Elevated hepatocyte growth factor levels in osteoarthritis osteoblasts contribute to their altered response to bone morphogenetic protein-2 and reduced mineralization capacity

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Résumé en anglais	PURPOSE: Clinical and in vitro studies suggest that subchondral bone sclerosis due to abnormal osteoblasts is involved in the progression of osteoarthritis (OA). Human osteoblasts isolated from sclerotic subchondral OA bone tissue show an altered phenotype, a decreased canonical Wnt/ß-catenin pathway, and a reduced mineralization in vitro as well as in vivo. These alterations were linked with an abnormal response to BMP-2. OA osteoblasts release factors such as the hepatocyte growth factor (HGF) that contribute to cartilage loss whereas chondrocytes do not express HGF. HGF can stimulate BMP-2 expression in human osteoblasts, however, the role of HGF and its effect in OA osteoblasts remains unknown. Here we investigated whether elevated endogenous HGF levels in OA osteoblasts are responsible for their altered response to BMP-2. METHODS: We prepared primary human subchondral osteoblasts using the sclerotic medial portion of the tibial plateaus of OA patients undergoing total knee arthroplasty, or from tibial plateaus of normal individuals obtained at autopsy. The expression of HGF was evaluated by qRT-PCR and the protein production by western blot analysis. HGF expression was reduced with siRNA technique whereas its activity was inhibited using the selective inhibitor PHA665752. Alkaline phosphatase activity (ALPase) and osteocalcin release were measured by substrate hydrolysis and EIA respectively. Canonical Wnt/β-catenin signaling (cWnt) was evaluated both by target gene expression using the TOPflash TCF/lef luciferase reporter assay and western blot analysis of β-catenin levels in response to Wnt3a stimulation. Mineralization in response to BMP-2 was evaluated by alizarin red staining. RESULTS: The expression of HGF was increased in OA osteoblasts compared to normal osteoblasts and was maintained during their in vitro differentiation. OA osteoblasts released more HGF than normal osteoblasts as assessed by western blot analysis. HGF stimulated the expression of TGF-β1. BMP-2 dose-dependently (1 to 100ng/ml) stimulated both ALPase and osteocalcin in normal osteoblasts whereas, it inhibited them in OA osteoblasts. HGF-siRNA treatments reversed this response in OA osteoblasts and restored the BMP-2 response. cWnt is reduced in OA osteoblasts compared to normal, and HGF-siRNA treatments increased cWnt in OA osteoblasts almost to normal. Smad1/5/8 phosphorylation in response to BMP-2, which is reduced in OA osteoblasts, was corrected when these cells were treated with PHA665752. The BMP-2-dependent mineralization of OA osteoblasts, which is also reduced compared to normal, was only partially restored by PHA665752 treatment whereas 28days treatment with HGF reduced the mineralization of normal osteoblasts. CONCLUSION: OA osteoblasts expressed more HGF than normal osteoblasts. Increased endogenous HGF production in OA osteoblasts stimulated the expression of TGF-β1 and reduced their response to BMP-2. Inhibiting HGF expression or HGF signaling restored the response to BMP-2 and Smad1/5/8 signaling. In addition, decreased HGF signaling partly corrects the abnormal mineralization of OA osteoblasts while increased HGF prevents the normal mineralization of normal osteoblasts. In summary, we hypothesize that sustained elevated HGF levels in OA osteoblasts drive their abnormal phenotype and is implicated in OA pathophysiology.
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