Results: Activation and inhibition of Sirt1 activity led to CD11b down-regulation and CXCRR2 up-regulation on healthy blood and BM neutrophils, suggestive of neutrophil mobilization from the BM to the periphery following treatment in vivo. Both SRT2183 and EX527 had a positive effect on clinical scores in CAIA mice. However, in EX527-treated mice the re-emergence of signs of joint inflammation was observed 14 days after cessation of treatment. Administration of SRT2183 was able to up-regulate IL-1β expression in healthy and CAIA mice, which we also observed in un-stimulated neutrophils in vitro. Iso-nicotinamide, a compound which activates sirtuins via an alternative mechanism, had a similar effect on IL-1β expression in vitro. Finally, Parp1 cleavage, a marker for cell death, was reduced in purified BM neutrophils following Sirt1 activation.

Conclusion: Sirt1 activity modulation, whether activation or inhibition, improved clinical scores in arthritis. This corresponds to the mobilization of neutrophils from the BM to the periphery. The selective increase of IL-1β following Sirt1 activation indicates that while activation or inhibition achieves a similar outcome, this is done through different molecular pathways. Our results underscore that systemic pharmacological modulation of Sirt1 activity for a complex disease, such as rheumatoid arthritis, is complicated and attention should be paid to the schedule and duration of treatment, as well as to the progressive involvement of various cell types, in order to maximize the beneficial effects.

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AB0045

MESENCHYAL STEM CELLS INHIBIT THE ACTIVATED COMPLEMENT C5 BY CLUSTERIN IN LUPUS NEPHRITIS

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Background: Dysregulation of clusterin (CLU) and over-activated complement C5 was involved in the development and progression of lupus nephritis (LN). Allo-
genetic mesenchymal stem cells (MSCs) transplantation has achieved good clini-
cal efficacy for refractory LN, however, the exact mechanisms remain to be
elucidated.

Objectives: To investigate the clinical effect of MSCs on SLE model mice (B6.
lpr), and explore the mechanisms of MSCs inhibiting the activated complement
C5 in vivo and in vitro.

Methods: 26-week-old female B6.lpr mice were randomly allocated in three
groups, which were given the following treatments, CTX (200mg/kg), MSCs (1 x
106), and an equal volume of PBS. 24 hours urine and peripheral blood were
collected periodically. All mice were sacrificed at 40 weeks of age. Urine protein
to creatinine ratio and plasma creatinine were quantified to evaluate renal disease.
Levels of C3, soluble C5b-9 (sC5b-9), CLU, and anti-dsDNA antibody were deter-
mined in the plasma by ELISA. Histopathological evaluation of renal lesions was
undertaken by HE, PAS, PASM and Masson staining under light microscopy.
Podocyte foot processes were assayed by the transmission electron microscopy.
Accumulation of immunocomplexes (IC), C3, C5b-9, and CLU were detected in
renal specimens by immunofluorescence or immunohistochemistry. Expressions
of CLU in MSCs were detected by real-time PCR and ELISA. MSCs-derived CLU
was purified and functional analysis was performed accordingly.

Results: Compared to the control mice, both proteinuria and plasma creatinine
were significantly improved in each treatment group. Plasma C3 was significantly
elevated in mice of MSCs and CTX groups. There were decline trends in plasma
levels of anti-dsDNA and SC5b-9 in treated mice when compared to the control
mice. Notably, plasma CLU was only significantly elevated in MSCs treated mice.
Pathological analysis showed that the proliferation of glomerular cells and foot
process fusion were significantly alleviated in MSCs treated mice. Immunofluores-
cence and immunohistochemistry showed that depositions of IC, C1q, C3 and
C5b-9 were significantly decreased in the MSCs group, although the expression
of CLU was obviously increased in these mice. Mechanistically, interferon-α pro-
moted the secretion of functional CLU by MSCs in vitro.

Conclusion: Allogeneic MSCs transplantation can effectively improve the clinical
outcome of lupus mice. Possible mechanisms of MSCs might be related to inhibit
the activated C5 via clusterin, which would be a potential treatment target in the
future.

REFERENCE

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