OVEREXPRESSION OF THE HUMAN INTERLEUKIN-1 ALPHA GENE CAUSES OSTEOPENIA IN MICE

INTRODUCTION:
The cytokine interleukin-1 (IL-1) plays an important role in inflammation. Recently we generated human IL-1 (hIL-1) alpha transgenic (Tg) mouse and reported macrophage- and neutrophil- dominant polyarthritis was induced in them. In the present study, we examined the bone density and structure of hIL-1 alpha Tg mice and wild-type (Wt) mice in order to delineate the specific effect of overexpression of hIL-1 gene upon bone metabolism.

MATERIALS AND METHODS:
The generation of hIL-1 alpha Tg mice has described previously (1, 2). Seven week old Tg mice and non-transgenic littermate Wt mice were used in this study. Mice were maintained under specific pathogen free conditions throughout experiments. Animals were maintained according to the protocol approved by the Committee on the Ethics of Animal Experiments in National Defense Medical College.

Blood samples were collected by cardiac puncture at sacrifice. The serum level of calcium (Ca), phosphate (Pi), osteocalcin and alkaline phosphate (ALP) were determined.

Histomorphometric analysis of trabecular bone was performed in an area 1.8 mm long from 0.1 mm below the growth plate at the proximal tibia metaphysis. The results were presented as mean value ± standard error of the mean (SEM).

Statistical comparisons were performed using Student’s t test for unpaired data. A value of p<0.05 was considered to be statistically significant.

RESULTS:
1. Radiographic analysis
The body size of Tg mice was smaller than that of Wt mice. Plain X-rays and µCT images (Figure 1) revealed decreased femoral bone density of in the Tg mice. In addiction, cortical thinning with an enlarged cavity was observed.

BMD of whole femora of Tg mice was decreased by 27.7% compared with Wt mice (Figure 2). The femora were divided longitudinally into 20 equal regions and the BMD of each region measured. Some regions of the femora were not significantly reduced in Tg mice.

2. Histological analysis
Histological examination of the tibiae of Tg and Wt mice revealed a reduction in cortical thickness and trabecular volume of the Tg mice. Histomorphometric analysis (Table 1) revealed a reduction of trabecular bone volume and trabecular thickness in Tg mice. Inhibition of several parameters of bone formation, including mineral apposition rate, bone formation rate, mineralizing surface and mineralized bone volume was also observed. In contrast, indices of bone resorption, including osteoclast number, resorption surface and osteoclast surface were not significantly different to Wt mice. These data suggests that decreased bone formation, especially a reduction of bone mineralization, rather than increased osteoclastic bone resorption is the prime cause of the osteopenia evident in Tg mice.

3. Biochemical analysis
Serum Ca, Pi and osteocalcin levels of Tg mice were not significantly different from those in wild type mice although the serum ALP level was lower in Tg mice compared to Wt mice.

DISCUSSION:
Our data indicated a significantly reduced BMD of whole femora of Tg mice compared with Wt mice thereby confirming that overexpression of hIL-1 alpha gene induce osteopenia.

We still have no logical explanation for our results that BMD and bone volume of Tg mice were reduced though no significant differences were observed in histomorphometric bone resorption parameters between Tg and Wt mice. It is reported that IL-1 could not directly induce osteoclast differentiation, but it could prolong the survival of osteoclasts and induce the multinucleation and pit-forming activity of them. Some factors might affect on the osteoclastogenesis in this Tg mice.

Little is known about the molecular mechanism of bone mineralization although it is apparent that ALP plays an important role. The suppression of bone mineralization might be, at least in part, a consequence of lower serum ALP present in Tg mice.

Our Tg mice showed general progressing arthritis and we regarded them to be a model mouse of general arthritis, such as rheumatoid arthritis (RA). In RA patients, the cause of general osteoporosis is still controversial. Our results are consistent with some previous reports indicating the presence of low bone turnover with reduced bone formation in non-steroid treated RA.

REFERENCE:

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