UKE Paper of the Month Oktober 2021

CD73-mediated adenosine production by T cell-derived extracellular vesicles constitutes an intrinsic mechanism of immune suppression

Enja Schneider*, Riekje Winzer*, Anne Rissiek, Isabell Ricklefs, Catherine Meyer-Schwesinger, Franz L. Ricklefs, Andreas Bauche, Jochen Behrends, Rudolph Reimer, Santra Brenna, Hauke Wasielewski, Melchior Lauten, Björn Rissiek, Berta Puig, Filippo Cortesi, Tim Magnus, Ralf Fliegert, Christa E. Müller, Nicola Gagliani & Eva Tolosa

Nature Communications, 2021; 12: 5911

ABSTRACT:
Immune cells at sites of inflammation are continuously activated by local antigens and cytokines, and regulatory mechanisms must be enacted to control inflammation. The stepwise hydrolysis of extracellular ATP by ectonucleotidases CD39 and CD73 generates adenosine, a potent immune suppressor. Here we report that human effector CD8 T cells contribute to adenosine production by releasing CD73-containing extracellular vesicles upon activation. These extracellular vesicles have AMPase activity, and the resulting adenosine mediates immune suppression independently of regulatory T cells. In addition, we show that extracellular vesicles isolated from the synovial fluid of patients with juvenile idiopathic arthritis contribute to T cell suppression in a CD73-dependent manner. Our results suggest that the generation of adenosine upon T cell activation is an intrinsic mechanism of human effector T cells that complements regulatory T cell-mediated suppression in the inflamed tissue. Finally, our data underscore the role of immune cell-derived extracellular vesicles in the control of immune responses.

STATEMENT:
Suppression of effector T cells is essential to prevent excessive damage of healthy tissue during an immune response, and regulatory T cells are crucially involved in this process. Our work opens a new view on the role of effector T cells in immune suppression. We show that activated CD8 T cells release extracellular vesicles containing CD73. These CD8 T cell-derived extracellular vesicles generate immunosuppressive adenosine, thereby constituting a T cell-intrinsic mechanism of immune suppression. The clinical relevance of the findings was proven in human autoimmunity, namely in samples obtained from the inflamed joints of patients with juvenile idiopathic arthritis. This paper results from the cooperation of several research laboratories at the UKE (Immunology, Internal Medicine, Biochemistry, Stroke Research and Neurosurgery), and highlights the tight collaborations established within the research consortium SFB 1328 "Adenine nucleotides in immunity and inflammation".

BACKGROUND:
This work was performed at the Institute of Immunology in the group of Prof. Eva Tolosa and is part of the PhD theses of Enja Schneider and Riekje Winzer, who share first authorship. The working group has a strong research interest in immune regulation with a focus on T cells and purinergic signaling. The project was supported by the German Research Council (SFB1328, FOR2879), the Hamburg State Excellence Research Program, the Werner Otto Foundation, the UKE intramural programs "FFM" and "Close the Gap", and the University of Hamburg (stipend to Enja Schneider).