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Targeting catalytic domains of gelatinase A and B using fully human antibody in the context of rheumatoid arthritis

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Statement of the Problem: Rheumatoid arthritis (RA) is an inflammatory autoimmune disorder characterized by progressive remodeling and degradation of extracellular matrix (ECM) in joint tissue leading to permanent bone deformity and loss of function. Matrix metalloproteinases (MMPs) are the major contributors to ECM degradation; elevated levels of MMPs correlate with the pathology of RA. Gelatinase A (MMP-2) is expressed by a large number of mesenchymal cells; whereas gelatinase B (MMP-9) is mainly expressed by macrophages and activated synovial fibroblasts. Studies have shown elevated MMP-2 and MMP-9 levels in synovial fluid (SF) of RA Patients. Several MMP inhibitors have been synthesized and tested in preclinical models of arthritis over the past one decade; however, no promising specific inhibitor of MMP-2 or MMP-9 has been developed so far. In the current study, we have targeted the catalytic domains of MMP-2 and MMP-9 by generating single chain variable fragment (scFv) antibodies against these domains.

Methodology & Theoretical Orientation: scFv antibodies were selected against these domains by antibody phage library based screening methods and characterized. *In vitro* assays of cell viability, proliferation, migration and collagen gel contraction assay (relevant to ECM remodeling during wound healing process) were conducted with and without antibodies using patient derived human synovial fibroblasts (HSF) and synovial fluid. Fibroblast/Cartilage co-culture experiments were done to assess the effect of antibodies on the degradation of cartilage by quantifying the amount of released glycosaminoglycans (GAGs) in culture supernatants.

Findings: Selected clone scFv M2-72, directed against MMP-2 was observed to neutralize the activity of MMPs in SF using an *in vitro* fluorogenic peptide assay. The antibody significantly inhibited the migration of HSF in response to patient derived SF in the transwell migration assay. scFv M2-72 significantly prevented cartilage degradation and further prevented collagen gel contraction and degradation. M2-72 may be a promising choice for RA treatment.

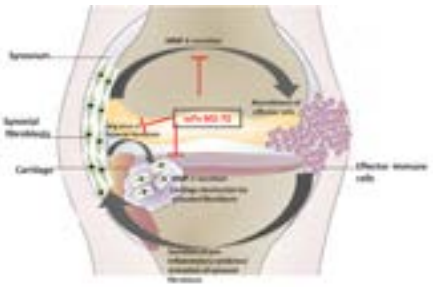

Figure 1: Targeting catalytic domains

Schematic showing the possible mode of action of scFv M2-72 mediated attenuation of various cellular processes involved in the pathology leading to RA. scFv M2-72 mediated neutralization of MMP-2 prevents recruitment of effector immune cells into synovium, thereby preventing the TNF-α, IL-β and IL-6 mediated activation of synovial fibroblasts. Reduced synovial activation leads to decreased MMP-2 expression. scFv M2-72 inhibits migration of synovial fibroblasts and prevents MMP mediated degradation of cartilage.

Recent Publications:

1. Mehta B B, Tiwari A, Sharma S, Shukla A, Sharma M, Vasishta R K, Sen R K, Sharma A and Luthra-Guptasarma M (2018) Blocking Osteopontin-Fibronectin interactions reduce extracellular fibronectin deployment and arthritic immunopathology. International Immunopharmacology 55:297-305.
2. Mehta B B, Tiwari A, Vasishta R K, Sen R K, Sharma A and Luthra-Guptasarma M (2018) Amelioration of collagen antibody induced arthritis in mice by an antibody directed against the fibronectin type III repeats of tenascin-C: Targeting fibronectin type III repeats of tenascin-C in rheumatoid arthritis. International Immunopharmacology 58:15-23.
3. Mehta J, Jandaik S, Urmila and Mehta B B (2016) Antibacterial activity and phytochemical screening of selected medicinal plants against Salmonella enterica serovars Typhimurium strains. IJBPAS 5(9):2119-2130.

Biography

Brij Bhushan Mehta pursued his PhD from the Department of Immunopathology at Post Graduate Institute of Medical Education and Research (PGIMER), India. His area of focus was to study pathogenesis of rheumatoid arthritis with project entitled "Modulation of extracellular matrix components relevant to rheumatoid arthritis". During his PhD, he also worked on tumor biology project entitled "Correlation of full length variants and truncated fragments of osteopontin and tenascin c with histopathological characteristics of breast cancer". Earlier, he worked on pathogenesis of malaria, as a Junior Research Fellow in project entitled "Identification and validation of new drug targets for selected pathogens", at Institute of Microbial Technology (C.S.I.R.), Chandigarh, India for two years during February 2009 – March 2011. He also has seven years of research experience in biological science with various areas of focus like Immunology, Cell Biology, Protein re-engineering and Biochemistry, Molecular Biology and Microbiology and this motivates him to pursue career in the field of biological sciences associated with human healthcare.

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