ANTI-INFLAMMATORY EFFECTS OF YOPM IN RHEUMATOID ARTHRITIS FIBROBLAST-LIKE SYNOVIOCYTES

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Introduction Fibroblast-like synoviocytes (FLS) are key players in the pathogenesis of rheumatoid arthritis (RA). During the onset of the disease, they are transformed into an aggressive phenotype that sustains the joint-destructive inflammatory environment of RA. This transformation is most likely due to the combination of cytokines, growth factors and cellular interaction, which leads to the stable activated phenotype. YopM is the outer protein M of Yersinia species. It has cell penetrating properties and can translocate into the cell by its two N-terminal α-helices. Interestingly, YopM is capable of down-regulating inflammatory response in host tissues infected with Yersinia.

Based on these findings – self-delivering ability and anti-inflammatory properties – we investigated the effect of isolated recombinant YopM on RA-FLS.

Material and methods We analysed the uptake of YopM into RA-FLS, using Cy3-coupled YopM and laser scanning microscopy. To analyse the effect of YopM on the inflammation in RA we used RA-FLS of four patients and investigated the production of MMPs and IL-6 using ELISA. Cells were preincubated with TNF-α for 24 h and then simultaneously incubated with TNF-α and YopM or treated with YopM during TNF-α stimulation without preincubation.
To unravel the signalling pathways involved in the effects of YopM, we investigated the activation of MAP kinases (ERK, AKT and p-38) after stimulation with TNF-α, IL-1 and EGF and NFκB signalling by Western Blot analysis.

**Results** In vitro, YopM penetrates the membrane of RA-FLS, is transported via vesicular structures into the cytosole and accumulates near the nucleus. When we investigated the effects of YopM on the expression of pro-inflammatory cytokines, we found a reduced expression of IL-6 after stimulation with TNF-α and incubation with YopM as compared to controls. The expression levels of MMP1 and MMP3 were significantly reduced after stimulation of RA-FLS with TNF-α and treatment with YopM in comparison with untreated controls. This reduction was also found after preincubation of the cells with TNF-α, indicating that YopM is also able to reduce an established inflammation. We investigated the mechanisms of this effect and found no differences in MAP kinases phosphorylation, but decreased phosphorylation of IκBα after stimulation with TNF-α, indicating a reduced activation of the NFκB pathway.

**Conclusions** YopM penetrates the cell membrane of RA-FLS and reduces the inflammatory response of the cells. Therefore, it might be an effective regulator of inflammation in RA and could constitute a new therapeutic agent for the treatment of the disease.
Anti-inflammatory effects of YopM in rheumatoid arthritis fibroblast-like synoviocytes

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