Research suggests origins of key cells in the thymus

May 31 2013

Medullary thymic epithelial cells (mTECs) allow the thymus to ensure that the body's T cells are able to distinguish between potentially harmful foreign antigens and those that are produced by the body itself. A Swiss-Japanese research team suggests that mTECs do not share a common progenitor with cortical-thymic TECs (cTECs) that produce T cells, but may actually evolve from them.

T-lymphocytes, or T cells, are a principal component of the body's adaptive immune system. Together, these cells express a large repertoire of antigen specific receptors that recognise foreign material derived, for example, from pathogens and tumour cells. The generation of these antigen receptors occurs during T cell development in the thymus. This constitutes, however, a random process that also includes the formation of antigen receptors which respond well to the body's own proteins, so-called self-antigens. To prevent T cells bearing a self-reactive antigen receptor to exit from the thymus to the rest of the body where they may cause autoimmunity, a mechanism is in place that involves mTECs. These specialised thymic epithelial cells express most of the body's self-antigens. T cells that recognise their specific antigen presented by mTECs will undergo a process of programmed cell death and are consequently deleted in the thymus.

Cross-country partnership

Very little is presently known about how cTECs and mTECs develop, or

how they relate to each other. A Swiss-Japanese research team now reports that mTECs derive from cells that already express β5t, a proteasome subunit that is densely concentrated in cTECs and no other cell types, including mTECs themselves. This finding, which is published in the May 27-30, 2013 edition of *PNAS*, suggests that mTECs may evolve from cTECs. This finding has not only implications for how mTECs develop, but also how they may have evolved.

The research project was led in Switzerland by Prof. Georg Holländer, Professor of Paediatric Immunology at the University of Basel and Action Research Professor of Paediatrics at the University of Oxford. In Japan, the project was led by Prof. Yousuke Takahama of the Institute for Genome Research at the University of Tokushima, which initially discovered the β5t proteasome subunit. Dr. Izumi Ohigashi of the Institute for Genome Research at the University of Tokushima and Dr. Saulius Zuklys at the University Children's Hospital of Basel serve as first authors.

Broad potential

Professor Holländer believes that the benefits of a better understanding of the origins and functions of mTECs and cTECs extend well beyond basic research. The team's findings suggest that evolutionary pressures have caused the body to check the quality of T cells that it produces. The T cell antigen receptor repertoire in evolutionary older species have a receptor, and did not require the body to implement quality control – but as the capacity developed to produce a seemingly infinite number of T cell antigen receptors the vital need to control their specificities has arisen. For this purpose the body may have "hijacked" existing cells, namely cTECs. Holländer also believes that the findings could inform attempts to reconstruct or develop in-vitro thymuses, which could in turn be used to help people who lack a normal thymus function because of inborn or acquired defects. "You can fix things if you know how they

are formed in the first place," he claims.

More information: Ohigashi, I. et al. Aire-expressing thymic medullary epithelial cells originate from β5t-expressing progenitor cells. *Proceedings of the National Academy of Sciences*, May 27-May 31, 2013. doi:10.1073/pnas.1301799110

Provided by University of Basel