Development of a therapeutic drug for hemophilic arthropathy via ferroptosis

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Introdution

Hemophilic arthropathy (HA) occurs in hemophilia patients due to repeated intra-articular hemorrhages, leading to severe joint deformities at a young age and impaired activities of daily living (ADL). Suppressing joint deformities in HA is important, but since there are no subjective symptoms such as pain and the condition is likely to progress, it is suggested that new drugs for suppressing joint deformities are needed. In this study, we investigated the involvement of ferroptosis mediated by HMOX-1 induced by intra-articular hemorrhage in HA.

Method

We identified target genes that cause HA using microarray data from a hemophilia model rat and confirmed that the ferroptosis pathway is activated immediately after intra-articular hemorrhage through enrichment analysis. We constructed an HA model in vitro by adding bovine whole blood to bovine chondrocytes using inhibitors of the identified target genes and evaluated the inhibitory effect on degeneration. In vivo, we evaluated the knee joints of mice.

Results

Microarray data showed increased expression of HMOX-1, and enrichment analysis confirmed significant enrichment of ferrotosis-related gene clusters. Cartilage degeneration was promoted by bovine whole blood loading, and the inhibitory effect of the HMOX-1 inhibitor ZnPP was demonstrated. Additionally, using a lipid peroxidation detection fluorescent reagent, an increase in lipid peroxidation reactions indicative of enhanced ferroptosis was observed following whole blood loading, and ZnPP administration was shown to suppress this reaction. In mice knee joint evaluations, intraperitoneal administration of ZnPP was confirmed to suppress knee joint swelling.

Discussion

As for future plans, we will confirm whether similar results can be obtained using ferroptosis inhibitors other than ZnPP in in vitro studies.

In in vivo studies, we will induce joint hemorrhage in F8-/- mice, which are HA model mice, by puncturing their hind limbs, and compare them with untreated mice. We will perform scRNA-seq using joint specimens from HA model mice and untreated mice.

Significance

The findings suggested that controlling ferroptosis by inhibiting HMOX-1 could be an effective treatment strategy for slowing down HA progression.