The immune system can compensate for malnutrition

Malnutrition remains the primary cause of immunosuppression worldwide. Despite profoundly impaired adaptive immunity associated with malnutrition, most humans can survive for extended periods of severe dietary restriction. How the immune system adapts to malnutrition to sustain immunity at barrier surfaces, such as the intestine, remains unknown. Vitamin A deficiency affects an estimated 250 million children in developing countries in the same regions where chronic parasitic worm infections are prevalent. How the immune system integrates dietary cues, like a vitamin deficiency, into the timing of immune responses is still not clear.

Yasmine Belkaid's team at the National Institute of Allergy and Infectious Disease (Bethesda, MD) posited that compensatory mechanisms might be in place to sustain defined branches of the immunity and, in particular, responses associated with the protection of barrier tissues. They fed pregnant mice a special vitamin A–deficient diet and then kept their offspring on the same regimen to generate vitamin A–deficient

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mice. They examined the effects of vitamin A deficiency on the intestinal populations of two types of mouse innate immune cells, ILC2 and ILC3, which play major roles in maintaining barrier immunity. While both ICL3 cells and their associated cytokines were significantly reduced in the vitamin A–deficient mice, the levels of ICL2 cells and their associated cytokines went up (*Science* **343**, 432–437; 2014).

Vitamin A supports adaptive immunity through its metabolite, retinoic acid. When retinoic acid was blocked, ILC3 cell populations diminished but ICL2 populations swelled. Introducing undifferentiated progenitor lymphoid cells into mice lacking innate lymphoid cells showed that mice injected with retinoic acid developed a population of cells dominated by ICL3, whereas mice injected with a retinoic acid signaling inhibitor developed a population dominated by ICL2 cells.

Both ILC2 and ICL3 cells are involved in innate immunity, but the former are known to help defend against infectious worms, whereas the latter are known to help defend against bacterial infections. Vitamin A–deficient mice and retinoic acid–inhibited mice did poorly compared with normal mice when challenged with the bacterium *Citrobacter rodentium* but showed lower loads of *Trichuris muris* worms than normal mice after being experimentally infected with their eggs.

The findings suggest that vitamin A deficiency can adaptively activate the immune system to help protect mice against worm infections. Belkaid said, "To our knowledge, this is the first study to show a beneficial adaptation of the immune system to nutritional deficiencies."

Kara Rosania

INTERFERING WITH THE PROGRESSION OF BREAST CANCER

The most common noninvasive lesion of the breast is ductal carcinoma *in situ* (DCIS). Only a fraction of DCIS lesions will progress to invasive breast tumors, but it is not currently possible to predict which ones. Therefore, although surveillance may be recommended for early stage lesions, treatment of DCIS is typically aggressive, including options like mastectomy, lumpectomy and radiation, all of which have serious systemic side effects. Some patients also undergo endocrine therapy, which can have life-threatening side effects including stroke, blood clots, bone loss and elevated risks of certain cancers. There is an urgent clinical need for minimally invasive therapies that can be selectively targeted to prevent progression of premalignant breast lesions without producing systemic toxicity.

RNA interference (RNAi) has been used to treat various tumor types in rodent models, including xenografts of human mammary tumors in mice, with few adverse side effects. But the development of RNAi-based cancer therapeutics relies on accurate identification of the genes to be targeted for silencing and on optimization of techniques for delivering RNAi effectively.

Results from a recent study now suggest that researchers led by Donald Ingber (Harvard University, Boston, MA) have addressed both challenges in developing a promising new treatment for DCIS. Brock's team applied computational gene network modeling to identify the gene *HoxA1* as a driver of early mammary cancer progression in transgenic mice. Next, they delivered HoxA1 RNAi molecules formulated as lipidoid nanoparticles to premalignant lesions in the epithelium of intact mammary glands of mice by direct injection through the nipple. This local route of delivery is relatively noninvasive and circumvents liver uptake and accumulation of nanoparticles, which can complicate systemic delivery.

This RNAi silencing of HoxA1 prevented loss of hormone receptor expression, suppressed cell proliferation and reduced mammary tumor incidence by 75% in mice during a 21-week study (*Sci. Transl. Med.* **6**, 217ra2; 2014). The results show that computational methods can be used to identify oncogene candidates for RNAi-based treatment and that localized gene silencing can reduce tumor incidence in mice. The strategy may be translatable to the prevention of mammary tumor progression in humans, although additional testing will be needed first. Amy Brock, a co-author of the paper who is now at The University of Texas at Austin, said, "Localized delivery of a therapeutic opens up new options for patients and doctors. We see this as a platform technology that can be personalized to individual patients and individual tumor types."

Monica Harrington