A signaling network inside blood-forming cells could lead to refinements in immunosuppressive therapy

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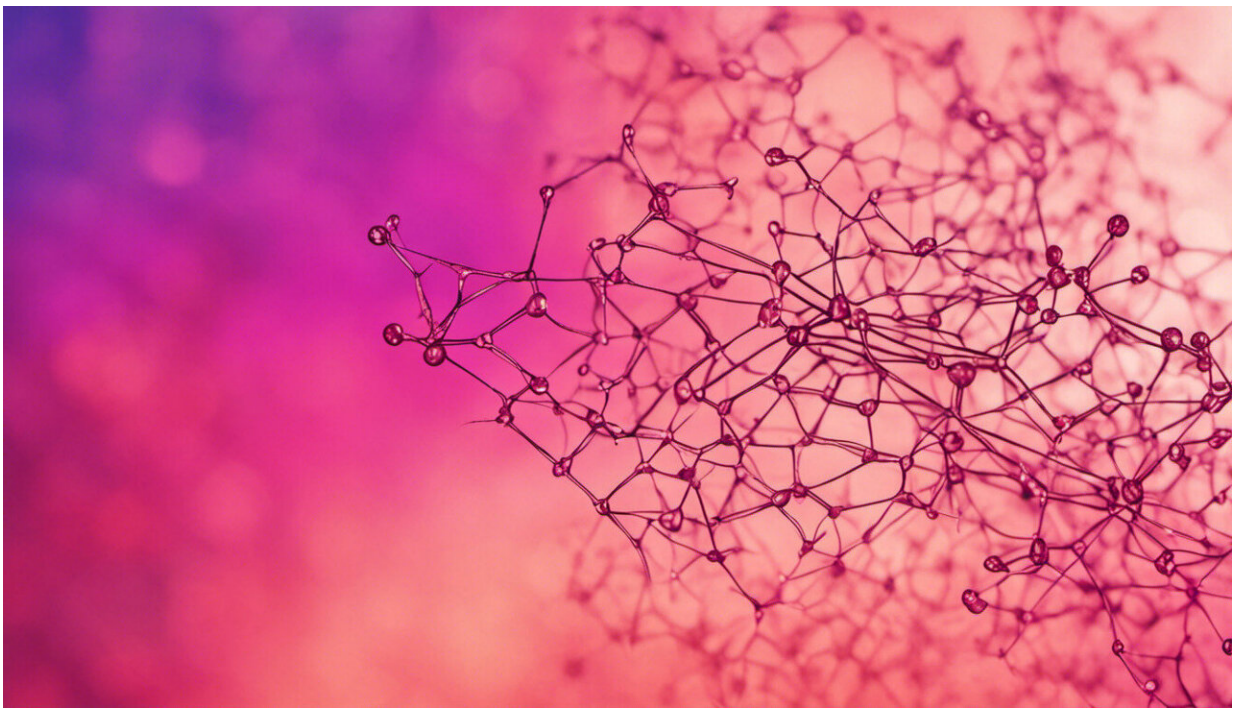

Credit: AI-generated image (disclaimer)

People who have had an organ transplant or have autoimmune diseases are more likely to become ill. Research into a key cellular signaling system suggests this may be partly due to previously unknown effects of treatment drugs, and it also reveals broader insights into how immunity

is controlled.

"Our findings may help explain why patients treated with immunosuppressive drugs are more susceptible to infections," says Jan Fric of Paola Castagnoli's research group at the A*STAR Singapore Immunology Network, "however, any clinical implications need to be checked through further study."

The team of A*STAR researchers and co-workers in Singapore and Austria investigated the calcium and calcineurin–NFAT signaling pathway in myeloid cells and their progenitors. NFATs are a family of transcription factors—proteins that bind to DNA and regulate specific genes. They control the continuous renewal of various types of blood cells that are derived from progenitor cells formed by the bone marrow. NFATs underpin a healthy immune system, including the manufacture of T-cells, which help to regulate the immune system and kill infected or diseased cells.

In studies with live mice and cultured human cells, the researchers uncovered new links in complex networks of signaling and control. These allow stem cells in the bone marrow to develop into different types of mature myeloid cells of the blood and immune system.

Fric explains that the team's findings also improve our understanding of how immunity is controlled. Specifically, the team reports that calcineurin, a protein that is activated by calcium ions, can activate the NFAT transcription factor system. This in turn inhibits the proliferation of granulocyte-monocyte progenitor (GMP) cells. Conversely, inhibiting the calcium and calcineurin–NFAT signaling pathway can enhance the proliferation of GMP cells. The GMP cells develop into myeloid cells, which are the first line of defense against infections.

The research also shows that a cell-surface receptor known as Flt3-L can

activate the calcium-calcineurin–NFAT signaling pathway, and it identifies various genes that are involved.

"The calcineurin–NFAT pathway is an important target of many drug therapies," Fric explains, "and we now need to further investigate the influence of such therapies on the development of myeloid cells in immunosuppressed patients."

Fric points out, however, that the immunosuppressive drugs concerned are quite successful and so caution is needed before changing clinical practice. "But our findings may provide evidence that could help to better control infections in treated and immunosuppressed patients," he concludes.

More information: Fric, J., Lim, C. X. F., Mertes, A., Lee, B. T. K., Viganò, E. et al. Calcium and calcineurin-NFAT signaling regulate granulocyte-monocyte progenitor cell cycle via Flt3-L. *Stem Cells* 32, 3232–3244 (2014). dx.doi.org/10.1002/stem.1813

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