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Positive Correlation of RANK Expression on Human Monocytes with Age: RANK Expressed on Human Monocytes may play a Role in Senile Osteoporosis

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Abstract

Background and aim: Receptor activator of NF-κB (RANK) is a member of the TNF receptor superfamily and a receptor for the RANK ligand (RANKL). We previously demonstrated that expression levels of RANK on monocytes are positively correlated with the level of osteoclastogenesis. In this study, we examined the expression of RANK^{high} on CD14^{+} monocytes from patients with osteoarthritis patients (OA) and healthy volunteers (HV).

Methods: Peripheral blood samples were obtained from both OA and HV. To study the expression of RANK^{high} on CD14^{+} monocytes, two-colour flow cytometry was performed. Using Spearman's test, we studied the relation between the age and RANK.

Results: Expression levels of RANK on monocytes were positively correlated with the age (P=0.0027).

Conclusion: RANK expressed on human monocytes may play a crucial role in senile osteoporosis and may be a novel target for osteoporosis treatment.

Keywords: Osteoclast; Arthritis; Osteoclastogenesis; Age; Osteoporosis age-related; Senile; Aging

Introduction

We previously demonstrated that the expression of receptor activator of NF-κB ligand (RANKL) on activated T cells from rheumatoid arthritis (RA) patients is elevated [1]. Atkins et al. [2] reported that CD14^{+} receptor activator of NF-κB (RANK) high cells are included in a circulating pre-osteoclast (Oc) pool. The detection of committed pre-OC in peripheral blood is important in order to manage diseases with abnormal osteoclastic activity. C-C chemokine receptor 6 (CCR6), a surface marker of Th17 cells at 6q27, play an important role in autoimmunity in RA [3]. Th17 cells express not only CCR6 but also CCL20. CCL 20 is also detected in fibroblast-like synoviocytes (FLS) of patients with RA [4].

We previously demonstrated that: 1) the rate of expression of CD14^{+} RANK^{high} on monocytes in untreated RA patients was higher than that of treated patients (Methotrexate or Bucillamine); 2) the rate of expression of CD14^{+} RANK^{high} on monocytes was decreased after disease activity improved with disease-modifying anti-rheumatic drugs (DMARDs) in RA patients; 3) total areas of OC from peripheral blood mononuclear cells (PBMC) of HV showed the correlation with the mean fluorescence intensities (MFI) of RANK; 4) the high-level expression of RANK on CD14^{+} cells showed the correlation with that of CCR6 in HV [5].

Thus, these findings suggested that the high-level expression of RANK on human monocytes is a crucially involved in joint destruction and osteoporosis. To study the association between age and RANK, we examined the expression of RANK^{high} on CD14^{+} monocytes from patients with OA and HV in current study. The pathogenesis of senile osteoporosis has not been fully elucidated. Thus, this study may give us a new pathogenic role of senile osteoporosis and a new target for treatment of osteoporosis. Informed consent was obtained from each patients and HV involved in the study.

Methods

Study population

Ten osteoarthritis (OA) patients (age: 57-70, 2 men, 8women) and 10 healthy volunteers (HV) (age: 26-50, 4 men, 6 women) were enrolled. None of them had been taking medications such as corticosteroid. OA patients were diagnosed by knee X-ray. This study was approved by ethics committee in the Institute of Rheumatology, Tokyo Women's Medical University.

The expression of CD14^{+} RANK^{high} on monocytes

Peripheral blood samples were obtained from the OA patients and HV. To study the expression of CD14^{+} RANK^{high} on monocytes, two-color flow cytometry was performed. Cells were acquired using FACS Calibur and LSRII flow cytometers (BD Biosciences, San Jose, CA, USA). Data analysis was performed using Flow Jo software (Treestar, Asland OR USA).

Statistical analysis

Data were analysed using Spearman's test. P-values less than 0.05 was considered significant

Results

CD14^{+} RANK^{high} and age Using Spearman's test, the age and RANK were significantly correlated (P=0.0027) (Figure 1). Black circles represent OA patients. A Gray circle represents HV.

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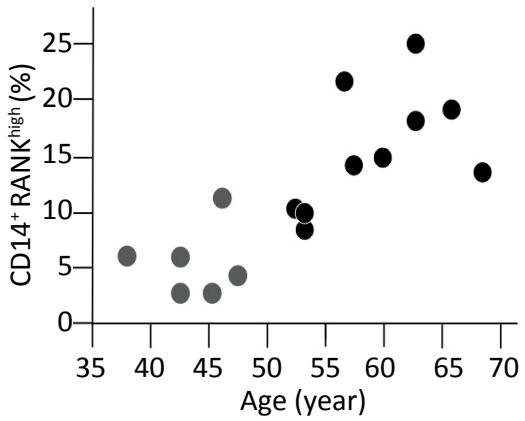

Figure 1: The association between RANK^{high} and age. Black circle represents OA patients.

Discussion

In this study, we demonstrated that the expression levels of RANK on monocytes were positively correlated with the age (P=0.0027). We previously demonstrated that the expression of RANK was diverse in each HV [5]. Surprisingly, the total areas of Oc from PBMC of HV were correlated with MFI of RANK [5].

Thus, it is suggested that the high-level expression of RANK on monocytes plays an important role in osteoporosis. Pacifici et al. [6,7] reported that monocytes per se may play an important role in osteoporosis. Thus, RANK expressed on human monocytes may play a critical role in senile osteoporosis.

The pathogenesis of osteoporosis remains to be elucidated. Many age-related factors can induce senile osteoporosis: an advanced age, decreased level of sexual hormones, dysmetabolism, consumption of bone- resorbing drugs, decreased physical activity [8] and nutritional deficits such as zinc deficiency [9]. Thus, many factors are involved in the pathogenesis of osteoporosis.

Age-related immune system remodeling could also be a pathogenetic factor for senile osteoporosis. Many cytokines, such as interleukin IL-6, IL-1, and tumour necrosis factor TNF-α, are elevated during senescence and these cytokines stimulate OC activity and lead to osteoporosis.

The mechanical unloading of bone and decline of the ovarian function with menopause also increase inflammatory cytokines that induce OC activity and catabolic signals [10,11]. Estrogens stimulate OPG production and inhibit IL-6 gene expression; thus, a decrease of estrogens leads to osteoporosis. As androgen levels decrease in men IL-6 increases.

Conclusion

The RANK-RANKL system involves both osteoclastogenesis and the immune system [12-14]. High-level expression of RANK on CD14^{+} cells, shown in a previous study, may induce osteoclastogenesis via activated T cells expressing RANKL. Thus, RANK expressed on human monocytes plays a critical role in both in joint destruction and senile osteoporosis.

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This study is preliminary report and subjects in this study are small. Thus more subjects and studies are needed to clarify the pathogenesis of senile osteoporosis.

In summary, we demonstrated a positive correlation of RANK expression on human monocytes with age. RANK expressed on human monocytes may play a role in senile osteoporosis. RANK expressed on monocytes may be a novel target for the treatment of not only joint destruction but also senile osteoporosis.

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