Tocilizumab (TCZ) decreases angiogenesis in Rheumatoid Arthritis through its regulatory effect on miR-146a-5p and EMMPRIN/CD147

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Background:

Angiogenesis is an important contributor to the development of Rheumatoid arthritis (RA).Tocilizumab (TCZ), an anti-IL-6 receptor antibody, is used in the treatment of RA patients, and has been shown to exert anti-inflammatory effects. However, its effects on angiogenesis are not fully elucidated, and the molecular mechanisms regulating this effect are unknown

Aim

We evaluated the concentrations of several pro- and anti-angiogenic factors and the expression levels of several microRNA molecules that are associated with RA and angiogenesis in serum samples obtained from 40 RA patients, before and 4 months after the initiation of TCZ treatment. Additionally, we used an *in vitro* co-culture system of fibroblasts (the HT1080 cell line) and monocytes (the U937 cell line) to explore the mechanisms of TCZ action.

Results

Serum samples from RA patients treated with TCZ exhibited reduced levels of EMMPRIN/CD147, enhanced expression of miR-146a-5p and miR-150-5p, and reduced angiogenesis as was manifested by the reduced number of tube-like structures formed by EaHy926 endothelial cell line. *In vitro*, the accumulation of the pro-angiogenic factors EMMRPIN, VEGF and MMP-9 in the supernatants was increased by co-culturing the HT1080 fibroblasts and the U937 monocytes, while the accumulation of the anti-angiogenic factor thrombospondin-1 (Tsp-1) and the expression levels of miR-146a-5p were reduced. Transfection of HT1080 cells with the miR-146a-5p mimic, decreased the accumulation of EMMPRIN, VEGF and MMP-9. When EMMPRIN was neutralized with a blocking antibody, supernatants derived from these co-cultures exhibited reduced migration, proliferation and tube formation in functional assays.

Conclusions

Our findings implicate miR-146a-5p in the regulation of EMMPRIN and propose that TCZ affects angiogenesis through its effects on EMMRPIN and miR-146a-5p.