RELEVANCE OF CD4+CD57+ T CELLS TO THE ACTIVITY OF RHEUMATOID ARTHRITIS.

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Introduction

Although cellular immune response is thought to be strongly associated with initiation and exacerbation of rheumatoid arthritis (RA), it has been still unclear what type of cells play a crucial part in creating symptoms of RA. Recently it was reported that expansion of CD57+ T cells, morphologically known to be large granular lymphocytes (LGL), are often detected in RA patients. Moreover, lymphoproliferative disorder of LGL having CD3 and CD57 antigen (T-LGL leukemia) is often complicated by the symptoms of RA. These facts suggest an implication of CD57+ T cells in the etiology of RA. In this study, we examined a relationship between frequency of circulating CD3+ CD57+ cells and clinical features in RA patients. Furthermore, cytokine analysis of these CD3+CD57+ cells was performed.

Materials and Methods

Heparinized peripheral blood leukocytes (PBL) were obtained from 57 patients with RA and 15 healthy controls, whose ages ranged from 37 to 81 years (mean; 58.5 years) and 38 to 77 (mean; 55.4 years) respectively. Cell surface antigens of PBL were detected by using a FACS Calibur flow cytometer with the CELLQuest program (Becton-Dickinson). Monoclonal antibodies used were FITC-αCD5 mAb, PE-αCD4 mAb, PerCP-αCD8 mAb and APC-αCD3 mAb, and four color analysis was performed. For intracellular cytokine analysis, PBL were stimulated with PMA and calcium ionophore in the presence of GolgiStop (Becton-Dickinson), and cell surface antigens were stained with FITC-αCD5 mAb, PerCP-αCD8 mAb and APC-αCD3 mAb. After fixing and permeabilizing cells, intracellular cytokines were stained with either PE-αIFN-γ mAb or PE-αIL-4 mAb and 4 color analysis was performed.

RA patients were clinically evaluated by modified health assessment questionnaire (MHAQ), visual analog scale (for pain) and face scale (for patient mood).

Results

As has been previously reported, % of CD57+ cells among CD3+ T cells in RA patients tended to increase in RA patients (mean ± SD; 12.2 ± 11.0 %) compared with controls (mean ± SD; 8.5 ± 4.5 %). There was a significant correlation between % of CD57+ / CD3+ cells and erythrocyte sedimentation rate (ESR) (r = 0.29, p < 0.05). When CD3+ cells were subdivided into CD4+ and CD8+ cells, this correlation was found only in CD4+ subset (Fig. 1). Interestingly, % of CD4+CD57+ T cells also had a significant correlation to MHAQ score (Fig. 2), as well as visual analog scale and face scale. Again, there was no significant correlation between % of CD8+CD57+ T cells and the above mentioned clinical scores.

Flow cytometric analysis of intracellular IFN-γ and IL-4 production revealed that 14.5 % of CD3+CD57+ cells produced IFN-γ, whereas only 2.8 % of CD3+CD57+ cells produced IL-4 in RA patients. Similar results were obtained in the control group. Frequency of IFN-γ producing CD4+CD57+ cells was significantly higher than that of CD4+CD57- cells in RA patients. As to CD8 subset, this difference in the frequency of IFN-γ producing cells was not detected between CD57+ and CD57- T cells (Fig. 3).

Discussion

Previously, it has been shown that the number of CD57+ T cells in peripheral blood, bone marrow and joint fluid is higher in RA patients than in normals. Although these cells are composed mainly of CD8+ cells, the frequency of CD4+CD57+ cells were also reported to increase in RA patients. In this study, we demonstrated that % of CD4+ but not CD8+ T cells with CD57 antigen correlated significantly with ESR, MHAQ, visual analog scale, and face scale in RA patients. These CD4+CD57+ T cells were thought to be Th1 type and the frequency of IFN-γ producing CD4+ cells was revealed to be much higher in CD57+ subset compared with CD57- subset. These results suggest that CD4+CD57+ T cells play a part in exacerbating clinical symptoms of RA.

From the well established fact that the occurrence of RA has strong association with particular MHC class II molecules (DRB1-0401, -0404, -0405 etc), and there exists the RA susceptibility sequence among them, it has been speculated that some arthritogenic peptides specifically bind to these MHC molecules, causing a sequence of inflammatory reactions in RA. CD4+CD57+ T cells may contribute to aggravation of synovitis by recognizing particular arthritogenic antigens with MHC class II molecules in RA.