Abstract

Knee osteoarthritis (OA) is a degenerative disease that causes a progressive degeneration of articular cartilage. It is one of the main causes of pain and disability that significantly affects the patients’ quality of life. Mechanical, biochemical, and genetic factors are mainly involved in OA pathogenesis.

The homeostasis of articular cartilage is mediated by a complex network of interactions mainly due to locally produced growth factors, extracellular matrix (ECM) components and circulating hormones. The current therapies for OA, mainly based on the use of intra-articular injection of hyaluronic acid (HA) associated or not to other drugs, are not effective to counteract OA progression. Nowadays the development of pharmacological treatments with the potential for structure-modifying activity in OA joint treatment has become a major focus in the field of OA research.

The aim of this study was to investigate the effects of hyaluronan amide derivative (HYADD®4-G) alone or in combination with human growth hormone (hGH) on human OA chondrocytes.

Firstly, we defined if OA cartilage express the receptors for hGH and hyaluronan (GHR and CD44) respectively. Then we isolated chondrocytes from the femoral condyles of OA patients undergoing knee arthroplasty and we treated them with different concentrations of hGH (from 0.01μg/ml to100μg/ml) with or without HYADD®4-G (1mg/ml).

Treated chondrocytes were analysed at different time points (from 24 hours to 7 days) to evaluate: phenotypical and functional characteristics: cell morphology, cell viability, cell metabolic activity, GH and CD44 receptors, typical chondrocytic markers (Collagen type 1, 2 and 10), release of factors involved in maintenance of cartilage homeostasis (IGF-1, FGF-2) or in inflammation (IL-6); and SOCS2 the negative regulator of GH.

We found that OA cartilage express an high percentage of GHR positive cells than healthy cartilage. By contrast, CD44 was express in low percentage on both OA and healthy cartilage. Different concentrations of hGH did not affected cell viability, metabolic activity, the expression of collagen type 2, 1, or 10 and did not induce the release of insulin like growth factor-1 (IGF-1) or fibroblast growth factor-2 (FGF-2). Conversely, hGH treatment increased the expression of CD44 and high concentrations of hGH induced IL-6 release.

HYADD®4-G, was able to create a favorable environment for chondrocytes by mimicking an hypoxic condition as occurs in the joint in vivo.
HYADD®4-G alone or combined with hGH modified the shape of this cells, reduced metabolic activity, IL-6 release and did not affect chondrocytic markers except SOCS2, that was increased and translocated into the nucleus, suggesting a direct cross-talk between these two molecules. Interestingly, all the parameters analyzed, except IL-6, proportionally decreased with increasing age of the patients.

In conclusion, these data demonstrated a peculiar effect of hGH and HYADD®4-G on different phenotypical and functional parameters of OA chondrocytes. hGH positively induced CD44 hyaluronan receptor, while HYADD®4-G positively induced SOCS2 involved in GH signalling pathway confirming a balancing effect among these two molecules that could be essential for the maintenance of cartilage homeostasis. Moreover, these data showed that, independently from hGH or HYADD®4-G treatment, an age-dependent effect of the markers analysed suggesting that their efficacy is not influenced by the age of OA patients.