Raising more than just hope for cancer treatment

Bedroom performance-boosting Viagra also boosts the immune system’s battle against cancer, report Serafini et al on page 2691.

In cancer patients, though the body generates tumor-specific antibodies, their efficacy is neutralized by the tumor itself. Tumors recruit cells such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells, which suppress the body’s immune system, thus allowing the tumors to escape immune recognition. Borrello’s team has been investigating ways to overcome this immunosuppression.

Suppression of T cells by MDSCs requires, among other things, nitric oxide production. The team reasoned, therefore, that reducing nitric oxide levels might boost immunity in cancer patients. They thus turned to Viagra. Besides its well-known vasodilatory effect, Viagra also reduces nitric oxide production through a separate but linked pathway.

The team gave Viagra to mice with colon carcinoma and found that the immune systems of the mice were indeed boosted. The mice had an increased number of cytotoxic T cells, and tumor outgrowth was reduced by 50–70%.

Viagra also provided a boost to T cells transferred to the mice using adoptive cell therapy, with tumor growth being reduced still further.

Viagra, either alone or in conjunction with transferred T cells, did not eradicate the tumors but did significantly slow their progression. Eradication would require a full understanding of the multiple, complex pathways that lead to tumor-induced immunosuppression. In the meantime, the immediate availability of Viagra means its potential clinical use can be readily tested. JEM

Me, myself, and eye

The lack of just one self-antigen in the thymus can launch a tissue-specific autoimmune attack, report DeVoss et al. (page 2727).

T cells are taught which antigens to ignore as they develop in the thymus. Those whose antigen receptors recognize self-proteins are normally eliminated, preventing them from escaping into the circulation and later attacking self-tissues. The transcription factor Aire (autoimmune regulator) drives the expression of many tissue-specific antigens in the thymus; without Aire, mice develop a panoply of autoimmune diseases. But so far no studies have proven the link between defects in Aire-induced expression of tissue antigens in the thymus and the development of autoimmunity against those tissues.

The team showed that one of the problems that crops up in aire−/− mice—a spontaneous autoimmunity of the eye—is due to a T cell attack on an eye-specific interphotoreceptor retinoid binding protein (IRBP). IRBP, the authors found, was expressed at a low level in the wild-type thymus, but was missing in the aire−/− thymus. Wild-type mice transplanted with thymi lacking IRBP developed the same eye disease, proving that the lack of thymic IRBP was solely responsible for the disorder.

Humans lacking Aire also develop retinopathy, although they more commonly develop other organ-specific autoimmune diseases. Given that aire−/− mice develop a range of tissue-specific autoimmune disorders, the authors plan to test whether those that are common to humans can also be pinned on the loss of a single antigen. JEM

IRF3 balances killing and cleaning

A clean house is a sign of a boring life. When more interesting or urgent matters arise, the housework has to wait. Similarly, when the body needs to fight infection, the liver’s clean-up work is impaired. Chow et al. (page 2589) now show why: switching on virus-fighting factor interferon also switches off the liver’s detoxification pathway.

Viral infection can cause metabolic disorders, including cholesterol and bone metabolism defects as well as Reye’s syndrome, a defect in which aspirin becomes toxic because the liver fails to break it down. Liver detoxification is partly regulated by a transcription factor called retinoid X receptor (RXR), which turns on drug metabolism genes. But RXR is turned off by viral infection, Chow and colleagues now find.

RXR gets down-regulated by interferon regulatory factor 3 (IRF3), the same factor responsible for promoting virus-killing interferon expression as part of the primary immune response.

The team’s work reveals a mechanism for crosstalk between immunity and metabolism—but why might cells need such crosstalk? “Fighting infection costs energy, and so does metabolism,” explains Chow. The simultaneous switching of resources in favor of the immune response and away from metabolism might thus be the body’s way of balancing the energy budget. JEM