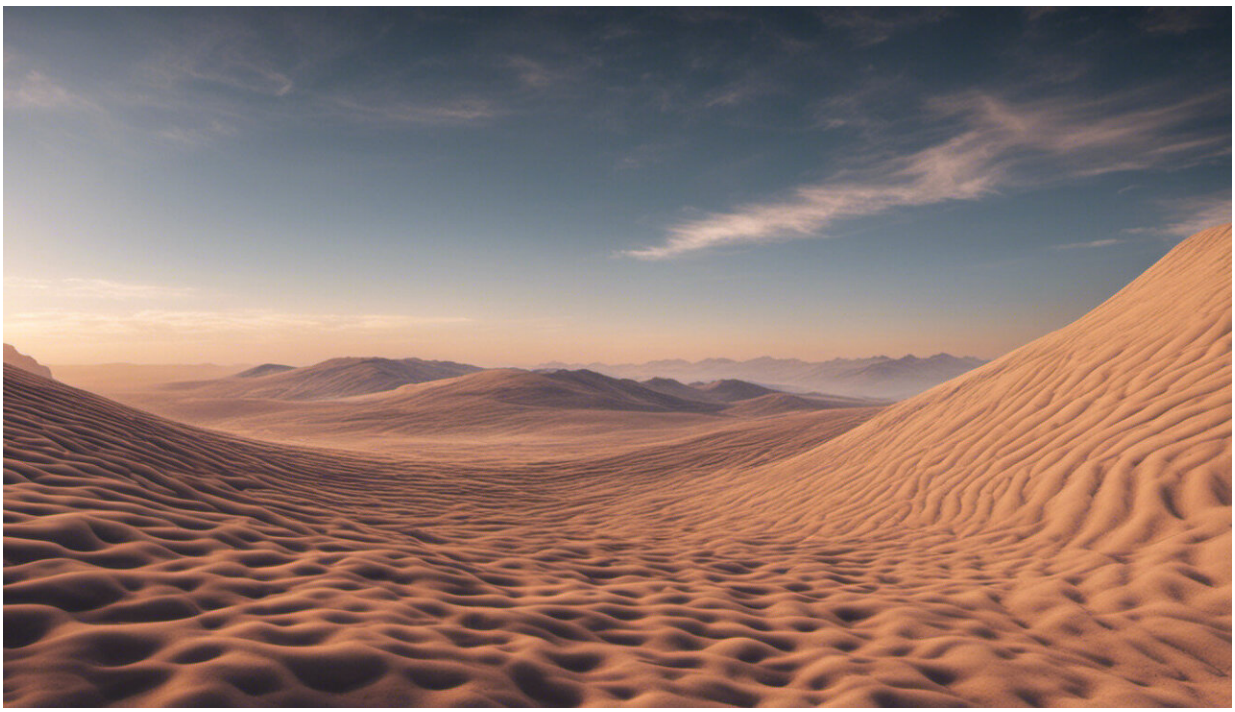
# New roles revealed for immune-regulatory protein may have significant clinical implications

July 15 2015



Credit: AI-generated image (disclaimer)

Surprising insights into the activities of a 'transcription factor' protein that controls genes in cells of the immune system could change medical practice and clarify the protein's role in immunity. Hongbing Yu and colleagues at A*STAR's Singapore Immunology Network investigated

NFATc2, a member of the 'nuclear factor of activated T cells' family of proteins.

Drugs that suppress NFAT activity are used to treat autoimmune diseases and prevent rejection of transplanted organs. "As NFAT inhibitors are globally in clinical use, our results are immediately relevant to improving medical treatment," says Yu. He suggests that understanding how to prevent the potentially serious side effects of these drugs may be a key benefit of the research.

The activity of NFAT inhibitors are known to depend on their effects on T cells, but studies in rodents had suggested they might also have significant effects on other immune cells, particularly dendritic cells. The main function of dendritic cells is to process foreign materials—antigens—and present them to the surface of T cells to stimulate the T cells into their immune responses. The dendritic cells themselves are stimulated by antigens binding to a protein receptor called dectin-1 that protrudes from the dendritic cell surface.

"We have performed the first systematic study of NFATc2 activity in dendritic cells under dectin-1 stimulation," says Yu. The investigation began by stimulating NFATc2 production and activity in mouse dendritic cells by binding of a fungal molecule to dectin-1. This allowed the wide range of genes and related processes that NFATc2 activated in response to the dectin-1 stimulation to be identified.

The role of NFATc2 in dendritic cells proved to be surprisingly varied. "We identified about 20 regulatory molecules known as cytokines and chemokines that are themselves directly regulated by NFATc2," Yu adds. He points out that each of these molecules has its own complicated function in regulating the immune system, and that examining their activities may allow better treatment of disease with NFAT inhibitors.

An equally important finding was that NFATc2 altered the chemical modification pattern of histone proteins associated with DNA within chromosomes. Such 'epigenetic' modification to affect genes critical to the immune system was hypothesized by the A*STAR team before undertaking the research, so it was both satisfying and significant to find their hypothesis confirmed, Yu recalls.

Yu emphasizes that this is an entirely new role for NFATc2, adding another layer of regulation to consider when NFAT inhibitors are used in clinical treatments. Exploring the significance of these surprises is the next challenge.

**More information:** "NFATc2 mediates epigenetic modification of dendritic cell cytokine and chemokine responses to dectin-1 stimulation." *Nucleic Acids Research* 43, 836–847 (2015). dx.doi.org/10.1093/nar/gku1369

Provided by Agency for Science, Technology and Research (A*STAR), Singapore