NEW THERAPEUTIC AVENUES IN RHEUMATOID ARTHRITIS: EXPLORING THE ROLE OF THE ADIPONECTIN-PEPITEM AXIS

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Abstracts

Introduction The inappropriate accumulation of leukocytes into the joint plays a significant role in the pathogenesis of rheumatoid arthritis (RA), making this process an ideal target for therapeutic intervention. We recently identified a novel immuno-protective pathway, in which a B-cell derived peptide (PEPITEM) suppresses T-cell migration into inflamed tissues. 

Objectives Here, we examined the functionality of the adiponectin-PEPITEM axis in patients with RA and in a murine model of arthritis.

Methods Peripheral blood lymphocytes (PBL) were isolated from healthy controls or from treatment naive patients with a new onset of clinically apparent RA. PBL were treated with adiponectin or PEPITEM, and their ability to migrate across cytokine endothelial cells was assessed using phase-contrast microscopy. Mice with collagen induced arthritis (CIA) were treated with PEPITEM prior to disease onset or at the first signs of inflammation and disease incidence, severity and leukocyte infiltration were evaluated.

Results In response to adiponectin, B-cells release PEPITEM, which limits T-cell migration across inflamed endothelium in a sphingosine-1-phosphate dependent manner. This immuno-protective pathway is lost in patients with RA, where circulating B-cells express reduced levels of adiponectin receptors compared to age-matched healthy controls, and fail to respond to adiponectin and suppress T-cell migration ex vivo. This defect can be rescued with exogenous PEPITEM. Administration of synthetic PEPITEM prior to disease onset prevents CIA, significantly reducing disease incidence, clinical score, leukocyte infiltration, and bone erosion when compared to controls. PEPITEM administered at the first signs of inflammation (therapeutic intervention) in CIA also reduced clinical score, leukocyte infiltration into the inflamed joint and bone erosion when compared to controls. Unlike the S1P agonist FY720, PEPITEM therapy did not affect leukocyte movement into and out of local draining lymph node.

Conclusions Patients with RA have a defect in adiponectin-PEPITEM axis, which potentially contributes to inappropriate accumulation of T-cells in the rheumatoid joint. Thus, re-establishing PEPITEM function to ‘turn off’ pathological recruitment of T-cells represents a novel and potentially powerful approach to treating patients with early rheumatoid arthritis.

REFERENCE

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PODOPLANIN (GP38), A MARKER OF SYNOVIAL INFLAMMATION, IS AN EXCELLENT THERAPEUTIC TARGET IN MOUSE COLLAGEN-INDUCED ARTHRITIS

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Abstracts

Introduction In patients with rheumatoid arthritis, synovial fibroblasts (SF) highly up-express the surface protein Podooplanin (PDPN) while its ligand, CLEC-2, is brought into the synovial membrane by platelets. PDNP is also up-expressed by synovial Th17 T cells from arthritic mice. Interestingly, IL-17 secretion by human Th17 T cells is triggered by direct cellular contacts with SF in a PDNP-dependent manner in vitro. PDNP is then an excellent biomarker and a potential regulator of joint inflammation. Despite these observations, in vivo experimental approaches that explore the therapeutic opportunity of targeting PDNP during the disease are missing.

Objectives We aimed at refining the understanding of PDNP expression patterns inside the mouse synovium. We explored the therapeutic benefits from an anti-PDPN antibody in mice with auto-immune arthritis.

Methods PDNP expression patterns were investigated from freshly isolated TNFa-overexpressing mouse synoviocytes by histology and FACS. The functions of PDNP expressing synoviocytes were sought by cell sorting and quantitative PCR analysis. An anti-PDPN antibody was administrated to collagen-induced arthritis (CIA) mice from day 26 post-immunisation. The CIA mouse disease activity was monitored daily until day 42 and their tissues (plasma, synovium, bones, lymph nodes) analysed by ELISA, FACS, histology, micro-CT, T cell in vitro stimulation and multiplex cytokine assays.

Results Joint inflammation triggered PDNP up-expression on a pro-inflammatory SF subset with concurrent accumulation of PDNP +anti-inflammatory macrophages. These populations disappeared with the resolution of inflammation. Anti-PDPN treated CIA mice were efficiently protected from arthritis as demonstrated by their clinical features, their reduced leucocyte and non-haematopoietic cell accumulations into the joints as well as their attenuated bone erosion and remodelling. The T cell cytokine expression profile was normal in these mice. The anti-collagen auto-antibody plasma titres were significantly reduced in the anti-PDPN treated CIA mice compare to the control group.

Conclusions We demonstrated for the first time that PDNP is expressed by pro-inflammatory and anti-inflammatory cell subsets during joint inflammation. Moreover, we are providing strong evidences that an anti-PDPN antibody restrains auto-immune arthritis in mice. This therapeutic benefit provided by the anti-PDPN antibody correlates with a reduction of circulating auto-antibody titres. This observation suggests that the anti-PDPN antibody might interfere with the micro-environment supporting B cell activation and/or plasma cell survival.