Cell competition in the thymus is crucial in a healthy organism

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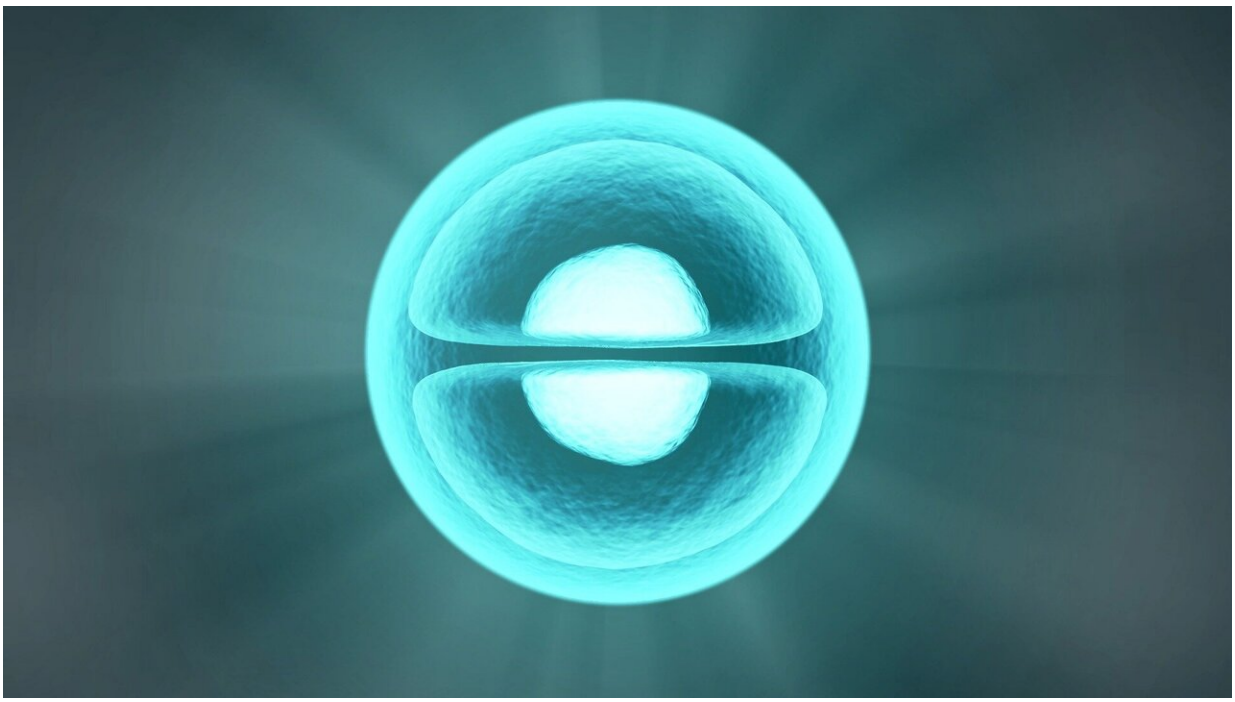

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T lymphocyte cells develop in the thymus. They are essential for fighting infections and preventing cancer. The thymus is located just above the heart. It is large in children and gradually reduces in size with age. In the thymus, T lymphocytes develop from progenitor cells, which originate in the bone marrow and travel to the thymus through the bloodstream. This is a continuous process in which cells enter the thymus, proliferate and

develop into T lymphocytes. In the end, these cells leave the thymus to scout and defend the body.

The development of T lymphocytes is a tightly regulated process. However, these cells can also accumulate errors and cause cancer. Blood cell cancers, which include T lymphocytes, are called leukemia. In a recent study, researchers at Instituto Gulbenkian de Ciência focused T cell acute lymphoblastic leukemia and how it is normally prevented. This rare type of leukemia is quite aggressive and severely impacts children and some adults.

The research team led by Vera Martins, principal investigator at Instituto Gulbenkian de Ciência, proposed to identify the cells that prevent this type of leukemia and show that they are involved in a process of cell competition in the thymus. In this process, younger (and healthier) cells replace older (and less healthy) ones. Thus, younger cells always "win" and purge the older ones, which have the potential of causing leukemia. Besides the leukemia prevention role of these cells, they were also shown to receive signals that provide information on how fast (or slow) they are supposed to develop. The speed at which the development of T lymphocytes occurs is adjusted according to the intrinsic needs of the pool of precursor cells.

The team of researchers used mice as a model organism, as their development of T lymphocytes is similar to what happens in humans, and made use of thymus transplants combined with different genetic models to explore cellular interactions and the genes involved in this complex process. Vera Martins says, "The competitive cell interactions occur early in development and are regulated by a cytokine (interleukin 7), which is important throughout several developmental processes of the T lymphocytes. We discovered that the availability of this cytokine defines the size of the competing cell population. It is through the adjustment of the duration of the cell cycle during proliferation that

interleukin 7 regulates the speed at which these cells differentiate and promote competition."

This study reveals that the development of T lymphocytes in a healthy thymus is not merely achieved because cells follow a predetermined path of extrinsic signals. Rather, it is achieved through the integration of external signals and intrinsic properties of the cells that contribute to the normal functioning of the thymus.

In the future, the researchers hope to determine the importance of space constraints and resource availability for T lymphocyte precursor cells in shaping the dynamics of competition. The team is also interested in understanding how deficiencies in cell competition in the thymus may promote the initiation of leukemia. With this work, the researchers hope to contribute to better prevention or earlier diagnostics of diseases about which very little is still known. "I am convinced that this approach, which integrates the healthy organism and the disease condition, is the best way to understand what causes leukemia and I hope that the generated knowledge will pave the way to the development of more adequate responses for whomever has to face such a severe disease."

This study is a clear example of the contributions of fundamental science to the understanding of what maintains individuals healthy and what changes to cause disease.

More information: Camila V. Ramos et al, Cell Competition, the Kinetics of Thymopoiesis, and Thymus Cellularity Are Regulated by Double-Negative 2 to 3 Early Thymocytes, *Cell Reports* (2020). DOI: 10.1016/j.celrep.2020.107910

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