Two distinct molecular pathways can make regulatory immune cells

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Finding a way to bypass the molecular events involved in autoimmunity - where the body's immune system mounts a self-directed attack - could lead to new treatments for autoimmune disorders and chronic infections. A study published in this week's issue of *PLoS Biology* describes genetic evidence that two distinct molecular pathways control the formation of regulatory T cells (Treg), a cell type vitally important in limiting undesirable immune responses.

Treg cells are like the peace-keepers of the immune defence system - they limit the actions of effector T cells, the foot-soldiers of the body. If the body lacks sufficient numbers of Treg cells, it loses the ability to tone down immune responses once invading pathogens are cleared. In addition, the body is unable to suppress T cell responses that recognize and target the body itself. The latter can lead to autoimmunity, which can destroy vital tissues and organs.

Under normal healthy conditions, the majority of Treg cells are derived from an organ called the thymus. New work from researchers at Cincinnati Children's Hospital Medical Center and The Scripps Research Institute in California, shows that if a gene called Carma1 isn't expressed normally, Treg development is impaired in the thymus. Mutations in Carma1 can result in a failure of the thymus to produce Treg cells, said senior investigator Kasper Hoebe, Ph.D., a researcher at Cincinnati.

But the study also points to a second molecular pathway - occurring in the peripheral lymphoid system - that is known to result in development

of Treg cells. This means if the process in the thymus breaks down, as in the case with Carma1 mutations, Treg cells created in the peripheral lymphoid system can compensate.

"We show that the two pathways for Treg development are molecularly distinct, and Treg can arise quite well in the peripheral lymphoid system, via mechanisms that are independent of the thymic process," Dr. Hoebe said. "This is important because it shows the flexibility of the immune system to regulate T cell responses. If we understand the molecular requirements of these pathways we can potentially use these as targets for therapeutic intervention - which is the eventual goal."

Possible therapies may include the ability to repress the self-destructive immune response in autoimmune disease by increasing Treg development, or achieving the opposite effect to treat chronic infectious diseases - inhibiting Treg development and promoting activation of destructive T cells.

More information: Barnes MJ, Krebs P, Harris N, Eidenschenk C, Gonzalez-Quintial R, et al. (2009) Commitment to the regulatory T cell lineage requires CARMA1 in the thymus but not in the periphery. PLoS Biol 7(3): e1000051. doi:10.1371/journal.pbio.1000051, biology.plosjournals.org/perls … journal.pbio.1000051

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