Study may explain mysterious cancer–day care connection [1]

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EXCERPTS

For years, scientists have noticed an interesting pattern of cancer among children. Those who went to day care early in life were less likely to later develop the most common childhood cancer: acute lymphoblastic leukemia (ALL). Now, a 7-year study appears to have unraveled the molecular mechanism driving ALL. The work may explain why early exposure to infections in places such as day cares seems to protect against the disease and why unrelated vaccines help guard against this cancer.

For Mel Greaves, a cancer cell biologist at the University of London's Institute of Cancer Research, the finding provides an explanation for the hypothesis he has long promoted: that when infants in modern societies are sheltered from routine infections, their immune systems are more likely to overreact during later infections, paving the way for ALL. "I see it as the missing link," he says of the new research.

Most childhood ALL involves a malfunction of B cells, the scouts of the immune system that patrol the bloodstream looking for intruders like viruses and bacteria; they make antibodies that help fight infections. But with leukemia, the immune system goes haywire, churning out flawed, immature B cells at a prodigious rate and crowding out healthy blood cells.

Normal B cells are a marvel of adaptability. As they mature, they reprogram their own DNA, enabling the immune system to produce millions of different B cells programmed to recognize the vast range of potential infections. The DNA rearrangement relies on a sequence of enzymes. First, proteins known as RAGs cut and paste whole chunks of DNA. After that, another enzyme, AID, goes to work "fine-tuning" the DNA by altering single nucleotides.

But Greaves and colleagues suspected this process could go awry, introducing mutations that create flawed B cells that could cause leukemia. In a series of experiments, they found evidence that much of the problem lay with a breakdown in the orderly sequence of gene editing during infections. Rather than the RAGs doing their business and then stepping aside for the AID, the AID kicked in simultaneously, potentially increasing the risk of gene-editing errors.

These tantalizing results came to a head in an experiment on mice with a genetic abnormality linked to childhood ALL. The condition, in which two genes associated with blood formation are fused together, is found in the cord blood of 1% of all newborns. But most children with it never go on to develop full-blown ALL. The researchers wondered if unregulated mutations set off by repeated infections later in childhood could make the difference, triggering the leukemia.

The scientists took mouse B cells with this genetic flaw. Some produced both RAG and AID enzymes, and other cells made only one of the two. They then simulated repeated illnesses by subjecting the rodents to five rounds of exposure to a molecule that acts as an antigen-a substance triggering an immune response. In this case, it mimicked a bacterial infection. At the same time, they removed the protein that usually acts as a traffic cop, coordinating when the enzymes kick in.

When the cells were injected into mice, all 14 mice that got B cells with both enzymes quickly got leukemia and died, the team reports online today in Nature Immunology. The mice with B cells producing just one enzyme were disease-free even 5 months later.

"That's a smoking gun," says Markus Müschen, the paper's senior author and a cancer researcher at the University of California, San Francisco (UCSF). "Now we know that this is AID and RAG. And now we know that this can be triggered by bacterial antigens."

The findings, Müschen says, hint at why several studies have found a link between a drop in ALL cases and the vaccine for Haemophilus influenzae type B (Hib), a bacterial infection that most commonly afflicts young children. The vaccine could trigger a mild immune response in infants that mimics the normal sniffles kids acquire in day cares, while preventing more intense infections that could lead to an immune system malfunction, he says.

The paper could become ammunition in the political fight over child vaccinations, if vaccine proponents argue it underscores the benefits of vaccines. The California State Senate last week passed a bill that removes the exemption allowing parents to opt out of vaccinations for their children based on personal beliefs. It's now before the State Assembly. The move comes on the heels of a measles outbreak centered at Disneyland, which public health officials have tied to a decline in vaccination rates.

Joseph Wiemels, a childhood leukemia researcher at UCSF who was not involved in the research, praises the work as important evidence of how infections can play a role in this sort of leukemia. It could also help explain seemingly contradictory findings that although early day care reduces ALL risk, that same risk is higher among children with more doctor visits. It could be that mild infections early in life, such as ones that often circulate in day cares, help build the immune system. More serious infections that warrant a trip to the doctor, however, could set off a damaging immune "storm," he says.

But Wiemels cautions against jumping to conclusions. The study offers a plausible explanation why a vaccine like Hib might help. But he notes that the scientists didn't actually test the impact of vaccines or previous illness. "They don't take these mice and vaccinate them or exercise their immune systems and then hit them."

Greaves says the most striking reduction in ALL is for children who spend time in early day care. Although the Hib vaccine appears to have a benefit, it's not perfect. And there's less evidence that other vaccines help, he says. "If it really worked as well as that, we wouldn't have leukemia."

One major unanswered question is whether certain infections are more likely to trigger the mutations leading to ALL. Greaves says although there is little evidence that a single virus is always the cause, he is working on a paper that pinpoints one virus in a cluster of leukemia cases. Meanwhile, Wiemels is preparing the results of a study that points to a link between a specific viral infection in pregnant women and childhood leukemia.

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Tags: health [4]

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