Life Sciences

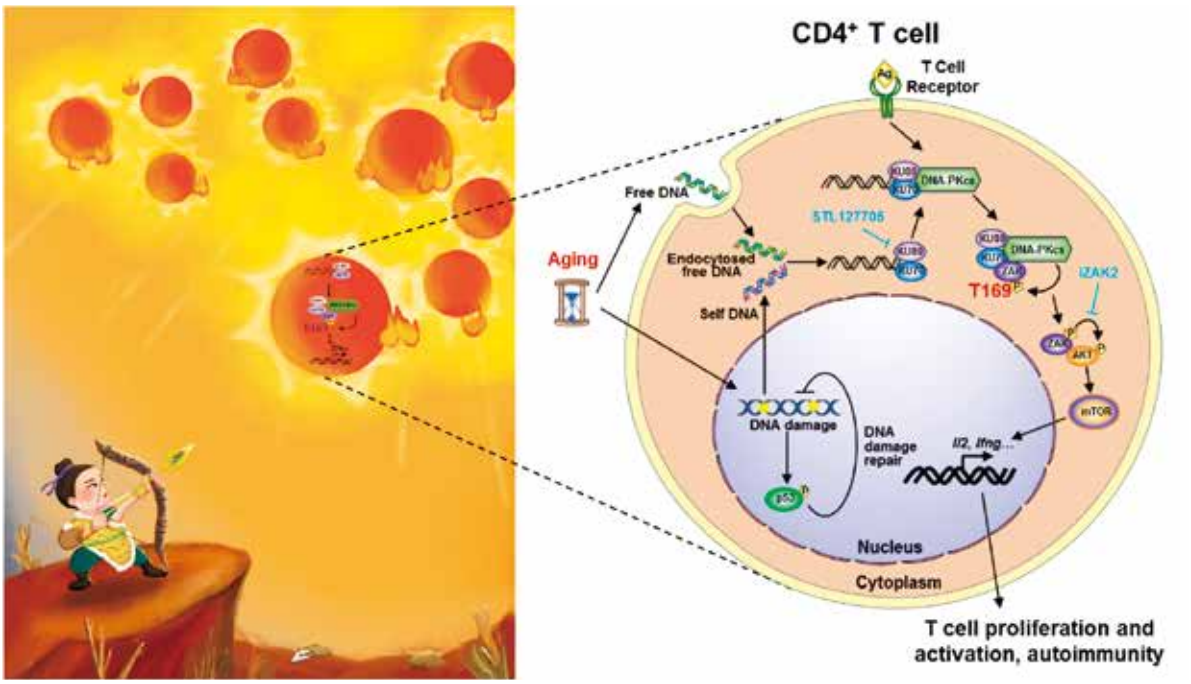
# Targeting DNA-sensing Pathway may Save the Elderly from Aging-related Autoimmune Inflammation

Aging is associated with an increased risk of autoimmunity, a consequence of T cell self-tolerance breakdown, which means the T cells become 'hot-headed' and begin to attack innocent cells, instead of the cells or pathogens that pose threats to the body.

For the elderly, although thymus atrophy causes a decrease in naive T cell output, the number of peripheral T cells does not decrease because of its homeostatic proliferation and activation under the aging state. However, the mechanism by which aging enhances homeostatic proliferation of T cells and thus promotes the development of autoimmune inflammation remains unknown.

In a study published in *Immunity* on March 4th, Dr. XIAO Yichuan's group at the Shanghai Institute of Nutrition and Health (SINH) of the Chinese Academy of Sciences (CAS), collaborating with Dr. ZHENG Mingyue's group at the Shanghai Institute of Materia Medica of CAS, reported that a DNA-sensing pathway plays an important role in T cell activation and aging-related autoimmune inflammation.

In this study, the researchers found that there is a huge accumulation of DNA in the cytoplasm of $CD4^+$ T cells of aged mice and humans. The accumulated DNA enhances the proliferation and activation of TCR-induced $CD4^+$ T cells, suggesting that DNA sensing can promote T cell functional activation. The researchers




Schematic representation of the cartoon and mechanism of DNA sensing in aged $CD4^+$ T cells promoting its activation and autoimmune inflammation. (Image by Dr. XIAO's lab)

screened the proteins that bind to T cell cytoplasmic DNA by mass spectrometry and immunoblotting, and found that DNA in T cells bind to KU complex (KU70/KU80), a protein typically associated with DNA damage repair, instead of cGAS, a cytosolic DNA sensor.

Besides, they revealed that the KU complex was abundantly expressed in the cytoplasm of T cells and its recognition of DNA in $CD4^+$ T cells promoted the activation of DNA-PKcs. This process in turn mediated the phosphorylation of ZAK at T169. The phosphorylated ZAK then activated the downstream AKT/mTOR pathway, enhancing the proliferation and activation of $CD4^+$ T cells. Thus, activation of the KU complex-mediated DNA-sensing pathway in $CD4^+$ T cells is a key mechanism leading to the development of autoimmune inflammation in aged mice.

The discovery of the newly identified DNA-sensing pathway inspires the researchers to explore potential therapeutic strategies of aging-associated autoimmune inflammation.

By using the Caloric Restriction (CR) or Fast-Mimicking Diet (FMD) mouse models, the researchers found that both modes of dieting significantly reduced DNA damage and cytoplasmic DNA accumulation in aged mouse $CD4^+$ T cells, thereby inhibiting ZAK-T169 phosphorylation and activation of downstream AKT/mTOR signaling. The process ultimately suppressed $CD4^+$ T cell activation and aging-associated autoimmune disease.

Based on the identified key protein kinase ZAK in the DNA sensing pathway, the researchers applied deep learning combined with molecular simulation to screen a library of approximately 130,000 compounds and obtained iZAK2, a small molecule compound that specifically inhibits ZAK kinase activity. iZAK2 was found to effectively inhibit DNA-induced $CD4^+$ T cell proliferation and activation, thereby alleviating the pathological symptoms of autoimmune disease in aged mice.

The findings of this study reveal a novel DNA-sensing pathway in aged $CD4^+$ T cells that is independent on cGAS/STING, which promotes T cell activation and proliferation and leads to the development of aging-associated autoimmune diseases. Further investigation and development of inhibitors that block DNA-sensing signaling in T cells may be beneficial for clinical treatment of aging-related autoimmune diseases.

(SINH)

**Reference**

Yan Wang, Zunyun Fu, Xutong Li, Yinming Liang, Siyu Pei, Shumeng Hao, . . . Yichuan Xiao, (2021) Cytoplasmic DNA sensing by KU complex in aged $CD4^+$ T cell potentiates T cell activation and aging-related autoimmune inflammation. *Immunity*. doi: 10.1016/j.immuni.2021.02.003.