

Editorial

Collagen-Binding Integrins in the Pathogenesis of Rheumatoid Arthritis

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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 $\beta 1$ 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 ($\alpha 1\beta 1$) and VLA-2 ($\alpha 2\beta 1$) 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 $\beta 1$ integrins such as fibronectin and laminin receptors ($\alpha 4\beta 1$ and $\alpha 5\beta 1$; and $\alpha 3\beta 1$ and $\alpha 6\beta 1$ respectively) are also found on naïve T cells. $\alpha 2\beta 1$ binds preferentially collagen I, whereas $\alpha 1\beta 1$ has collagen IV as a preferred ligand [4-6]. $\alpha 1\beta 1$ and $\alpha 2\beta 1$ integrins 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]. $\alpha 2\beta 1$ 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 $\alpha 2\beta 1$ but not $\alpha 1\beta 1$ integrin [11]. TCR-activation of Th17 cells induces their attachment via $\alpha 2\beta 1$ 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 $\alpha 2\beta 1$ but not $\alpha 1\beta 1$ costimulates non-polarized effector T cells to produce IFN γ [16]. Along these lines, an earlier study has shown that collagen I ($\alpha 2\beta 1$ ligand) can activate IL-2-dependent synovial T cell clones to produce IFN γ [17]. Interestingly, we found that $\alpha 1\beta 1$ 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, TNF α 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 $\alpha 1\beta 1$ 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 $\alpha 1\beta 1$ 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 $\alpha 2\beta 1$ integrin [25]. Blockade of $\alpha 2\beta 1$ with a blocking antibody also reduces the severity of arthritis in mice by reducing Th17 cell activity [25]. In addition, $\alpha 2$ 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 $\alpha 1\beta 1$ and $\alpha 2\beta 1$ integrins 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.

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