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Identification of an impaired adenosinergic lymphocytic phenotype in ANCA-associated vasculitis patients mediated by downregulation of miRNA-31

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ANCA-associated vasculitides are autoimmune diseases causing vascular damage of predominantly small vessels. They are characterized by anti-neutrophil cytoplasmic autoantibodies and pauci-immune vascular inflammation. Clinical observations and previous studies demonstrated lymphocytes were crucially involved in the pathogenesis of ANCA-associated vasculitides. Experimental data showed purinergic signaling had tremendous effects on lymphocytes and the immune response. Adenosine triphosphate exerts pro-inflammatory influence, e.g. by differentiating naïve T cells into pro-inflammatory ones and induction of pro-inflammatory cytokines. On the contrary, anti-inflammatory effects like inhibition of T cell activation and proliferation are characteristic for adenosine. It is known purinergic signals not only depend on purine receptors, but also on expression of ectonucleotidases CD39 and CD73 besides CD26 binding adenosine deaminase which all control concentrations of adenine nucleotides and adenosine. However, the adenosine generating system has not been studied in ANCA-associated vasculitis so far. We hypothesized lymphocytes from patients with ANCA-associated vasculitis show a reduced adenosine generating capacity caused by altered expression of CD39, CD73, and CD26.

Our study identified a new lymphocytic phenotype in patients diagnosed with ANCA-associated vasculitis characterized by reduced CD39 and CD73 frequency, and enhanced CD26 expression, respectively. This phenotype indicates an impediment of lymphocytic adenosine production, since adenosine generating enzymes CD39 and CD73 were reduced and adenosine degrading CD26 was increased. This impaired adenosinergic lymphocytic phenotype was present in both the CD4+ and the CD4- faction of peripheral blood lymphoid cells. Impairment of adenosine generation by lymphocytes was most evident in the CD4- group with the CD4- CD45RA+ CD25+ subset particularly deviant in AAV patients. Our data indicate this phenotype is an intrinsic, immanent characteristic of disturbed adaptive immunity in ANCA-associated vasculitis, since it was independent from disease duration, time in remission, relapse rate, disease activity, and autoimmune serology. By contrast, the impaired adenosinergic lymphocytic phenotype was associated with clinical manifestations of ANCA-associated vasculitis like inflammatory state and renal function supporting the idea of this phenotype to be involved in the pathogenesis of ANCA-associated vasculitis.

Results of micro ribonucleic acid quantification enabled us to identify a posttranslational mechanism that is most likely responsible for the impairment of adenosine producing capacity in ANCA-associated vasculitis. We provided evidence for the first time, downregulation of micro ribonucleic acid-31 in patients potentially causes inhibition of CD73 transcription enhancing hypoxia inducible factor-1α, leading to decreased CD73 expression in lymphocytes. Hence, CD73 is highlighted by our study to be pivotal for anti-inflammatory processes relying on adenosinergic signaling, since it is indispensable for adenosine generation from adenine nucleotides. This is in consistence with the literature describing extracellular adenosine as anti-inflammatory mediator inhibiting T cell driven inflammation. Thus, the impaired adenosinergic lymphocytic phenotype also is in line with other studies reporting pro-inflammatory T cell subsets in ANCA-associated vasculitis. In conclusion, our study highlights the potency of adenosine shaping the immune system and generated a new clue not only to the pathogenesis, but also indicators for future therapy options of ANCA-associated vasculitides.