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Dextran Sulfate Methotrexate Pro Drug for Treatment of Collagen-Induced Arthritis by Scavenger Receptors

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Editorial Note

Rheumatoid Arthritis (RA) is a chronic autoimmune disease that causes pain and impairment in the joints. Activated macrophages have a key role in the initiation and progression of RA. The scavenger receptor, one of several receptors overexpressed on activated macrophages, is a particular biomarker for targeted therapy of a variety of chronic inflammatory disorders, including RA. This study synthesizes and characterizes a dextran sulfate-graft-methotrexate combination that has good SR target ability in activated RAW cells. Furthermore, when compared to therapy with dextran-graft-methotrexate, increased accumulation and powerful inflammatory inhibition are detected in the afflicted joint following intravenous injection, as evidenced by histology and pro-inflammatory cytokines. Our findings point to SR-expressed activated macrophages as a possible treatment target for RA.

Nano carriers features many advantages, such as specific accumulation at the target sites, prolonged circulation kinetics, sustained release, and increased efficacy with reduced toxicity at low dose. Thus, the employment of nano scale drug delivery system may be necessary to overcome the defects of current therapeutic regimens of RA. Methotrexate (MTX) was a widely used cytotoxic agent for chemotherapy of malignancies yet now is a first-line conventional drug for RA therapy. However, severe drug resistance and multiple adverse effects of MTX have long been hampering the long-term use of this agent. Therefore, directing drugs to inflamed sites and reducing distribution in unwanted organs may readily solve these problems.

Biocompatibility test is a key preclinical evaluation of a new drug before application *in vivo*. Herein, hemolysis was conducted as an effective method frequently used for hemo compatibility evaluation. Hemolysis is a phenomenon of red blood cell analysis and hemoglobin discharge caused by varied physiochemical factors. Therefore, a drug proved to trigger hemolysis will most probably be rejected to be administrated *in vivo*. In this study, the biocompatibility of DS-g-MTX and Dex-g-MTX was detected through spectroscopy on the basis of the published work, no hemolysis was found in any groups of DS-g-MTX or Dex-g-MTX, confirming favorable biocompatibility.

Dextran Sulfate (DS) is a hydrophilic polysaccharide that selectively binds to class A of SR *via* ligand-receptor recognition. An amphiphilic block copolymer composed of DS and poly (caprolactone) (PCL, a hydrophobic block) was synthesized according to a published report. Systematic in vitro and in vivo studies demonstrated that the copolymer possessed the ability to target the activated macrophages and selectively accumulate in the affected joints of Collagen-Induced Arthritis (CIA) mice via passive and/or active targeting strategies. Therefore, DS becomes a useful ligand toward SR on the activated macrophages for targeted therapy of RA.

Histo pathological analyses of knee joints were carried out in order to assess the anti-inflammation efficiency of varied MTX formulations. Three joints of every group were analyzed for histopathology. Inflammatory cells stained blue invaded into the hyperplastic synovium, filled up the joint space, and spread on the surface of articular cartilage. The joint space became increasingly narrow, while the articular cartilage, eroded by pro-inflammatory cytokines and proteinases, was rough and thin. Comparatively speaking, there existed fewer inflammatory regions in the images of DS-g-MTX and Dex-g-MTX. Moreover, the morphology of articular cartilage remained almost integral, showing that both conjugates inhibited the recruitment of inflammatory cells. Despite the impressive capability of Dex-g-MTX in anti-inflammation, hyperplasia of synovium and a bit erosion of articular cartilage were clearly observed. As expected, the HSS and modified OARSI scores of control group were much higher than the two MTX conjugates groups. Both DS-g-MTX and Dex-g-MTX groups proved to effectively inhibit synovitis and protect articular cartilage, when DS-g-MTX showed a more remarkable effect. A certain extent of anti-inflammation function can also be detected in free MTX.

Conclusion In this work, the macrophage-targeted DS-g-MTX and untargeted Dex-g-MTX as a control were synthesized for treatment of RA. The two conjugates with precise chemical structures self-assembled into spherical micelles of around 100 nm in diameter under the physiological environment, which was suitable for passive targeting delivery into the affected joints through the EPR effect. In addition, DS-g-MTX could selectively target to the activated macrophages, which resulted from the specific recognition of DS to SR. Therefore, compared with Dex-g-MTX and free MTX, DS-g-MTX showed less cytotoxicity to normal cells, more selective biodistribution, and stronger anti-inflammation effect in the inflamed area. Furthermore, DS-g-MTX group led to significant alleviation of synovitis and protection of articular cartilage by inhibiting the expression of pro-inflammatory cytokines. Finally, the macrophage-targeted prodrug, that is, DS-g-MTX, showed great potential for targeted treatment of RA. As is widely believed, the cell-targeted polymer conjugates hold broad prospect in the targeted treatment of RA. An increasing amount of prodrugs will be developed and tested to gain excellent clinical outcome. In the future, drugs designed via nanotechnology may prevent patients from synovitis, articular cartilage, bone erosion, and even joint replacement.