RNA binding proteins help T cells pick their weapons before battle

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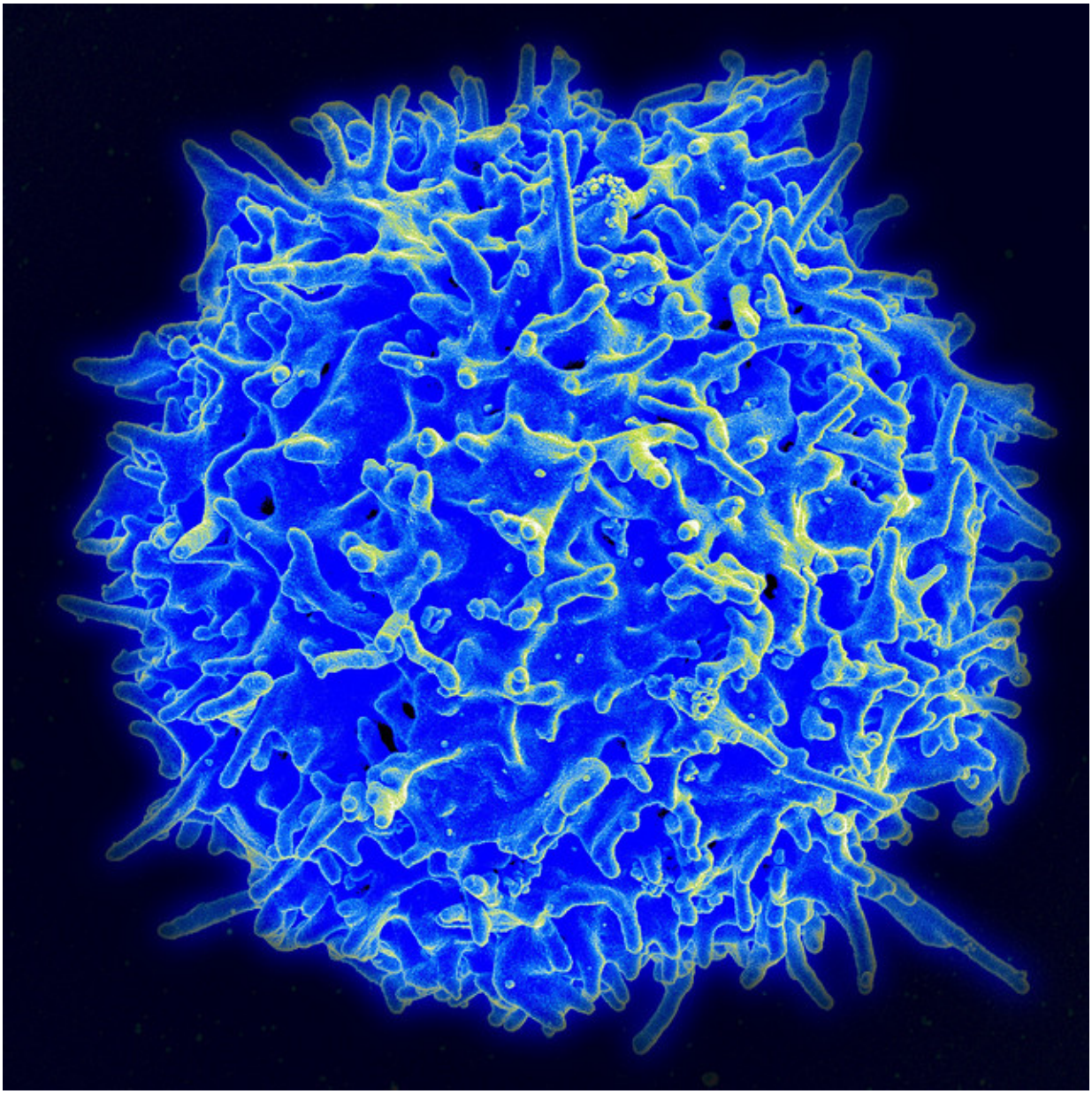

Scanning electron micrograph of a human T lymphocyte (also called a T cell) from the immune system of a healthy donor. Credit: NIAID

Scientists at the Babraham Institute have shown that two RNA binding proteins hold the key to a stronger immune response to influenza in mice. Their findings, published today in *Nature Communications*, reveal that the absence of these proteins changes the potency of T cells that arise at the start on an infection. Further research could lead to implications for therapies that harness the immune system, and for vaccine design.

Researchers from the Turner lab focused on the activity of the RNA binding proteins ZFP36 and ZFP36L1. By studying mice lacking these RNA binding proteins, the researchers were able to show that their absence in T cells during the initial phase of a viral infection leads to a superior cytotoxic immune response.

When the researchers infected mice with influenza, those lacking their RNA binding proteins in T cells showed signs of fighting the infection more successfully than those with the proteins present. The researchers also transferred cells that lacked ZFP36 and ZFP36L1 into normal mice and found that even small numbers of transferred T cells provided the same advantage for fighting an influenza infection.

Their results were surprising, explains Dr. Georg Petkau, a postdoctoral researcher who led the work: "One striking observation of our study is that although the absence of RNA binding proteins in T cells results in stable accelerated differentiation and enhanced cytotoxicity, this does not lead to signs of disease or tissue damage, which is often a logical consequence of overt cytotoxicity during an immune response."

The researchers speculate that the lack of negative knock-on effects could be due to accelerated viral clearance and could be explained by a faster resolution of infection in young mice. It would be interesting to see whether upon recurrent infections a large accumulation of memory cells showing enhanced cytotoxicity in absence of RNA binding proteins would become potentially dangerous with age. Understanding how these RNA binding proteins limit T cell activation may also have implications for autoimmune disease formation in aged individuals.

The priming of the immune response once a pathogen is detected is a critical step that significantly changes the course of an immune response; it is the point at which immune cells decide to adjust the quality and duration of the immune response to a threat. In a sense, the T cells in this study have to choose their weapons before they start to battle the infection and this choice is made by RNA binding proteins. By understanding more about how the immune system processes information within hours of infection and how RNA binding proteins integrate signals to activate T cells, the researchers hope to inform how we approach vaccine design and cell therapies.

"Going forward, we want to investigate how the absence of RNA binding proteins affects the formation of immune memory and whether the superior cytotoxic traits acquired early in the response are epigenetically imprinted and maintained in the memory phase," explained Dr. Martin Turner, head of the Immunology research program. Therefore, the researchers will seek to explain their findings by investigating how the stable cytotoxic program is set up early after activation by looking at changes in the epigenome.

More information: Georg Petkau et al, The timing of differentiation and potency of CD8 effector function is set by RNA binding proteins, *Nature Communications* (2022). DOI: 10.1038/s41467-022-29979-x

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