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Loss of immunological tolerance as a driving force of inflammation in the NSG-UC mouse model of ulcerative colitis

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To date, no comprehensive analysis of autoantibodies in sera of patients with ulcerative colitis has been conducted. To analyze the spectrum of autoantibodies serum-IgG from UC patients and non-UC donors were screened by using a human protein microarray. Screening yielded a remarkable number of 697 differentially reactive antigens, most of which are expressed on immune cells suggesting a general lack of tolerance in a subgroup of UC patients. From this analysis, CD99 emerged as a biomarker to discriminate between non-UC and UC patients. *In vitro*, incubation with CD99 induced the frequencies of CCR4 expressing CD4+ cells (effector memory regulatory T cells) and TSLPR expressing CD11b+ macrophages and CD14+ monocytes in peripheral blood mononuclear cells (PBMC), indicating an anti-inflammatory response. In vivo, challenge with CD99 aggravated disease symptoms and pathological phenotype in NOD-scid IL2Rγ^{null} (NSG) mice reconstituted with PBMC from UC donors and challenged with ethanol (NSG-UC) indicating failure to induce tolerance in this mouse model. Treatment with sirolimus, which is known to promote Treg suppressed inflammation as indicated by decreased clinical and histological scores and IFNγ mRNA levels and increased frequencies of effector memory regulatory T-cells. In contrast, treatment with an anti-CCR4 antibody resulted in depletion of CCR4 expressing CD4+ T-cells and aggravated inflammation. Thus, autoimmunity seems to be a driving force in the NSG-UC mouse model. Future studies have to show whether this also applies to the human disease and whether shifting the immunological equilibrium towards tolerance might be a promising therapeutic alternative.

Biography

Roswitha Gropp has over 25 years of experience in preclinical development and inflammatory diseases. She recently took on a different view considering the inflammatory process in UC as an uncontrolled wound healing process. This hypothesis assumes that epithelial damage induces the release of signals to evoke a Th2 characterized inflammatory response that ultimately results in repair of the colon. Using agent based modeling first disease maps were developed to describe the inflammatory milieu and the dynamics of the inflammatory response. This approach together with immunological profiling of patients allows for a better understanding of underlying mechanisms ultimately leading to individualized therapies.

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