th2 cytokine gene cluster (IL-4, IL-5 and IL-13) and a cluster of chemokine genes (eotaxin, TCA-3, MCP-1, 3, 5, MIP-1α and 1β, RANTES). In future studies to address the role of αEβ7 in immunoregulation it will be essential to

utilize αE null/null and control mice that are congenic at the Th2 and chemokine loci, and to use conditional knockout mice with disruption of the gene targeted to specific leukocyte subsets.

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