Background Local bone destruction in rheumatoid arthritis, psoriasis arthritis or ankylosing spondylitis is a serious health burden and the major cause of disability and severely reduced quality of life in these diseases. This damage to the bony structures is exclusively mediated by a special cell type, the osteoclast (OC). Therefore, it is important to understand factors and pathways regulating the generation of OCs under inflammatory conditions. As PTEN is a lipid phosphatase and one of the main antagonists of the PI3-kinase, we analysed the impact of the PI3-Kinase/PTEN axis on OC generation and bone biology in an animal model of inflammatory bone loss.

Methods We induced osteoclastogenesis in wt and PTEN deficient bone marrow cells and measured the generation of OCs, their resorptive capacity and induction of OC differentiation markers in vitro. Moreover, we analysed mice with a monocyte/macrophage-specific deletion of PTEN (myeloid specific PTEN-/-) by bone histomorphometry and crossed these mice into hTNFtg animals.

Results We show that myeloid specific PTEN-/- mice have increased osteoclastogenesis in vitro and in vivo when compared to wild-type animals. However, under non-inflammatory conditions, enhanced osteoclastogenesis did not result in systemic bone loss in vivo. However, when we crossed myeloid specific PTEN-/- into hTNFtg mice we found significantly decreased grip strength scores in myeloid specific PTEN-/-/hTNFtg mice compared to wt hTNFtg mice. Joint swelling scores, however, were not different between both groups. In line, myeloid specific PTEN-/-/hTNFtg mice displayed enhanced local bone destruction as well as OC formation in the inflamed joints, whereas the extent of synovial inflammation was not different between the groups. Analysis of the synovial membranes of wt and myeloid specific PTEN-/- animals revealed similar relative compositions of the cellular infiltrate including macrophages, which serve as OC precursors. This suggests that increased capacity for osteoclastogenic differentiation rather than enhanced recruitment of precursor cells is responsible for the enhanced local generation of OCs.

Conclusions Taken together, these data demonstrate that sustained PI3-Kinase activity in myeloid cells specifically elevated the osteoclastogenic potential of these cells, leading to enhanced inflammatory local bone destruction. Therefore, targeting the PI3-Kinase pathway therapeutically may be especially useful for the prevention of structural joint damage.

References

A9.8 LOW-DOSE IL-2 THERAPY SELECTIVELY EXPANDS REGULATORY T CELLS AND AMELIORATES ESTABLISHED DISEASE IN (NZBxNZW) F1 LUPUS MICE

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Background Our previous studies in the (NZBxNZW) F1 model provide strong rationales for an IL-2 based immunotherapy of lupus in order to restore regulatory T cell (Treg) mediated tolerance that is impaired due to an acquired IL-2 deficiency (Humrich et al., 2010). However, because of its pleiotropy, other cells than Treg can be activated by IL-2 in a dose dependent manner, which may induce unwanted side effects or even trigger autoimmunity.

Objectives To determine an optimal regimen for an IL-2 based immunotherapy that is capable to induce a sufficient expansion of CD4+Foxp3+ Treg in vivo while only marginally affecting other conventional T cells (Tcon) and other potentially harmful cells. Although higher doses of IL-2 resulted in a more pronounced proliferation and expansion of Treg, this was accompanied by a considerable increase in CD4+ memory/effector Tcon and NK/NKT cells. Clinically, regimens with both 5ng/g and 25ng/g were almost equally sufficient to influence nephritis and to decrease mortality in mice with established disease.

Conclusions These studies show that a low-dose IL-2 regimen selectively targets Treg and is clinically effective and also safe in murine lupus providing essential rationales for the clinical introduction of an IL-2 based immunotherapy in SLE.

A9.9 TREATMENT WITH BGP-15, A NOVEL INSULIN SENSITISER ATTENUATES COLLAGEN-INDUCED ARTHRITIS IN DBA/1 MICE

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Background and Objectives BGP-15, a small synthetic hydroxylamine derivative is a member of a new class of insulin-sensitising medications also known as chaperone-inducers. Beside its beneficial effects on glycemic control and insulin sensitivity in patients with Type 2 diabetes, BGP-15 is known to induce heat shock protein Hsp72 and heat shock transcription factor HSF1, which in turn are involved in joint inflammation. Moreover, BGP-15 also inhibits poly-ADP-ribose polymerase (PARP) and the phosphorylation of c-JUN N-terminal kinase via Hsp72 overexpression. Therefore it might also play a role in the regulation of inflammatory joint disease. Our objective was to evaluate the in vivo effects of BGP-15 on collagen-induced arthritis (CIA) in DBA/1 mice.

Materials and Methods Arthritis was induced by intradermal injection of bovine type II collagen (bCII) and incomplete Freund’s adjuvant (CFA) in male DBA/1 mice. BGP-15 was administered either one week prior to the first immunisation (prophylactic experiment, n:12 in both groups) or upon the appearance of symptoms (therapeutic experiment, n:12 in both groups) in drinking water. Arthritis incidence and severity was assessed for 28 days following the second immunisation (boost) with bCII and CFA on day 21. Histological evaluation was carried out on hind paws using Imagepro® software. Anticollagen antibodies were measured by enzyme-linked immunosorbent assay. The cellular composition of the draining lymph nodes was measured by flow cytometry.

Results BGP-15 significantly reduced the incidence of CIA by 28% and also reduced both paw swelling (p ≤ 0.01) and grip strength (p ≤ 0.05) in the prophylactic experiment. In the therapeutic experiment BGP-15 significantly attenuated both paw swelling (p ≤ 0.01) and grip strength (p ≤ 0.05). Histological evaluation of the hind paws demonstrated reduced area of inflammation (p ≤ 0.05), area of erosion (p ≤ 0.01) and number of osteoclasts (p ≤ 0.05) in the