Estrogen-dependent switch tempers killing activity of immune cells

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The sex hormone estrogen tempers the killing activity of a specific group of immune cells, the cytotoxic T cells (CTLs), which are known to attack tumor cells and cells infected by viruses. The key player in this process is a cytotoxic T cell molecule which has been known for a long time and which scientists have named EBAG9.

Cancer researchers Dr. Constantin Rüder and Dr. Armin Rehm together with immunologist Dr. Uta Höpken of the Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch and Charité - University Medicine Berlin, Germany, have now unraveled the function of EBAG9. Modulated by estrogen, EBAG9 tempers the activity of CTLs. In the absence of EBAG9, the activity of CTLs is enhanced.

The sex hormone estrogen plays a critical role in the regulation of growth and the development of cells. It is also crucial for cell-type-specific gene expression in various tissues. Deregulation of this system results in breast and ovarian cancer.

Those tumors are successfully treated with drugs such as tamoxifen. Researchers suggest that this drug inhibits tumor growth by blocking the estrogen receptors of the tumor cells. However, up to now it has been unclear what effect this inhibition has on the immune system.

In a previous study, Japanese researchers detected large amounts of EBAG9 in estrogen-dependent tumors. Dr. Rehm and his colleagues wondered what effect elevated levels of estrogen would have on

cytotoxic T cells that attack tumors. They assumed that EBAG9 could transmit this effect of estrogen and therefore wanted to know what would happen if they knocked out the gene for EBAG9 in mice.

After knocking out the gene for EBAG9, they found that in the absence of EBAG9 the "brake" of the immune cells is loosened. The immune cells can release much more of the tumor-killing enzymes than in the presence of EBAG9. The deathly harbingers are stored in granules (secretory lysosomes) in the cytotoxic T cells. They have greater quantities of these granules at their disposal once the blockage of the immune cells through EBAG9 is lifted.

These findings of the researchers in Berlin may also explain why drugs like tamoxifen act on tumor cell growth. One argument is that once the estrogen receptors of the tumor cells are inhibited by the drug, the sex hormone can no longer promote tumor growth. At the same time EBAG9 can no longer inhibit the cytotoxic T cells. The immune cells are ready to attack and destroy the tumor cells.

"In this way, tamoxifen not only inhibits tumor growth but may also be able to enhance the effect of the immune system," Dr. Rehm said. His working hypothesis is that EBAG9 acts as a molecular switch which regulates the immune cells.

As a next step, he and his colleagues plan to study cytotoxic T cells from patients with estrogen-dependent tumors to see if EBAG9 levels are increased.

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