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Nanomedicine based delivery to systems for the treatment of degenerative arthritis

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Osteoarthritis (OA) and Rheumatoid arthritis (RA) are the most common forms of joint diseases affecting over 250 million people worldwide. As with most auto-immune and inflammatory diseases, the severity of arthritis is aggregated by the activation of inflammatory responses mediated by biochemical agents such as cytokines, chemokines, prostaglandins, growth factors, proteases and nitric oxide (NO). Current treatments results in severe systemic side effects such as cardiovascular failure, kidney dysfunction, diabetes, gastrointestinal bleeding and osteoporosis. Here we demonstrate the activity of a naturally derived protein purified from cow's milk as an alternative treatment option for OA. Two different forms of the protein, metal saturated (P^{M+}) and unsaturated (P^{M-}) were used. Furthermore in order to increase efficient delivery and increase bioavailability, a novel non-toxic, biodegradable polymeric nanoformulation was utilised to encapsulate the bioactive proteins. Characterization techniques such as dynamic light scattering and scanning electron microscopy revealed particle size range to be between 180nm-220nm and have a spherical morphology. Differential scanning calorimetry demonstrated an enhanced thermal stability of protein loaded nanoparticles as compared to the void (unloaded) nanoparticles. Fourier transform infrared spectroscopy analysis confirmed the interactions of protein with nanoparticles through the enhanced chemical bonding and X-ray diffraction patterns revealed no change in the crystalline structure between protein loaded and void nanoparticles.

The cellular and molecular efficacy of these nanoparticles was examined on osteoarthritic chondrocytes (cartilage cells) to evaluate its anti-inflammatory and regenerative activity. Nanoparticles were observed to be non-toxic to cells and were able to internalise within 2 hours as determined by confocal microscopy. The non-toxicity was further confirmed with cytotoxic and apoptotic assays which showed no significant change in cell integrity even after treatment with increasing concentrations. The anti-inflammatory activity of nanoparticles, determined through various assays, showed significant inhibition of agents reported to initiated cartilage degradation and inflammation. Chondrocytes treated for 24 hours with P^{M+} nanoparticles significantly down-regulated the production of nitric oxide and prostaglandins as compared to P^{M-} and void particles. Gene expression analysed with real-time PCR revealed the down regulation of key inflammatory mediators such as matrix metalloproteinases (MMP)-1, MMP-2, MMP-3, MMP-9, MMP-13, MMP-14, MMP-15, nitric oxide synthase 2, cytokines interleukin-1β and tumour necrosis factor-α. Moreover, P^{M+} nanoparticles were able to increase expression of aggrecan and type II collagen. Protein expressions of MMP-3, MMP-9 and NOS2 were down regulated with P^{M+} treatments. Ex-vivo loop assay testing the absorbance of nanoparticles in different sections of the mouse intestine revealed an increased absorbance of P^{M-} and P^{M+} nanoparticles within 2 hours in the jejunum and ileum whereas void nanoparticles only showed a significant absorbance after 4 hours. Furthermore, P^{M-} showed an increased absorbance in the jejunum and P^{M+} within the ileum. These findings collectively demonstrate the regenerative and anti-inflammatory activity of natural bioactives loaded nanoparticles and its potential use as a nanotherapeutic for arthritis and other rheumatic related diseases.

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