RHEUMATOID ARTHRITIS

Autophagy, autoantigens and autoantibodies


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In a new study, researchers link autophagy and post-translational changes (including protein carbamylation) in early rheumatoid arthritis (RA). "Our findings support the view that carbamylation represents an early trigger that precedes the appearance of RA-specific autoantibodies," explains corresponding author Maurizio Sorice.

Many autoantibodies in RA are directed against post-translationally modified protein antigens, such as the anti-citrullinated protein antibodies (ACPAs). Indeed, positivity for anti-cyclic citrullinated peptide (CCP) antibodies is a widely used diagnostic marker of RA. However, autoantibodies against proteins with other post-translational modifications, such as carbamylated proteins, have emerged in the past few years.

In a previous study, Sorice and his group implicated autophagy as a trigger of anti-CCP antibody production by linking autophagy and protein citrullination. In the new study, Sorice and colleagues sought to verify if autophagy can similarly induce protein carbamylation.

In vitro, induction of autophagy in human fibroblasts with tunicamycin (a reticulum stress inducer) or rapamycin (an activator of mTOR) resulted in carbamylation of multiple proteins, including vimentin. In a similar experiment with fibroblast-like synoviocytes, the induced levels of protein carbamylation were considerably higher in cells from patients with RA than in cells from patients with osteoarthritis.

To understand the in vivo relevance of this process, the researchers investigated cells from drug-naive patients with early active RA (who had a mean disease duration of 26 weeks). Monocytes from these patients had higher levels of carbamylated proteins than monocytes from healthy individuals; the amount of carbamylation correlated with the expression of an autophagic marker. Only 7 out of the 30 patients had detectable serum levels of anti-carbamylated protein antibodies, suggesting that this process occurs before the generation of autoantibodies.

> "Only 7 out of the 30 patients had detectable serum levels of anti-carbamylated protein antibodies"

"In a follow-up study, we will evaluate whether assessing post-translational processing of proteins, including carbamylation, represents a useful tool for evaluating the future risk of disease progression," says Sorice.

Jessica McHugh

ORIGINAL ARTICLE Manganelli, V. et al. Autophagy induces protein carbamylation in fibroblast-like synoviocytes from patients with rheumatoid arthritis. *Rheumatology (Oxford)* https://doi.org/10.1093/rheumatology/key174 (2018)

RHEUMATOID ARTHRITIS

CD82 halts synovial fibroblast motility

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A study published in *Annals of the Rheumatic Diseases* has identified a function for the tetraspanin CD82 in rheumatoid arthritis (RA). "CD82 at sites of cartilage invasion may reduce RA synovial fibroblast (RASF) motility, keeping them at the site of cartilage destruction," says corresponding author Elena Neumann.

CD82 is already well-characterized in tumour cells; by altering cell adhesion CD82 can function as a suppressor of tumour metastasis, preventing the escape of cancer cells from solid tumours. In the new study, the researchers identify a similar function of CD82 in RASFs, but with potential for very different clinical outcomes. Unlike the protective function in tumours, the tethering function of CD82 in the joints might lock RASFs into an inflammatory niche.

Consistent with previous studies, the researchers detected high expression of CD82 in the synovium of patients with RA, with specific localization at the site of inflammation and cartilage invasion and in areas of close proximity to the vasculature.

To test the function of CD82 in this niche, the researchers used either lentiviral overexpression or siRNA knockdown of *CD82* in RASFs. Results from cocultures, Boyden chamber and scratch assays show that the more CD82 is expressed by these cells, the less able they are to move around or to uncouple from cell–cell contact with a human endothelial cell monolayer.

Importantly, the paper also shows that pro-inflammatory cytokines induce surface expression of CD82 by RASFs, and that this induction mirrors the effect of CD82 overexpression on cell motility. This finding indicates a vicious cycle of inflammation driven by pro-inflammatory cytokine induction of CD82 that anchors RASFs at the site of inflammation, thus exacerbating joint destruction.

> "…CD82 in the joints might lock RASFs into an inflammatory niche."

Aside from a potential explanation for the persistence of inflammation in the joint, this finding might open the door to new targeted therapeutic strategies, and Neumann notes that it might also explain some of the therapeutic effects of existing DMARDs.

"The potential to target tetraspanins and to inhibit or modify RASF motility specifically in disease-affected joints would be a highly interesting option," she adds, "but this is a challenge due to the ubiquitous presence of fibroblasts in almost all connective tissues."

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ORIGINAL ARTICLE Neumann, E. et al. Tetraspanin CD82 affects migration, attachment and invasion of rheumatoid arthritis synovial fibroblasts. *Ann. Rheum. Dis.* https://doi.org/10.1136/annrheumdis-2018-212954 (2018)