A71 HISTONE DEACETYLASE INHIBITORS SUPPRESS IL-6 PRODUCTION BY RHEUMATOID ARTHRITIS FIROBLAST-LIKE SYNOVIOCYTES AND MACROPHAGES VIA MODULATION OF mRNA STABILITY RATHER THAN BLOCKADE OF NF-κB SIGNALLING

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Background and objectives Interleukin 6 (IL-6) is a key inflammatory cytokine in the pathobiology of rheumatoid arthritis (RA) and biological therapies targeting the IL-6 receptor have shown clinical benefit. The production of inflammatory cytokines is tightly regulated by reversible acetylation and deacetylation of histones and transcription factors. Histone deacetylase (HDAC) inhibitors (HDACi) are effective therapeutics in animal models of arthritis and have anti-inflammatory effects in RA synovial macrophages and tissue. Here, we examined the effects of HDACi on IL-6 production by RA FLS, and the molecular mechanisms underlying regulation of IL-6 expression by HDACi.

Materials and methods RA FLS and macrophages were treated with IL-1β, TNFα, LPS or poly (I:C) in the absence or presence of the HDACi trichostatin A (TSA). IL-6 production was measured by ELISA. The expression and stability of IL-6 mRNA was analysed by quantitative PCR. Activation of NF-κB and MAP kinase signalling pathways was assessed by immunoblotting. The nuclear translocation and DNA binding activity of NF-κB and AP-1 components was assessed by immunoblotting and ELISA-based DNA-binding assays.

Results TSA potently suppressed RA FLS IL-6 production induced by IL-1β, TNF and TLR ligands LPS and poly (I-C) ($p < 0.05$). Treatment with TSA did not modulate early signalling events occurring after IL-1β receptor triggering: phosphorylation of IκBα, as well as p38, ERK and JNK MAP kinases remained unaffected by HDACi. Furthermore, changes in activity of AP-1 components c-Jun, JunB and JunD in response to IL-1β were not modulated by TSA. While TSA also failed to affect NF-κB activity at early time points following stimulation, it induced a significant reduction in nuclear retention of NF-κB subunits p65 and p50 in FLS 24 h after IL-1β stimulation. However, TSA-mediated inactivation of NF-κB did not coincide with reduction of IL-6 mRNA accumulation, detectable 4 h following stimulation with IL-1β. IL-6 mRNA demonstrated accelerated degradation in the presence of TSA. Similar effects of TSA were observed in macrophages, indicating regulation of IL-6 mRNA stability as a common mechanism responsible for suppression of IL-6 production by HDACi.

Conclusions Inhibition of HDAC activity in RA FLS efficiently blocks the production of IL-6, and modulation of IL-6 mRNA stability is a potential mechanism underlying this regulation both in RA FLS and macrophages. Enhanced nuclear export of NF-κB mediated by HDACi might lead to suppressed

transcription of other inflammatory mediators. Our findings suggest that therapies targeting HDAC activity may be useful in suppressing inflammation in RA.