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The humanized antibody h8G12 prevented arthritis through targeting both TNF-α and RANKL in DBA/1 monoarthritic mice

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Statement of the Problem: The TNF-α and RANKL are the key pathogenic factors in the onset and progression of rheumatoid arthritis (RA). TNF-α inhibitors have shown good clinical therapeutic effects of relief inflammation and joint swelling, but single application of TNF-α agents have a relatively weak protection from cartilage and bone destruction. RANKL are largely produced from inflamed synovium and cause activation of osteoclasts during the bone remodeling cycle, and an anti-RANKL antibody denosumab possesses a potential to inhibit joint destruction as well as systemic osteoporosis. The purpose of this study is to prepare humanized bispecific antibody (h8G12) targeting both TNF-α and RANKL and to evaluate its therapeutic effects on arthritis.

Methodology & Theoretical Orientation: The h8G12 was produced from co-transfected Chinese hamster ovary (CHO) cells. The identification, purification and characterization of h8G12 were detected by SDS-PAGE, Western blot and indirect ELISA. To evaluate its therapeutic effects, the monoarthritis model mice were prepared though intra-articular injection of rhTNF-α and rhRANKL.

Findings: The confluence rate of co-transfected CHO cells reached 80% at about 48 h after resuscitation. The concentration of h8G12 antibody in supernatant was kept at a steady state at 96 h after cell passaging. HE staining showed that h8G12 significantly inhibited more than 50% inflammatory cell infiltration in the joint cavity, peripheral soft tissue and bone marrow. Destruction of cartilage in h8G12-treated mice was significantly lower than that in positive control group. Interestingly, the joint structure and the thickness of articular cartilage of the mice in treated group had no significant difference with those in normal ones. The h8G12 inhibited the differentiation of osteoclasts and significantly decreased the number of osteoclast-like cells.

Conclusion & Significance: The h8G12 ameliorated inflammation and bone destruction through targeting TNF-α and RANKL. The h8G12 may be a good candidate for inflammatory bone diseases.

Biography

Wenming Zhao has focused on researching the therapeutic strategies and mechanisms in rheumatoid arthritis (RA). His major findings are biological therapies for collagen-induced arthritis (CIA) including OPG recombinant protein, RANKL-TNF homologous vaccine and humanized antibody. He also devotes to discover the mechanisms of Ahr signal pathway in joint bone destruction. This study investigated the effects of humanized antibodies h8G12 on relief of bone destruction.

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