EFFECTS OF DEXAMETHASONE AND LOVASTATIN ON THE EXPRESSION OF BMP2 IN BONE MARROW STROMA CELLS CULTURED FROM PATIENTS WITH OSTEONECROSIS

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INTRODUCTION
Osteonecrosis (ON), commonly caused by high dose of steroidial anti-inflammatory drugs intake, is one of most debilitating skeletal complications. It has been reported that 1/3 of the cases of ON was associated with steroid treatment(1-2). Previous study of our Lab found that glucocorticoid shifted the properties of osteogenesis to adipogenesis in pluripotent marrow cell line from mouse. These effects may be one of the important mechanisms of the pathogenesis of ON. The lipid lowering agents, statins, prevented these steroid effects in vivo and in vitro(3-5). However, the effects of steroid and statin in human bone marrow stem cells remain unclear. We proposed that for the patients with steroid treatment, the different responses for the individual’s stroma cells to steroid are related to the susceptibility of ON development. In this study, we tested this hypothesis and investigated the effects of dexamethasone and lovastatin on the expressions of bone morphogenetic protein 2 (BMP2) in the bone marrow stroma cells cultured from osteonecrotic patients. Bone marrow stroma cell cultured from age-controlled patients of osteoarthritis (OA) or joint trauma of the hip joint were used as control.

METHODS
Bone marrow fluid aspiration from iliac crest was performed in 3 ON, 3 OA and 2 trauma patients after surgical treatment for the hip disorder. The mean age of the patients were 58.7 in ON group and 62.9 in non-ON group. Five ml of bone marrow fluid were used for percol separation and the nucleated stroma cells were used for culture. The third passage cultures were used for experiments. Drug treatment for cultures were dexamethasone (10⁻⁶ M), lovastatin (10⁻⁶ M) and dexamethasone plus lovastatin for 4 days. BMP2 mRNA expressions were evaluated by RT-PCR. Different responses to drugs between ON group and non-ON group were compared.

RESULTS
After 4 days of treatment, dexamethasone significantly suppressed BMP2 mRNA expression in stroma cells from ON patients, while there was only 20 % decreased in non-ON patients. Lovastatin significantly increased BMP2 expression, and completely reversed this suppressive effect of dexamethasone in both groups. In comparison with the drug effects on stroma cells between ON and non-ON patients, the suppressive effect of dexamethasone was more pronounced, while the reverse effect of lovastatin was less effect in ON group (Fig.1 and 2).

DISCUSSION
Previous reports indicated that 12-15% of patients, received long-term steroid treatment, developed ON. However, the well-defined mechanism of the pathogenesis of steroid-induced ON remains being investigated. Our previous studies showed that dexamethasone suppressed the osteogenic activity and promote the adipogenesis in the murine pluripotent bone marrow cell line(6,7). These effects were suggested to be an important factor to cause ON. This concept was latterly confirmed in the chicken in vivo study (8). However, these effects have not been confirmed in the human bone marrow stem cells. In this study, we confirmed the similar osteogenic effects of dexamethasone andLovastatin in human stroma cells as those in the murine pluripotent bone marrow stem cells line. More importantly, we found that the bone marrow stroma cells of ON patients have more susceptible to the suppressive effect of dexamethasone on BMP2 expression. This result suggests that the differences of the susceptibility of bone marrow stoma cells to steroid might be one of the important factors contribute to the development of steroid-induced ON. Lovastatin stimulated the osteogenesis and reversed the steroid suppressive effect in bone marrow stroma cells in non-ON cases. However, this reverse effect is mild in ON cases. These results suggest that the individuals with higher susceptibility to develop ON might be less responsive to the reverse effect of lovastatin on steroid.

Fig. 1   BMP2 mRNA expressions in bone marrow stroma cell cultures from one representative ON case and non-ON case by RT-PCR

Fig. 2   BMP 2 expressions in bone marrow stroma cell cultures of 3 ON and 5 non-ON patients detected by RT-PCR and densitometry

REFERENCES