A Yin and Yang in Epithelial Immunology: The Roles of the $\alpha_E(CD103)\beta_7$ Integrin in T Cells

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The proper function(s) of cell-surface receptors is crucial for the regulation of adaptive immune responses. One such receptor is the $\alpha_E(CD103)\beta_7$ integrin, whose history in science is closely linked with the evolution of our knowledge of immune regulation. Initially described as a marker of intraepithelial T-lymphocytes, this leukocyte integrin is now seen as a dynamically regulated receptor involved in the functional differentiation of some cytotoxic T cells as well as regulatory T cells, thus presumably contributing to the fine-tuning of immune reactions in epithelial compartments. In this brief overview, we delineate our current view on $\alpha_E(CD103)\beta_7$ in T-cell-mediated immune responses.

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FROM RAGS TO RICHES—THE CAREER OF THE $\alpha_E(CD103)\beta_7$ INTEGRIN

Back in the late 1980s, when the $\alpha_E(CD103)\beta_7$ integrin was discovered, the picture seemed plain and simple: the antigen defined by several new monoclonal antibodies was a specific marker for intestinal intraepithelial T cells in humans, mice, and rats, presumably contributing to their tissue-specific localization (Cerf-Bensussan et al., 1986, 1987; Kilshaw and Baker, 1988). Almost three decades of research and approximately 1,000 publications later, the insight into the versatile expression pattern, putative functions, and disease associations of this fascinating molecule is ever-increasing.

Structurewise, the α_E chain is unusual among integrins, as it is the only integrin that contains a so-called X (extra)-domain (containing a post-translational cleavage site) in addition to a "thigh"-, two "calf"- and a 7-bladed "propeller" extracellular domains shared with all 18 integrin α-subunits, and the I (inserted)-domain that is present in eight others (Campbell and Humphries, 2011; Hadley and Higgins, 2014). It forms heterodimers with the β_7-subunit resulting in the complete $\alpha_E(CD103)\beta_7$ receptor (Hamann et al., 1994; Micklem et al., 1991; Shaw et al., 1994) (Figure 1a). The α_E-chain is encoded by the *ITGAE* gene and has been termed CD103, although this appellation has been extended to the complete $\alpha_E(CD103)\beta_7$ receptor. Although α_E dimerizes exclusively with β_7, the latter is somewhat more promiscuous as it can also pair with α_4 (CD49d) forming the $\alpha_4(CD49d)\beta_7$ receptor (lymphocyte Peyer's-patch adhesion molecule).

The attention focused on the $\alpha_E(CD103)\beta_7$ integrin increased considerably once its ligand, epithelial cell-expressed E-cadherin, had been identified (Cepek et al., 1994; Higgins et al., 1998; Karecla et al., 1995). Through its metal ion-dependent coordination site motif (Cepek et al., 1994), the $\alpha_E(CD103)\beta_7$ integrin binds to an E-cadherin domain distinct from the one mediating homotypic interactions (Cepek et al., 1994; Karecla et al., 1996; Taraszka et al., 2000). Indeed, $\alpha_E(CD103)\beta_7$ is the first (and only) integrin interacting with a cadherin. Tumor-infiltrating leukocytes expressing $\alpha_E(CD103)\beta_7$ adhere more firmly to autologous E-cadherin-expressing tumors under shear flow (Franciszkiewicz et al., 2013). Evidence for binding to other putative epithelial or mesenchymal ligands is indirect and candidate ligands still remain elusive (Brown et al., 1999; Jenkinson et al., 2011; Strauch et al., 2001). However, a non-epithelial ligand for $\alpha_E(CD103)\beta_7$ would provide a convenient explanation for the dominance of $CD103^+/CD4^+$ regulatory T cells (T_{reg}) in the murine dermis, as well as the high frequency of $\alpha_E(CD103)\beta_7$-expressing cytotoxic T-lymphocytes (CTLs) within the intestinal lamina propria (Braun et al., 2015; Schön et al., 1999; Suffia et al., 2005).

The $\alpha_E(CD103)\beta_7$ integrin is found on an illustrious array of preferentially epithelia-associated cells of the adaptive immune system, in particular on some $CD8^+$ CTLs and $CD4^+$ T_{reg} and resident memory T cells (T_{RM}). Of note, $\alpha_E(CD103)\beta_7$ is also expressed by some innate lymphoid cells, such as innate lymphoid cell 1 in human palatine tonsils and small intestine (Bernink et al., 2015; Fuchs et al., 2013), innate lymphoid cell 2 in murine dermis (Roediger et al., 2013), and innate lymphoid cell 3 in human amniotic fluid (Marquardt et al., 2016). Expression of $\alpha_E(CD103)\beta_7$ on mast cells has been known for more than two decades (Brown et al., 2004; Sanmugalingam et al., 2000; Smith et al., 1994; Tegoshi et al., 2005; Wright et al., 2002). Last but not least, a robust body of experimental evidence has accumulated for $\alpha_E(CD103)\beta_7$ being expressed by dendritic cell

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Abbreviations: CTL, cytotoxic T-lymphocyte; FoxP3, forkhead-box-P3; GvHD, graft-versus-host-disease; ICAM-1, intercellular adhesion molecule-1; LFA-1, lymphocyte function-associated antigen 1; TGF-β, transforming growth factor-β; T_{reg}, regulatory T cell; T_{RM}, resident memory T cell; WT, wild-type

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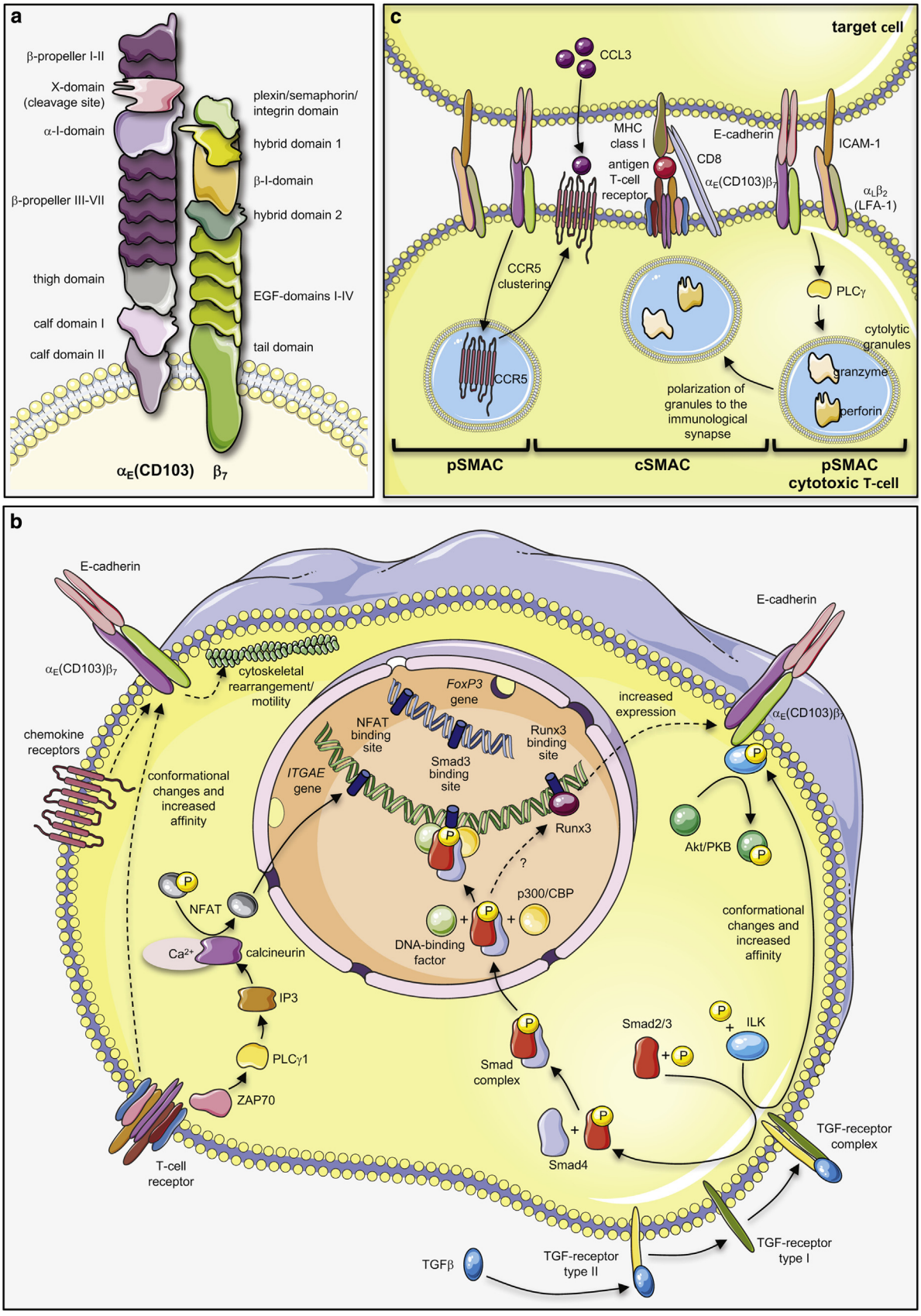

Figure 1. Structure and putative functions of the $\alpha_E(CD103)\beta_7$ integrin. (**a**) Domain structure of the $\alpha_E(CD103)\beta_7$ integrin. The propeller, calf, and thigh domains of the $\alpha_E(CD103)$ chain are shared with all known integrin α-subunits, whereas the α-I-domain is found in eight others. The X-domain containing a proteolytic cleavage site is unique to $\alpha_E(CD103)$. Intracellular signaling is primarily dependent on the tail domain of the β_7-chain, which also contains four EGF-like domains, two so-called hybrid domains separated by the β-I-domain, and a plexin/semaphorin/integrin domain. (**b**) Involvement of $\alpha_E(CD103)\beta_7$ in selected