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RHEUMATOID ARTHRITIS

Autophagy: a dual role in the life and death of RASFs

Rheumatoid arthritis synovial fibroblasts (RASFs) are key cells in the pathogenesis of RA, in part due to the inflammatory mediators they produce. Many of these newly synthesized proteins need to be folded in the endoplasmic reticulum (ER), which can lead to ER stress. Removal of the unfolded or misfolded proteins, either by the nonlysosomal ubiquitin–proteasome pathway or by autophagy, relieves this stress and is essential for cell survival. So, autophagy can be cytoprotective, but this process can also result in autophagic cell death. What role does autophagy have in regulating the survival of RASFs? A paper in *Arthritis & Rheumatism* from Kerstin Klein and colleagues from the University Hospital Zurich, Switzerland, provides the first evidence that autophagy has both a cytoprotective and a cytodestructive role in RASFs.

RASFs and osteoarthritis synovial fibroblasts (OASFs) were obtained from synovial tissue samples of patients with RA or OA undergoing joint replacement surgery. The cells were treated with thapsigargin (an inducer of ER stress) or MG132 (a proteasome inhibitor) and levels of autophagy and cell survival were assessed.

> “...autophagy has both a cytoprotective and a cytodestructive role in RASFs...”

“Our key finding was that synovial fibroblasts derived from RA and OA patients show different susceptibilities to reagents inducing autophagy,” says Klein. “Consistent with previous data, we showed that autophagy induction by proteasome inhibition or ER stress is more pronounced in RASFs than in OASFs.”

With regard to cell survival, the authors found that more RASFs than OASFs underwent a non-apoptotic death following thapsigargin-induced ER-stress. By contrast, less RASFs than OASFs underwent apoptosis following MG132-mediated proteasome inhibition. These results suggest that autophagy has a double role in RASFs: this pathway can promote cell death in the context of ER stress but can protect against cell death in the context of proteasome inhibition.

“In contrast to the apoptosis-resistant phenotype of RASFs, we have identified a potential ‘Achilles’ heel’ of these cells by inducing autophagic cell death pathways,” explains Klein. “Future studies have to identify the endogenous signals regulating autophagy *in vivo* and will aim to further analyse the molecular pathways underlying the observed effects”.

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Original article Kato, M. *et al.* Dual role of autophagy in stress-induced cell death in rheumatoid arthritis synovial fibroblasts. *Arthritis Rheum.* doi: 10.1002/art.38190