Antiparasitic drug reverses neurodevelopmental deficits

An almost century-old drug restores normal metabolism in a mouse model of autism spectrum disorder (ASD), a new study reports (*Transl. Psychiatry* **4**, e400; 2014). Metabolism and mitochondrial function are well-known regulators of neurotransmission and synaptic plasticity and likely play an important role in the development of several neurodevelopmental disorders such as ASD, which is almost universally characterized by metabolic disturbances.

Exposure to serious infection during pregnancy or during early development causes metabolic changes that can increase the risk of neurodevelopmental disorders in offspring. Robert Naviaux, scientist at University of California San Diego School of Medicine and lead author of the study, said, "It's wrong to think of genes and the environment as separate and independent factors. Genes and environmental factors interact. The net result of this interaction is metabolism." The maternal immune activation (MIA) mouse model of neurodevelopmental disorders, which replicates this phenomenon, produces offspring with symptoms that

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are biologically similar to those of ASD. In this model, pregnant females are exposed to a simulated viral infection by injection of the double stranded RNA poly(IC), which activates an evolutionarily conserved metabolic response to threat, called the 'cell danger response.' Cells that are threatened stiffen their membranes, dramatically reducing communication between cells. "Cells behave like countries at war," Naviaux explained. "When a threat begins, they harden their borders. They don't trust their neighbors. But without constant communication with the outside, cells begin to function differently. In the case of neurons, it might be by making fewer or too many connections." Pathological persistence of this cell danger response has been observed in patients with ASD.

Naviaux's group focused on the role of nucleotides and other signaling mitokines, which are generated by distressed mitochondria, in eliciting the cell danger response. Using the antipurinergic drug suramin, which historically has been used to treat the parasitic disease trypanosomiasis or African sleeping sickness, the researchers blocked the extracellular signaling pathway used by mitokines in the MIA mouse model. The treatment reversed the cell danger response, and the related inflammation and behavioral and metabolic changes were corrected in the mice.

Unfortunately, suramin is unsafe for long-term, chronic use, limiting its clinical applications. Still, the study's authors believe that if an optimal treatment window can be identified, the drug could be used in the short term to remove the metabolic dysfunction underlying neurodevelopmental disorders like autism so that behavioral and developmental therapies can be more effective.

Kara Rosania

IMMUNE THERAPY FOR LIVER CANCER

Hepatocellular carcinoma (HCC), the most common type of liver cancer in the US, is often treated by removing the tumor. But relapse after resection is very common, and there are currently no effective therapies for reducing recurrence. Approaches that activate a patient's immune system to fight cancer recurrence have been tested but so far have induced only weak responses. Now, Yukai He (Medical College of Georgia, Augusta) and colleagues have found a way to boost the efficacy of immune stimulation against liver cancer. They used an antigen-engineering technique to modify the sequence of a protein commonly expressed by liver cancer cells, alpha-fetoprotein (AFP), so that the immune system would recognize it as a target and work to eliminate the cancer cells (*Hepatology* **59**, 1448–1458; 2014). The modified AFP was delivered using a lentivector vehicle that targets dendritic cells, which present the modified AFP as an antigen to the immune system, activating T cells to attack it.

He's team tested the therapeutic potential of this strategy in mouse models. Mice were immunized with a lentivector expressing either modified or wild-type AFP. Compared with wild-type AFP, modified AFP effectively activated T cells, resulting in greater numbers of AFP-specific T cells. These T cells also recognized wild-type AFP and killed tumor cells that expressed the wild-type version. Furthermore, immunization with modified AFP completely protected mice that were challenged with an otherwise lethal dose of AFP-expressing tumor cells.

In mice, administration of the carcinogen diethylnitrosoamine (DEN) can be used to induce HCC. But immunization with modified AFP hindered development of HCC in mice treated with DEN. Tumor nodule numbers were lower in mice immunized with modified AFP after exposure to DEN than in those immunized with wild-type AFP. Immunization with modified AFP also increased infiltration of AFP-specific T cells into the liver, which could contribute to protection against tumor recurrence.

The results show that sequence optimization of AFP can increase its immunogenicity, enabling it to activate AFP-specific T cells and generate an effective antitumor response that prevents HCC after both tumor-cell challenge and carcinogen exposure in mice.

He and his research team believe that the results provide "a practical roadmap" to develop effective immune therapies for HCC in humans. He plans to continue to move the research toward human applications. "Now that we know it works in mice, we have to make sure it works in people," He said in a press release.

Monica Harrington