TRPV1 as an anti-ferroptotic target in osteoarthritis

Jana Riegger

Division for Biochemistry of Joint and Connective Tissue Diseases, Department of Orthopedics, University of Ulm, 89081 Ulm, Germany

eBioMedicine 2022;84: 104279
Published online xxx
https://doi.org/10.1016/j.ebiom.2022.104279

Osteoarthritis (OA) is the most common joint disease worldwide and considered as uncurable, which is mainly attributed to its complex pathophysiology, affecting the whole joint. Progressive cartilage degeneration represents the most prominent hallmark of OA. This degeneration is driven by various pathomechanisms, comprising cell death, oxidative stress, and excessive catabolism.[1,2] Because of its exceptional hypocellularity, chondrocyte death has detrimental consequences on cartilage. Various forms of programmed cell death, based on different underlying mechanisms, have been identified in OA cartilage during the last years. However, oxidative stress might play a crucial role in all forms.[1,2] In contrast to non-lytic apoptotic cell death, which is considered as a clean way to eliminate damaged cells, necroptosis and pyroptosis are highly pro-inflammatory due to membrane rupture and subsequent release of intracellular components.[2,3] Taken together, not only the fact that chondrocytes undergo programmed cell death, but also the "how", might have a decisive impact on disease progression and has thus become a hot topic in OA research.

One decade ago, Dixon et al. first proposed a new form of programmed cell death, namely iron-dependent ferroptosis, which is mainly characterized by lipid peroxidation.[4] By the interaction with reactive oxygen species, free iron can promote the formation of lipid oxidation products. The lipid repair enzyme glutathione peroxidase 4 (GPX4) requires glutathione to convert cytotoxic lipid hydroperoxides into a non-toxic form, a crucial mechanism to prevent ferroptosis. Direct inhibition of GPX4 activity or impairment of cysteine uptake and subsequent glutathione depletion results in accumulation of lipid peroxides and thus initiates ferroptosis.[5]

Despite previous reports of ferroptotic cell death in murine OA models, first evidence for iron-induced chondrocyte death in human OA was only given in 2022. Mioa et al. described iron accumulation in synovial fluid and degenerated cartilage from OA patients and confirmed concurrent reduction in GPX4 levels and enhanced ferroptosis.[6] A few months later, Lv and colleagues shed further light on the underlying mechanisms of ferroptosis in chondrocytes, as recently published in *eBioMedicine*.[7] By means of a single cell RNA sequencing on human OA cartilage, they determined the molecular signature of a ferroptotic chondrocyte cluster, which was distinguished by genes involved in oxidative stress, lipid oxidation, Fe2+ response, and ferroptosis, while markers associated with other modalities of cell death were hardly detectable. Considering the lack of distinct biomarkers or criteria to determine ferroptotic chondrocytes, this finding is of high relevance. Moreover, the authors identified transient receptor potential vanilloid 1 (TRPV1) channel as a potential anti-ferroptotic target. In fact, TRPV1 was substantially downregulated during the progression of OA as demonstrated in human cartilage and a murine injury-induced OA model. Lv and colleagues confirmed that activation of TRPV1 by capsaicin (CPS) significantly protected isolated chondrocytes from chemically induced ferroptosis in vitro, while pharmacological inhibition or siRNA-mediated silencing of TRPV1 impaired the cell protection. Intra-articular injection of CPS not only prevented chondrocyte ferroptosis but also preserved the expression of TRPV1 in injury-induced OA. The anti-ferroptotic effects were attributed to the enhanced expression of GPX4 as a downstream target of TRPV1, which was confirmed in human cartilage and the murine OA model. Interestingly, another mechanosensitive ion channel, namely Piezo 1, was previously associated with chondrocyte ferroptosis. In contrast to TRPV1, Piezo 1 activation upon mechanical overload and subsequent calcium influx increased ferroptosis, while the inhibition of the ion channel increased GPX4 expression and reduced ferroptosis.[8]

In accordance to previous reports, Lv and colleagues demonstrated that prevention of ferroptosis leads to chondroprotection, which might result from attenuated release of pro-inflammatory mediators due to reduced cell lysis, but also the upregulation of GPX4, which has additionally been described as negative regulator of the catabolic MAPK/NF-kB pathway.[6] Moreover, the authors discussed the reduced cartilage destruction and attenuated synovitis upon CPS-mediated TRPV1 activation by the potential inhibition of M1 macrophage polarization, as recently described in a rat OA model.[9]

Overall, Lv and colleagues not only underline the essential role of GPX4 in preventing ferroptosis and cartilage degeneration, but also provide a new therapeutic target to promote GPX4 expression, namely TRPV1. However, it should be considered hat TRPV1 sensitization

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2022.104258

E-mail address: jana.riegger@uni-ulm.de

was found to be involved in chronic joint pain, implying that intra-articular application of agonists might exacerbate pain in OA.[10] In view of these controversial results concerning the role of TRPV1, further studies are needed. Nevertheless, it is indisputable that programmed cell death substantially contributes to OA progression and thus represents a relevant therapeutic target. When addressing chondrocyte death, it should be kept in mind that inhibition of one mode of cell death might promote a shift towards a different, potentially more detrimental, pathway.[2] And in the end, programmed elimination of damaged chondrocytes might to some extent be beneficial regarding the maintenance of the tissue homeostasis by preventing accumulation of dysfunctional cells.

Contributor

J.R. designed and wrote the present commentary solely.

Declaration of interests

None to declare.

Acknowledgement

This work was supported by the European Social Fund and by the Ministry of Science, Research and Arts Baden-Wuerttemberg.

References

1 Riegger J, Joos H, Palm H-G, et al. Antioxidative therapy in an ex vivo human cartilage trauma-model: attenuation of trauma-induced cell loss and ECM-destructive enzymes by N-acetyl cysteine. *Osteoarthrit Cartil*. 2016;24:2171–2180.
2 Riegger J, Brenner RE. Evidence of necroptosis in osteoarthritic disease: investigation of blunt mechanical impact as possible trigger in regulated necrosis. *Cell Death Dis*. 2019;10:683.
3 Yang J, Hu S, Bian Y, et al. Targeting cell death: pyroptosis, ferroptosis, apoptosis and necroptosis in osteoarthritis. *Front Cell Dev Biol*. 2021;9:789948.
4 Dixon SJ, Lemberg KM, Lamprecht MR, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. *Cell*. 2012;149:1060–1072.
5 Yang WS, Kim KJ, Gaschler MM, et al. Peroxidation of polyunsaturated fatty acids by lipoxygenases drives ferroptosis. *Proc Natl Acad Sci U S A*. 2016;113:E4966–E4975.
6 Miao Y, Chen Y, Xue F, et al. Contribution of ferroptosis and GPX4's dual functions to osteoarthritis progression. *EBioMedicine*. 2022;76:103847.
7 Lv Z, Han J, Li J, et al. Single cell RNA-seq analysis identifies ferroptotic chondrocyte cluster and reveals TRPV1 as an anti-ferroptotic target in osteoarthritis. *eBioMedicine*. 2022. https://doi.org/10.1016/j.ebiom.2022.104258.
8 Wang S, Li W, Zhang P, et al. Mechanical overloading induces GPX4-regulated chondrocyte ferroptosis in osteoarthritis via Piezo1 channel facilitated calcium influx. *J Adv Res*. 2022.
9 Lv Z, Xu X, Sun Z, et al. TRPV1 alleviates osteoarthritis by inhibiting M1 macrophage polarization via Ca(2+)/CaMKII/Nrf2 signaling pathway. *Cell Death Dis*. 2021;12:504.
10 Kelly S, Chapman RJ, Woodhams S, et al. Increased function of pronociceptive TRPV1 at the level of the joint in a rat model of osteoarthritis pain. *Ann Rheum Dis*. 2015;74:252–259.