Uncovering the molecular mechanisms behind immune system activation could help in future gene therapies

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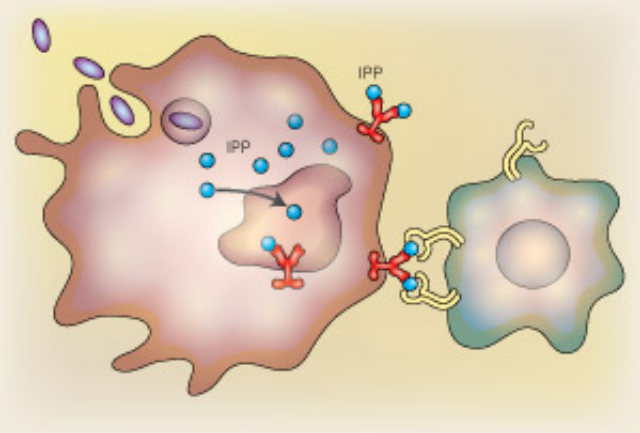

During bacterial infection (purple discs), or cell transformations such as tumor growth, cells accumulate IPP antigens (light blue circles), which then bind to butyrophilin 3A1 (red). Together, they stimulate the T-cell receptors (TCR) of gamma delta T cells (right). Credit: A*STAR Singapore Immunology Network

The ability to recognize antigens from invading microbes and damaged host cells allows the human body to trigger powerful immune responses. A particular group of white cells, known as gamma delta T cells (γδ T cells), is activated during initial infection in response to the accumulation of an antigen called isopentenyl pyrophosphate (IPP). However, as IPP does not bind directly with γδ T-cell receptors, researchers assumed that another molecule was responsible for presenting IPP to γδ T cells.

Now, Gennaro De Libero and co-workers at the A*STAR Singapore Immunology Network and A*STAR Singapore Bioimaging Consortium—together with scientists from Switzerland, Australia and the United Kingdom—have shown that a protein called butyrophilin 3A1 (BTN3A1) activates human γδ T cells by binding with IPP. Their discovery could lead to targeted therapies for tumors and other diseases that require a heightened, rapid immune response.

"In our preliminary studies, we found that a γδ T-cell antigen-presenting molecule (APM) was distributed in many tissues and was different from all the other known APMs," explains De Libero. "We exploited a novel strategy to identify the gene encoding the APM."

In initial investigations into human γδ T cells, the team found that their data was complicated by high background readings from other white-cell activity. To minimize this interference, they generated transgenic mice capable of expressing specific human γδ T-cell receptor chains. Through careful screening, the researchers found that only certain human cells were able to present IPP and activate the γδ T cells.

"By pinpointing these cell types, we were able to use the mouse–human hybrid cells to map the human chromosome and find the locus in which the gene encoding the unknown APM was located," explains De Libero. "By applying molecular and cellular techniques, we then identified the molecule as BTN3A1."

Using mass spectroscopy, the researchers were able to visualize the formation of BTN3A1-antigen complexes. IPP antigens bind to a small cleft in BTN3A1 to form a stable complex, which in turn stimulates the γδ T-cell receptors (see image). When BTN3A1 is inhibited, fewer IPP antigens are presented to γδ T cells, weakening the immune response.

The team found that BTN3A1 is widely expressed in the body,

particularly in tumor cells where host IPP is prevalent. BTN3A1 could therefore play a vital role in new gene therapies.

"BTN3A1 might be exploited to present stimulatory antigens to human γδ T cells," says De Libero. "This could be used to preferentially kill tumor cells."

More information: Vavassori, S., Kumar, A., Wan, G. S., Ramanjaneyulu, G. S., Cavallari, M. et al. Butyrophilin 3A1 binds phosphorylated antigens and stimulates human γδ T cells. *Nature Immunology* 14, 908–916 (2013). dx.doi.org/10.1038/ni.2665

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