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SPONDYLOARTHROPATHIES

Is the UPR key to removing misfolded HLA-B27 heavy chain dimers?

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Researchers have shown the endoplasmic reticulum (ER) stress pathway known as the unfolded protein response (UPR) is involved in the degradation of HLA-B27 heavy chain dimers. HLA-B27 is associated with spondyloarthritis, with as many as 95% of patients with ankylosing spondylitis being HLA-B27-positive. "Our findings," says Antony Antoniou, corresponding author of the study, "extend the role of EDEM1 and HRD1 in the degradation of misfolded proteins and confirm earlier reports that these proteins participate in MHC class I degradation."

"The hypothesis that had dominated the field of how HLA-B27 mediates disease," explains Antoniou, "[was that] HLA-B27 presenting peptides triggered an autoimmune response". However, he claims the current theory is that misfolding of the protein itself "could be a toxic event leading to activation of the UPR, which can then lead to an enhanced proinflammatory response." Therefore, his team wanted to show that modulation of the UPR can remove these dimers.

The researchers found that HLA-B27 dimers are long-lived. With overexpression and pharmacological assays in HeLa cells, they also showed that the transcription factor XBP1 and one of its targets, ER degradation-enhancing α-mannosidase-like protein 1 (EDEM1), are involved in the degradation of HLA-B27 dimers. Importantly, the researchers discovered that the ER stress pathway could be activated (by treatment with tunicamycin, thapsigargin or MG132) to remove potentially pathogenic forms of HLA-B27, thereby showing that this pathway might be therapeutically modulated in patients.

Dominique Baeten, an independent expert from the University of Amsterdam, comments "It's an interesting molecular study," but he warns that further *in vivo* studies are needed as "the hypothesis that B27 misfolding contributes to disease has only been shown in very artificial models such as cell lines and transgenic rats, and several groups have failed to detect increased ER stress or UPR in spondyloarthritis patients."

Nicholas J. Bernard

Original article Guiliano, D. B. *et al*. EDEM1 targets misfolded HLA-B27 dimers for endoplasmic reticulum associated degradation. *Arthritis Rheum*. doi:10.1002/art.38809