PILR deficient neutrophils showed enhanced adhesion and spreading on IC compared to WT. IC adhesion-dependent H2O2 production of neutrophils was also increased in PILR -/- mice compared to WT animals.

Conclusions: PILR deficiency resulted in deteriorated renal damage in murine antibody-mediated glomerulonephritis compare to WT mice. The present study indicated that PILR negatively regulates antibody-mediated leukocyte recruitment by inhibition of m 2 integrin activation.

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IMMUNOSUPPRESSIVE TREATMENT ALTERS SECRETION OF ILEAL ANTIMICROBIAL PEPTIDES AND GUT MICROBIOTA, AND FAVORS SUBSEQUENT COLONIZATION BY UROPATHOGENIC ESCHERICHIA COLI

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Introduction: The immune system controls the gut microbiota. Transplant recipients are treated with immunosuppressive (IS) therapies which could impact host-microbial interactions. We examined the impact of IS drugs on gut microbiota and on the secretion of ileal antimicrobial peptides.

Methods: Mice were treated for 14 days with prednisolone, mycophenolate mofetil, tacrolimus, a combination of these 3 drugs, everolimus or water. Faeces were collected before and after treatment initiation. Ileal samples were collected after sacrifice. Faecal and ileal microbiota was analyzed by pyrosequencing of 16S rRNA genes, and C-type lectins were assessed in ileal tissues by RT-qPCR.

Results: Prednisolone decreased Bacteroidetes and increased Firmicutes in the faeces. While prednisolone disrupted faecal microbial community structure, no single OTU was consistently affected in experimental replicates. In ileal samples, the genus Clostridia sensu stricto was dramatically reduced in the prednisolone and combined IS drug groups. These modifications corresponded to an altered expression of C-type lectins, Reg3 and Reg3. Interestingly, the combined IS treatment enabled a commensal Escherichia coli to flourish, and dramatically increased colonization by uropathogenic E. coli strain 536.

Conclusions: IS treatment alters innate antimicrobial defenses and disrupts the gut microbiota which leads to overgrowth of indigenous E. coli and facilitates colonization by opportunistic pathogens.

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DUAL BLOCKADE OF THE HOMEOSTATIC CHEMOKINE CXCL12 AND THE PRO-INFLAMMATORY CHEMOKINE CCL2 IS AS EFFECTIVE AS CYCLOPHOSPHAMIDE IN PROLIFERATIVE LUPUS NEPHRITIS

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Introduction: Induction therapy of proliferative lupus nephritis still requires the use of unselective immunosuppressive drugs with significant toxicities. More specific drugs with equal efficacy but fewer side effects are needed. In search of suitable molecular targets we considered monocyte chemoattractant protein (MCP-1/CCL2) and stromal cell-derived factor (SDF-1/CXCL12), which both contribute to the onset and progression of proliferative lupus nephritis yet through different mechanisms. We hypothesized that dual antagonism of the homeostatic chemokine CXCL12 and the pro-inflammatory chemokine CCL2 could be as potent on lupus nephritis as the unselective and toxic immunosuppressant cyclophosphamide (CYC).

Methods: We used l-enantiomeric RNA Spiegelmer chemokine antagonists, i.e. the CCL2-specific mNOX-E36 and the CXCL12-specific NOX-A12. Female MRLlpr/lpr mice were treated (subcutaneous injection) from week 12 to 24 of age of age either with single regimen of anti-CXCL12 (13.4mg/kg) or anti-CCL2 (14.4 mg/kg) or both along with standard regimen with cyclophosphamide (CYC) (30mg/kg).

Tissues were harvested for histopathological evaluation at the end of the treatment period. Blood and urine samples were obtained at monthly intervals for the estimations of urinary albumin (ELISA: Bethyl Labs, Montgomery, TX, USA) as well as serum and urinary creatinine (Jaffé reaction: DiaSys Diagnostic Systems, Holzheim, Germany). Inflammatory gene profile was determined by RTPCR. All experiments were performed according to German animal protection laws and had been approved by the local government authorities.

Results: Dual blockade was significantly more effective than monotherapy in preventing proteinuria and BUN. Dual blockade was also more effective in controlling the histopathological indices of disease activity and chronicity. Dual blockade reduced IgG immunoglobulins, CD3+ lymphocytes and macrophages more efficiently than monotherapy. Dual blockade also reduced renal IL-6, IL-12p40, CCL5, CCL-2 and CCR2 mRNA expression. Effects of dual blockade on kidney functional parameters are at par with CYC standard regimen.

Conclusions: Dual blockade of CCL2 and CXCL12 can be as potent as CYC to suppress the progression of proliferative lupus nephritis in female MRLlpr/lpr mice probably because the respective chemokine targets mediate different disease pathomechanisms, i.e. systemic autoimmunity and peripheral tissue inflammation.

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INCREASED RECRUITMENT OF HUMAN LYMPHOCYTE SUBSETS IN RENAL FIBROSIS AND CHRONIC KIDNEY DISESASE

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Introduction: Lymphocytes occupy pivotal roles in immune-mediated kidney diseases. However the respective contributions of different lymphocyte subsets in diseased human kidneys are not certain, with previous studies limited by the methodology of immunohistochemistry to identify infiltrating cells.