Austin Journal of Clinical Immunology

Austin Publishing Group

Open Access Full Text Article

Editorial

Collagen-Binding Integrins in the Pathogenesis of Rheumatoid Arthritis

Mohammed-Amine El Azreq and Fawzi Aoudjit*

Department of Microbiology Immunology, LAVAL University, Canada

***Corresponding author:** Fawzi Aoudjit, Research Center CHU Quebec, T1-49 Boulevard Laurier, G1V 4G2, Quebec, Canada, Email: fawzi.aoudjit@crchul.ulaval.ca

Received: January 08 2014; Accepted: January 13 2014; Published: January 17 2014

Integrins are α/β heterodimeric cell surface receptors, which mediate cell-cell interactions and adhesion to the surrounding extracellular matrix (ECM). T cells express several ECM receptors among which the very late activating antigens (VLA-1 to VLA-6) that constitute the β1 subfamily of integrins [1-3]. Following T cell activation, these receptors coordinate T cell adhesion and migration through basement membranes and interstitial tissue to reach inflammatory and infectious sites, but can also regulate their activation [1-3]. The collagen-binding integrins VLA-1 (α1β1) and VLA-2 (α2β1) have recently gained more attention as putative regulators of T cell-mediated immunity and inflammation [1,3]. They are expressed only on effector T cells; whereas other β1 integrins such as fibronectin and laminin receptors (α4β1 and α5β1; and α3β1 and α6β1 respectively) are also found on naïve T cells. α2β1 binds preferentially collagen I, whereas α1β1 has collagen IV as a preferred ligand [4-6]. α1β1 and α2β1integrins were found in human *in vitro*-derived non polarized $CD4^+$ and $CD8^+$ effector T cells [7], as well as in $CD4^+$ and $CD8^+$ T cells isolated from virus-infected mice [8]. α2β1 integrin is expressed in Th1 but not in Th2 cells [9,10], and we showed that Th17 cells, a more recently described $CD4^+$T cell subset, express α2β1 but not α1β1 integrin [11]. TCR-activation of Th17 cells induces their attachment via α2β1 to collagen I and II, two abundant matrix proteins in the synovium, and both types of collagen co-stimulated TCR-dependent IL-17 production [11]. Both integrins costimulate TCR-dependent proliferation of non-polarized effector T cells [7] and we and others have shown that they also promote the survival of effector T cells [12-15]. We also found that α2β1 but not α1β1costimulates non-polarized effector T cells to produce IFNγ [16]. Along these lines, an earlier study has shown that collagen I (α2β1 ligand) can activate IL-2-dependent synovial T cell clones to produce IFNγ [17]. Interestingly, we found that α1β1 up-regulates the production of the osteoclastogenic cytokine receptor activator of nuclear factor kappa-B ligand (RANKL) by non-polarized effector T cells [18].

Rheumatoid arthritis (RA) is an autoimmune disorder characterized by a massive infiltration of immune cells to the joints, leading to synovitis, cartilage erosion and bone damage. RA was initially described as a Th1 disease but more recently Th17 cells have emerged as major effector T cells in RA [19]. Th17 cells have been detected in the synovium of RA patients and their frequency correlated with the severity of RA. Data from animal models also demonstrated the importance of Th17 cells in the pathogenesis of RA. IL-17 stimulates the production of inflammatory cytokines and chemokines such as IL-1, TNFα and IL-6, by macrophages, chondrocytes and fibroblast like synoviocytes (FLS) leading to the recruitment of additional Th17 cells and other inflammatory cells such as neutrophils. IL-17 also stimulates FLS and osteoblasts to produce RANKL, which is critical for the development of osteoclasts; the cells responsible for bone erosion associated with RA(Reviewed in [20]).

The first link between collagen-binding integrins and RA was provided by an early study in which Hemler's group demonstrated the expression of these molecules in T cells isolated from synovial fluids of RA patients [21]. Other studies have confirmed the expression of α1β1 integrin in RA synovial T lymphocytes, and that these cells exhibit a partially distinct repertoire of T-cell receptor (TCR), which could be potentially associated with a higher pathogenicity [22,23]. Blockade of α1β1 reduced the severity of anti-collagen-induced arthritis [24]. Although this animal model is dependent on monocytes and neutrophils rather than on T cells. Most recently, we reported that synovial Th17 cells from RA patients as well as from collagen-induced arthritic mice express high levels of α2β1 integrin [25]. Blockade of α2β1 with a blocking antibody also reduces the severity of arthritis in mice by reducing Th17 cell activity [25]. In addition, α2 integrin knock-out mice were shown to have reduced arthritis, which is associated with a reduction in FLS activation and production of metalloproteinase [26]. Together these studies suggest that α1β1 and α2β1integrins regulate tissue damage in the RA synovial microenvironment.

Further understanding of the molecular mechanisms by which these receptors regulate the pathogenesis of RA is likely to lead to the development of new therapeutic avenues in RA and other autoimmune disease.

References

1. Dustin ML, de Fougerolles AR. Reprogramming T cells: the role of extracellular matrix in coordination of T cell activation and migration. Curr Opin Immunol. 2001; 13: 286-290.
2. Hogg N, Laschinger M, Giles K, McDowall A. T-cell integrins: more than just sticking points. J Cell Sci. 2003; 116: 4695-4705.
3. Pribila JT, Quale AC, Mueller KL, Shimizu Y. Integrins and T cell-mediated immunity. Annu Rev Immunol. 2004; 22: 157-180.
4. Chan BM, Wong JG, Rao A, Hemler ME. T cell receptor-dependent, antigen-specific stimulation of a murine T cell clone induces a transient, VLA protein-mediated binding to extracellular matrix. J Immunol. 1991; 147: 398-404.
5. Heino J. The collagen receptor integrins have distinct ligand recognition and signaling functions. Matrix Biol. 2000; 19: 319-323.

Citation: El Azreq MA , Aoudjit F. Collagen-Binding Integrins in the Pathogenesis of Rheumatoid Arthritis. Austin J Clin Immunol. 2014;1(2): 1006.

6. Vandenberg P, Kern A, Ries A, Luckenbill-Edds L, Mann K. Characterization of a type IV collagen major cell binding site with affinity to the alpha 1 beta 1 and the alpha 2 beta 1 integrins. J Cell Biol. 1991; 113: 1475-1483.

7. Rao WH, Hales JM, Camp RD. Potent costimulation of effector T lymphocytes by human collagen type I. J Immunol. 2000; 165: 4935-4940.

8. Andreasen SØ, Thomsen AR, Koteliansky VE, Novobrantseva TI, Sprague AG, de Fougerolles AR, et al. Expression and functional importance of collagen-binding integrins, alpha 1 beta 1 and alpha 2 beta 1, on virus-activated T cells. J Immunol. 2003; 171: 2804-2811.

9. Goldstein I, Ben-Horin S, Li J, Bank I, Jiang HL, Chess Expression of the alpha1beta1 integrin, VLA-1, marks a distinct subset of human CD4+ memory T cells. J Clin Invest. 2003; 112: 1444-1454.

10. Sasaki K, Tsuji T, Jinushi T, Matsuzaki J, Sato TK. Chamoto, et al. Differential regulation of VLA-2 expression on Th1 and Th2 cells: a novel marker for the classification of Th subsets. Int Immunol. 2003; 15: 701-710.

11. Boisvert M, Chetoui N, Gendron S, Aoudjit F. Alpha2beta1 integrin is the major collagen-binding integrin expressed on human Th17 cells. Eur J Immunol. 2010; 40: 2710-2719.

12. Aoudjit F, Vuori K. Engagement of the alpha2beta1 integrin inhibits Fas ligand expression and activation-induced cell death in T cells in a focal adhesion kinase-dependent manner. Blood. 2000; 95: 2044-2051.

13. Gendron S, Couture J, Aoudjit F. Integrin alpha2beta1 inhibits Fas-mediated apoptosis in T lymphocytes by protein phosphatase 2A-dependent activation of the MAPK/ERK pathway. J Biol Chem. 2003; 278: 48633-48643.

14. Lin YP, CC Su, J Y Huang, HC Lin, YJ Cheng, Liu MF, et al. Aberrant integrin activation induces p38 MAPK phosphorylation resulting in suppressed Fas-mediated apoptosis in T cells: implications for rheumatoid arthritis. Mol Immunol. 2009; 46: 3328-3335.

15. Ray SJ, SN Franki, RH Pierce, S Dimitrova, V Koteliansky, Sprague AG, et al. The collagen binding alpha1beta1 integrin VLA-1 regulates CD8 T cell-mediated immune protection against heterologous influenza infection. Immunity. 2004; 20: 167-179.

16. Boisvert M, Gendron S, Chetoui N, Aoudjit F. Alpha2 beta1 integrin signaling augments T cell receptor-dependent production of interferon-gamma in human T cells. Mol Immunol. 2007; 44: 3732-3740.

17. Ofosu-Appiah W, Warrington RJ, Morgan K, Wilkins JA. Lymphocyte extracellular matrix interactions. Induction of interferon by connective tissue components. Scand J Immunol. 1989; 29: 517-525.

18. Gendron S, Boisvert M, Chetoui N, Aoudjit F. Alpha1beta1 integrin and interleukin-7 receptor up-regulate the expression of RANKL in human T cells and enhance their osteoclastogenic function. Immunology. 2008; 125: 359-369.

19. Lubberts E. IL-17/Th17 targeting: on the road to prevent chronic destructive arthritis? Cytokine. 2008; 41: 84-91.

20. Komatsu N, Takayanagi H. Autoimmune arthritis: the interface between the immune system and joints. Adv Immunol. 2012; 115: 45-71.

21. Hemler ME, Glass D, Coblyn JS, Jacobson JG. Very late activation antigens on rheumatoid synovial fluid T lymphocytes. Association with stages of T cell activation. J Clin Invest. 1986; 78: 696-702.

22. Ben-Horin S, Goldstein I, Koltakov A, Langevitz P, Ehrenfeld M, Rosenthal E, et al. The effect of blockade of tumor necrosis factor alpha on VLA-1+ T-cells in rheumatoid arthritis patients. J Clin Immunol. 2007; 27: 580-588.

23. Goldstein I, Simon AJ, Ben Horin S, Matzri S, Koltakov A, Langevitz P, et al. Synovial VLA-1+ T cells display an oligoclonal and partly distinct repertoire in rheumatoid and psoriatic arthritis. Clin Immunol. 2008; 128: 75-84.

24. De Fougerolles AR, Sprague AG, Nickerson-Nutter CL, Chi-Rosso G, Rennert PD, Gardner H, et al. Regulation of inflammation by collagen-binding integrins alpha1beta1 and alpha2beta1 in models of hypersensitivity and arthritis. J Clin Invest. 2000; 105: 721-729.

25. El Azreq MA, Boisvert M, Cesaro A, Pagé N, Loubaki L, Allaeys I, et al. α2β1 Integrin Regulates Th17 Cell Activity and Its Neutralization Decreases the Severity of Collagen-Induced Arthritis. J Immunol. 2013; 191: 5941-5950.

26. Peters MA, Wendholt D, Strietholt S, Frank S, Pundt N, Korb-Pap A, et al. The loss of α2β1 integrin suppresses joint inflammation and cartilage destruction in mouse models of rheumatoid arthritis. Arthritis Rheum. 2012; 64: 1359-1368.

Austin J Clin Immunol - Volume 1 Issue 2 - 2014
ISSN : 2381-9138 | www.austinpublishinggroup.org

Citation: El Azreq MA , Aoudjit F. Collagen-Binding Integrins in the Pathogenesis of Rheumatoid Arthritis. Austin J Clin Immunol. 2014;1(2): 1006.