Ready and Vigilant: Immune Cells on Standby

When pathogens invade the body, the immune system must react immediately to prevent or contain an infection. But how do our defence cells stay ready when no attacker is in sight? Scientists from Vienna have found a surprising explanation: They are constantly stimulated by healthy tissue. This keeps them active and ready to respond to pathogens. Based on this insight, future medications could be devised to selectively enhance our immune system's attention. The study has been published in the journal *Nature Immunology* (DOI: 10.1038/s41590-024-01804-1).

Communication is crucial in immune defence. When a virus infects a cell, the cell releases signalling molecules. This alerts immune cells, and our immune system is rapidly activated. Immune cells process such signals through the JAK-STAT signalling pathway – named after Janus, the two-faced Roman god of beginnings and endings. This pathway links signal detection on the cell surface to the core regulatory machinery of immune cells, activating a set of genes and putting the immune cells into attack mode.

Even when there is no immediate threat, our immune cells must remain vigilant. At the same time, they should not cause damage through unnecessary activity, as it is the case with autoimmune diseases. How our defence cells maintain this balance is poorly understood. A team of research groups from Vienna (www.jak-stat.at) has now put forward an explanation in the journal *Nature Immunology*: "The same JAK-STAT signalling pathway that activates immune cells during an infection also keeps them on standby when no pathogens are in sight," explains Christoph Bock, Principal Investigator at CeMM and Professor at the Medical University of Vienna. When encountering a pathogen, the immune cells thus only need to increase the signalling intensity, which is much faster than turning on a completely new signalling pathway.

To reach this conclusion, the team examined twelve mutant mouse models, each with a genetically altered component of the JAK-STAT signalling pathway. These mice were raised free of diseases and compared with genetically unaltered mice. It was observed that the mutant mice lacked some of the characteristic gene activity and epigenetic regulation of the standby state. Something similar happened when defence cells were removed from their tissue environment and kept in cell culture: They lost their characteristic standby state and even parts of their identity as immune cells.

The team analysed the gene expression and epigenetics of immune cells and tissue samples collected by seven research teams from Vienna. "Our analyses were only possible due to the establishment of uniform laboratory standards and robust statistical methods," explains bioinformatician Nikolaus Fortelny (first author and now Professor at the University of Salzburg). "We showed that

JAK-STAT signalling has different functions when immune cells are on standby than during the active response to pathogens," explains Matthias Farlik (also a first author and now group leader at the Medical University of Vienna).

"JAK-STAT signalling is a central mechanism of our body for communicating immune signals," summarizes Thomas Decker (Professor at the Max Perutz Labs and the University of Vienna) the relevance of the study. "Our study provides insights into the role of the immune system: not only does it react to attacks, but it also maintains vigilance without causing unnecessary damage," adds Mathias Müller (Professor at the University of Veterinary Medicine Vienna). Genes of the JAK-STAT signalling pathway are sometimes pathologically altered in individuals with immune diseases and cancer. Therefore, this research also provides possible approaches for future therapies.

Pictures in the attachment
Image 1: The study authors Nikolaus Fortelny & Christoph Bock
Image 2: The study author Matthias Farlik during laboratory work at the CeMM
Image 3: Biomedical sequencing of RNA at CeMM

The Study "JAK-STAT signaling maintains homeostasis in T cells and macrophages" was published in *Nature Immunology* on April 24, 2024. DOI: 10.1038/s41590-024-01804-1
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The **CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences** is an international, independent and interdisciplinary research institution for molecular medicine under the scientific direction of Giulio Superti-Furga. CeMM is oriented towards medical needs and integrates basic research and clinical expertise to develop innovative diagnostic and therapeutic approaches for precision medicine. Research focuses on cancer, inflammation, metabolic and immune disorders, and rare diseases. The Institute's research building is located on the campus of the Medical University and the Vienna General Hospital.
www.cemm.at

The **Medical University of Vienna (MedUni Vienna)** is one of the longest-established medical education and research facilities in Europe. With almost 8,000 students, it is currently the largest medical training centre in the German-speaking countries. With more than 6,000 employees, 30 departments and two clinical institutes, twelve medical theory centres and numerous highly specialised laboratories, it is one of Europe's leading research establishments in the biomedical sector. MedUni Vienna also has a medical history museum, the Josephinum.

The **Max Perutz Labs** are a research institute established by the University of Vienna and the Medical University of Vienna to provide an environment for excellent, internationally recognized research and education in the field of Molecular Biology. Dedicated to a mechanistic understanding of fundamental biomedical processes, scientists at the Max Perutz Labs aim to link breakthroughs in basic research to advances in human health. The Max Perutz Labs are located at the Vienna BioCenter, one of Europe's hotspots for Life Sciences, and host more than 40 research groups, involving around 400 scientists and staff from more than 50 nations.
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The **University of Veterinary Medicine**, Vienna in Austria is one of the leading academic and research institutions in the field of Veterinary Sciences in Europe. About 1,500 employees and 2,500 students work on the campus in the north of Vienna which also houses five university clinics and various research sites. Outside of Vienna the university operates Teaching and Research Farms. Two research institutes on Vienna's Wilhelminenberg as well as a teaching and research estate in Lower Austria and a branch in Tyrol also belong to the Vetmeduni. The Vetmeduni plays in the global top league: in 2023, it once again took top place in the subject "Veterinary Science" in the world-wide Shanghai University Ranking.
http://www.vetmeduni.ac.at

The **Paris Lodron University of Salzburg**, PLUS, boasts six faculties with 34 departments and 87 degree programmes in digital and analytical, natural and life sciences, social sciences and cultural studies, law and economics, and theology. Almost 18,000 students are enrolled in bachelor's, master's and doctoral programmes here. Founded in 1622 by Prince Archbishop Paris Lodron and reestablished in 1962, today the PLUS is the largest educational institution in Salzburg.
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