

Traffic cops of the immune system: Molecule called IKBNS in charge of regulatory immune cell maturation

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A certain type of immune cell—the regulatory T cell, or Treg for short—is in charge of putting on the brakes on the immune response. In a way, this cell type might be considered the immune system's traffic cops.

Now, scientists at the Helmholtz Centre for Infection Research (HZI) have looked into the origin of Tregs and uncovered a central role played by the protein IkBNS. Armed with this knowledge, the researchers hope to manipulate Tregs in order to either inhibit or activate the <u>immune</u> system. Biochemist Prof. Ingo Schmitz and his team have now published their findings in the scientific journal *Immunity*.

The immune system is a complex network of different types of cells and chemical messengers. The regulatory cells and other immune cells exist together in a delicate balance. Any disturbance of this balance could have serious consequences: If there are too many Tregs, the immune system might be "thwarted" and little would stand in the way of infections or tumors spreading throughout the body. By contrast, if there are too few Tregs, other immune cells could get out of control and attack the body's own tissues: autoimmune diseases like rheumatoid arthritis or the chronic inflammatory bowel disease ulcerative colitis may be a consequence. Tregs also play an important role following an organ transplant as they decide whether the body will accept or reject the donor organ.



But what it is exactly that makes immature <u>immune cells</u> choose the "police officer career" had eluded scientists. Schmitz and his team from the HZI, the Otto von Guericke University Magdeburg, the Charité Universitätsmedizin Berlin, the Harvard Medical School Boston, the TWINCORE in Hanover, the Eberhard Karls University Tübingen and the Heinrich Heine University Düsseldorf were now able to demonstrate that the transcription factor IkBNS contributes considerably to Treg development. The molecule promotes formation of the protein Foxp3, the Tregs' central feature. IkBNS influences the large NFkB family of transcription factors. These signaling molecules trigger a number of different inflammatory responses elicited by the immune system. "It was therefore all the more surprising for us when we identified IkBNS' central role in Treg maturation. Essentially, these are cells capable of constraining inflammation – even though IkBNS in no way influences the function of regulatory T cells," explains Dr. Marc Schuster, one of Schmitz' colleagues at HZI and the article's first author. The researchers tested their hypothesis regarding IkBNS' central role in Treg development in mice that are missing this factor. Since cells that lack IkBNS do not "become cops," the immune system's effector cells are undamped and could trigger chronic inflammation of the intestine.

The results have confirmed that further research on IkBNS is of interest from a medical perspective as well. On the one hand, it allows predicting diseases: If IkBNS is fraught with errors, this could trigger autoimmune disorders. On the other hand, one potential therapeutic goal might be "to manipulate IkBNS in such a way that we can control the number of Tregs," explains Schmitz, who, in addition to his HZI research, also has a chair at the Otto von Guericke University Magdeburg. "IkBNS stabilization could benefit autoimmune disease therapy. As far as infections or tumors are concerned, we would need to inhibit IkBNS to decrease the number of regulatory T cells. Of course, all that is still in the very distant future." But because IkBNS also plays an important role in effector cell activation, an intervention might have unforeseen



consequences. "This is a challenge you face with many different therapeutic targets," adds Schmitz.

More information: Marc Schuster, Rainer Glauben, Carlos Plaza-Sirvent, Lisa Schreiber, Michaela Annemann, Stefan Floess, Anja A. Kühl, Linda K. Clayton, Tim Sparwasser, Klaus Schulze-Osthoff, Klaus Pfeffer, Jochen Huehn, Britta Siegmund, Ingo Schmitz The atypical NFkB inhibitor IkBNS mediates regulatory T cell development by regulating Foxp3 induction, *Immunity*, 2012

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