千葉大学
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RESEARCH NEWS STORY

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Chiba University

How Systemic Immune Regulation Is 'Hijacked' During Tumor Progression

Researchers discover how tumors manipulate the immune system to tolerate them through the thymus and reveal a potential strategy to counteract it

Tumors can evade immune attack by manipulating the thymus, the organ where T cells are trained. Researchers from Japan discovered that specialized immune cells called plasmacytoid dendritic cells transport tumor antigens to the thymus, promoting immune tolerance to tumors. Disrupting this process in mice enhanced anti-tumor immunity and reduced tumor growth. The findings reveal a previously unrecognized mechanism of tumor immune evasion and identify CCR9 as a potential target for future cancer immunotherapies.

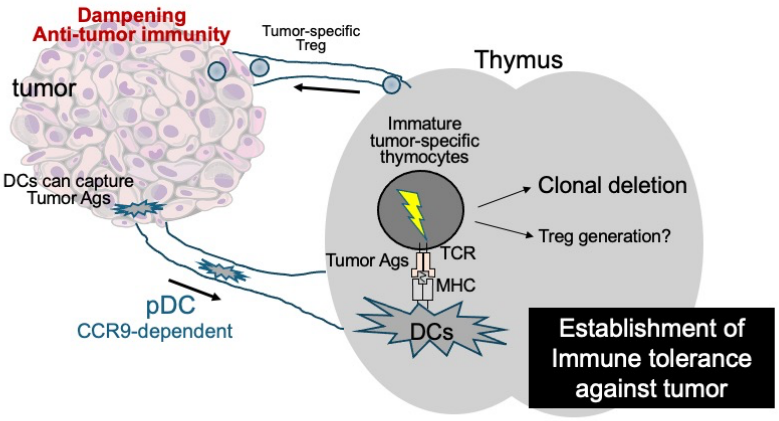

Image title: The CCR9-dependent thymic tolerance pathway
Image caption: Researchers found that plasmacytoid dendritic cells (pDCs) carry tumor antigens to the thymus in a CCR9-dependent manner, promoting immune tolerance to tumors. The findings identify CCR9 as a potential target for future immunotherapies aimed at strengthening anti-tumor immunity.
Image credit: Professor Motoko Y. Kimura from Chiba University, Japan
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The immune system plays a critical role in protecting the body from cancer by recognizing and eliminating abnormal cells before they can develop into tumors. This process relies on T cells that can recognize tumor-derived antigens presented by dendritic cells (DCs). However, tumor cells frequently evade immune surveillance and establish immune tolerance through various mechanisms, most of which are thought to occur within the tumor microenvironment. In contrast, whether such tolerance is also established in the thymus as central tolerance to tumor antigens remains unclear.

To address this knowledge gap, researchers from Chiba University, Japan, have discovered a mechanism by which tumors can manipulate the thymus, the organ that trains immune cells, to tolerate their presence rather than fight them. The team was led by Professor Motoko Y. Kimura and first author Dr. Yangsong Wang, both from the Graduate School of Medicine at Chiba University. The study was published in the journal *Science Advances* on July 23, 2026.

The thymus is an organ where T cells develop and are trained to distinguish self and non-self. The study found that as tumors grow, plasmacytoid DCs (pDCs) accumulate in the thymus and help transport tumor antigens there, triggering the elimination of developing T cells capable of recognizing tumors.

"Our findings suggest that tumors can hijack the physiological machinery of central tolerance to induce systemic immune unresponsiveness against themselves," says Prof. Kimura.

The team made this discovery by studying tumor-bearing mice, where they observed that pDC accumulation began within 2 weeks of tumor implantation and persisted as the tumors continued to grow. They found that the migration of pDCs to the thymus is regulated by a chemokine receptor called CCR9. In mice lacking CCR9, the accumulation of thymic pDCs during tumor progression was largely prevented, indicating that CCR9 is required for this process.

They identified two distinct pDC populations that contribute to this immune evasion. One population originated from common dendritic cell progenitors (CDP-pDCs), while the other arose from common lymphoid progenitors (CLP-pDCs).

CDP-pDCs carry tumor-derived antigens from the tumor to the thymus, where they are presented to developing T cells. As part of its normal training process, the thymus eliminates T cells that react to these antigens. This removes T cells that could otherwise recognize and attack the tumor, reducing anti-tumor immune responses. Meanwhile, CLP-pDCs release IFN-α within the thymus, where they alter the thymic environment, suppressing the production of new T cells and further weakening anti-tumor immunity.

Importantly, the researchers found that disrupting CCR9 could interfere with this immune tolerance mechanism. Mice lacking CCR9 developed smaller tumors and maintained the tumor-specific $CD8^+$ T cell population, indicating a stronger anti-tumor immune response.

“Our findings reveal a previously unrecognized mechanism of tumor immune evasion through manipulating thymic function, and identify CCR9 as a potential therapeutic target in cancer immunotherapy. By blocking the migration of tumor antigen-carrying pDCs from tumors to

the thymus, it may be possible to enhance anti-tumor immunity and improve responses to existing treatments such as immune checkpoint inhibitors," says Dr. Wang.

The findings may have implications beyond cancer. The researchers note that chronic or dormant infections that persist in the body for long periods could potentially exploit similar thymic tolerance pathways to evade immune responses.

Looking ahead, the team suggests that future therapies could combine immune-activating treatments with approaches that block thymic tolerance mechanisms. Such approaches could potentially enhance immune responses against cancer and chronic infections, improving long-term treatment outcomes.

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About Professor Motoko Y. Kimura from Chiba University, Japan

Dr. Motoko Y. Kimura is a Professor at Chiba University whose research focuses on T cell development, differentiation, and function. Her laboratory of Experimental Immunology investigates the fundamental mechanisms of T cell-mediated immunity, including how T cells develop in the thymus, maintain immune tolerance, and contribute to autoimmune diseases, inflammatory disorders, and cancer. In addition to basic immunology research, the laboratory pursues the development of new cancer immunotherapies based on insights gained from studying T cell biology. Prof. Kimura hopes her research will reveal fundamental principles of life and ultimately contribute to the treatment of human diseases.
Laboratory website
Additional information about the Experimental Immunology Laboratory

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Authors: Yangsong Wang,[1] Ryo Koyama-Nasu,[1] Yukihiro Endo,[1] Ichita Hasegawa,[1] Atsushi Onodera,[2,3] Mingyu Chen,[4] Kiyoshi Hirahara,[5,6] Shinichiro Motohashi,[7] Toshinori Nakayama[8], and Motoko Y. Kimura[1,6]
Affiliations:
[1]Department of Experimental Immunology, Graduate School of Medicine, Chiba University
[2]Institute for Advanced Academic Research (IAAR), Chiba University
[3]Research Institute of Disaster Medicine, Chiba University
[4]Division of Molecular Regulation of Inflammatory and Immune Diseases, Research Institute for Biomedical Sciences, Tokyo University of Science
[5]Department of Immunology, Graduate School of Medicine, Chiba University
[6]Chiba University, Synergy Institute for Futuristic Mucosal Vaccine Research and Development (cSIMVa)
[7]Department of Medical Immunology, Graduate School of Medicine, Chiba University
[8]Deceased.
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Expert Contact: Motoko Y. Kimura
Graduate School of Medicine, Chiba University
Email: kimuramo@chiba-u.jp

Media Contact: Yuka Masshardt
Academic Research & Innovation Management Organization (IMO), Chiba University
Address: 1-33 Yayoi, Inage, Chiba 263-8522 JAPAN
Email: ymasshardt@faculty.gs.chiba-u.jp