FC11.1

NOVEL MABS TO C5AR 2ND LOOP REVERSE DISEASE IN MODELS OF INFLAMMATORY ARTHRITIS

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C5a is a potent inflammatory mediator produced during complement activation. Unregulated C5a signalling through its receptor (C5aR) on neutrophils and other leukocytes is implicated in the pathogenesis of autoimmune diseases including rheumatoid arthritis and systemic lupus erythematosus. Considerable effort has gone into development of C5aR antagonists for human therapy. We took neutrophils from genetically modified human C5aR knock-in mice in which the mouse C5aR coding region was replaced with human C5aR sequences and immunized wild-type mice to generate high affinity antagonist monoclonal antibodies (mAbs) to human C5aR. These mAbs inhibit C5a-induced neutrophil migration and calcium-flux, and bind to a region of the 2nd extracellular loop of C5aR loop that seems to be critical for receptor activity. This study investigated the effectiveness of these mAbs in the K/BxN serum-transfer model of inflammatory arthritis. Human C5aR knock-in mice were given 1-10 mg/kg mAb intraperitoneally, before or after inflammatory arthritis developed. Mice treated with anti-C5aR mAb one day before serum transfer did not develop swelling or clinical signs of arthritis in contrast to controls. Histopathology of the joints in anti-C5aR mAb-treated mice revealed a complete block of the massive influx of leukocytes and cartilage erosion seen in controls. Furthermore, and most significantly, a single 1 mg/kg dose of anti-C5aR mAb given 5 days after initiation of disease completely reversed inflammation. In the collagen-induced arthritis (CIA) model, injection of anti-C5aR mAb after development of inflammation also reversed inflammation to baseline. These potent new antibodies to human C5aR are in preclinical development.

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FC11.2

TARGETING MIF FOR INFLAMMATORY DISEASES

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The cytokine macrophage migration inhibitory factor (MIF) participates in fundamental events in innate and adaptive immunity. The profile of activities of MIF in vivo and in vitro is strongly suggestive of a role for MIF in the pathogenesis of many inflammatory diseases, including rheumatoid arthritis (RA), asthma, and sepsis. MIF also has a unique relationship with glucocorticoids, in that despite antagonizing their effects, the expression of MIF is in fact induced by glucocorticoids. Thus, MIF functions as a physiological counter-regulator of the anti-inflammatory effects of glucocorticoids. Therapeutic MIF antagonist may therefore provide a specific means of 'steroid sparing'. Since MIF are highly conserved among different species, it is hard to develop high affinity antibodies due to immune tolerance.We developed a proprietary technique to break the immune tolerance and selected high affinity mouse monoclonal antibodies against MIF.The antibody can neutralize MIF activity in cell based assays, and is very effective in a LPS induced mouse sepsis model. Using this antibody as a tool, we are studying the function of MIF in comparison with the function of LPS.We found that LPS induced iNOS expression and NO secretion are dependent on the secretion of MIF.We also found that although both LPS and MIF induce G1 arrest in macrophage cell line Raw264.7, their functions are independent to each other.

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FC11.3

SUPPRESSION OF COLLAGEN-INDUCED ARTHRITIS AND CYTOKINE PRODUCTION BY A NOVEL ORALLY-ACTIVE CYTOKINE INHIBITOR

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Macrophage migration inhibitory factor (MIF) is a pro-inflammatory cytokine involved in both innate and adaptive immune responses. MIF is expressed in human RA synovium, and genetic or mAb-induced MIF deficiency result in inhibition of animal models of arthritis. MIF has a unique tertiary protein structure which enables