BONE MORPHOGENETIC PROTEIN, FIBROBLAST GROWTH FACTOR AND STANNIOCALCIN 1 EXPRESSIONS IN CARTILAGE EXPLANTS IN OSTEOARTHRITIS

ABSTRACT INTRODUCTION:

Increased gene and mRNA expressions of bone morphogenetic proteins, hBMP-4 and hBMP-2B have been identified in chondrocyte cultures derived from knee joints of patients suffering from osteoarthritis, but could not be identified in chondrocyte cultures of patients with cartilage defects in their knee joint without signs of osteoarthritis. The gene expression of hBMP-4 as well as the mRNA expression of hBMP-2B has until now been quoted in the literature as producing a vital regulatory protein in the development of the mesoderm induction of teeth, limb formation, bone induction, and fracture repair, but has never been described as participating in articular chondrogenesis. The ability of 14 human BMPs has been measured, among those, the hBMP-4 gene, to induce osteogenic transformation in a mouse pluripotent stem cell line, and hBMP-4 was capable of inducing all the typical markers for osteoblast differentiation in pluripotent as well as mesenchymal stem cells such as alkaline phosphatase, osteocalcin, and matrix mineralisation. Furthermore, Fibroblast Growth Factor, exon 3 (hFGFEX3) expression also appeared to be increased in the chondrocyte cultures from the same osteoarthritis patients. Fibroblast growth factors (hFGF1 - hFGF23) control the embryonic development as well as the adult tissue homeostasis, by binding and activating FGF receptors. Besides BMPs, FGFs are responsible for and regulating the subsequent development of most organs in the vertebrate body and are among the factors stimulating fibroblast proliferation. Finally, it was found that mRNA expression of Stanniocalcin 1 (hSTC-1) also was increased in the same osteoarthritis patients. Stanniocalcin 1 mRNA, signaling an extracellular inorganic phosphate regulator, is induced during capillary morphogenesis in 3D collagen matrices.

METHODS:

All patients consented to the use of tissue for analysis and scientific publication. Cartilage specimens (fibrocarrilage-like) were obtained from the knee joint of two patients with patellofemoral osteoarthritis, and cartilage specimens were obtained from the knee joint of two patients with femoral condyle cartilage defects, with no signs of osteoarthritis. The tissue was processed in cGMP class 100 cell culture laboratories. The explant cultures were allowed cell number expansion. The tissue culture flasks were grown to a density of approximately 70% confluence. The mRNA was isolated and subjected to Affymetrix Gene Chip arrays for gene expression analysis allowing the detection approximately of 12,600 genes/mRNAs per chip.

RESULTS SECTION:

The gene chip analysis showed increased expressions of the gene for hBMP-4 and the mRNA for hBMP-2B of the patients KM and HL, both suffering from patellofemoral hypertrophic osteoarthritis (see figure 1). The same analysis of the cells from the two patients with femoral condylar solitary cartilage defects, Outerbridge grade III – IV, but without any signs of osteoarthritis, showed no expression of these genes and messages (log value compared to the O.A. patients were ~ -1.0 to -1.4). The studies of the gene chip analyses of the same specimens showed a considerable increase in the gene expression of fibroblast growth factor, exon 3 (hFGF, exon 3) in the patients with osteoarthritis, whereas the patients with cartilage defects to their femoral condyle did not show any expression of this gene. Finally, mRNA for Stanniocalcin 1 (hSTC-1) also showed increased expression in the patients with osteoarthritis, whereas the patients with the non-ostearthritic condylar cartilage defects showed no expression of mRNA for Stanniocalcin 1 (see figure 2).

DISCUSSION:

The increased gene – and mRNA expressions identified in the patients with patellofemoral hypertrophic osteoarthritis, which is appearing as patchy, soft hypertrophic fibrocartilage with some exposure of the subchondral bone, indicates a possible involvement of bone morphogenetic proteins normally present in osteoblasts. BMPs, for example hBMP-4, are postulated to play a role in the osteoarthritic process, including the synovial thickening. This BMP is also found in periosteum. However, one of the BMPs, Osteogenic protein 1 (hBMP-7) that plays a regulatory role in enchondral ossification and in chondrogenic effect, was not expressed in any cartilage explants and no osteoarthritis showed no expression of these genes/mRNAs (log decrease value ~ -1.0 to -1.4).

Figure 1. Patients KM (blue) and HL (purple), both patients with patellofemoral osteoarthritis in their knee had increase expression of the gene for hBMP-4 and the mRNA for hBMP-2B: the two patients, MT (yellow) and IB (green) with cartilage defects on their femoral condyles and no osteoarthritis showed no expression of these genes/mRNAs (log decrease value ~ -1.0 to -1.4).

Figure 2. Patient KM (blue) and HL (purple), both patients with patellofemoral osteoarthritis in their knee had increased expression of the genes for fibroblast growth factor, exon 3 (hFGF, exon 3), and of mRNA for Stanniocalcin 1 (hSTC-1); the two patients, MT (yellow) and IB (green) with cartilage defects on their femoral condyles and no osteoarthritis showed no expression of these genes/mRNAs (log decrease value ~ 1 to 2.5).

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