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ANTIBIOTIC TREATMENT IN INFANCY CAN HASTEN THE ONSET OF TYPE-1 DIABETES IN MICE

Exposure to antibiotics disrupts the balance of bacterial communities in the gut microbiome and may spur the onset of type-1 diabetes, an autoimmune disease.

FOCUS OF STUDY:

During early childhood, the body's resident bacteria—the microbiome—are important for the proper establishment of the immune system. With the incidence of type-1 diabetes (T1D) increasing globally, Dr. Martin Blaser (New York University), advisor to CIFAR's Humans & the Microbiome program, and a team of researchers investigated if antibiotic treatment during infancy quickens T1D development by eliminating some of the bacteria normally present in the gut. The study found that male mice raised on antibiotics, at doses similar to those used to treat childhood infections, had altered microbiomes and were more prone to T1D.

BACKGROUND:

Microbes are no longer solely regarded as culprits of disease; growing research supports the idea that bacteria could be essential for good health. During early childhood, diverse bacterial communities in the gut help calibrate the immune system so that it responds appropriately to infection. A failure to do so can trigger autoimmune disease, in which the immune system responds to the body's own cells as foreign invaders and destroys them. In T1D, the body's insulin-producing cells are destroyed and the resulting high blood sugar can cause severe short- and long-term damage.

T1D typically occurs in childhood and, unlike type-2 diabetes, it is not linked to weight or diet. As T1D becomes more common and occurs at younger ages, researchers are exploring whether changes to the early microbiome, influenced by practices such as early-life antibiotics use, are supporting the disease development.

FINDINGS:

Male rat pups that were genetically susceptible to T1D and given repeated doses of antibiotics had double the rates of T1D compared to untreated pups (53% compared to 26%). In contrast, continuous low-dose antibiotics treatment had no effect.

Antibiotics diminished the microbial diversity in the gut, reducing the numbers of protective bacteria, such as Bifidobacteria, that support the developing immune system. Instead, the balance shifted towards potentially harmful bacteria, which are normally maintained at lower levels through competition with other microbes.

The pups that went on to develop T1D contained strikingly different bacterial communities from those that remained healthy. Based on this, the researchers

developed a diagnostic model of 10 types of bacteria whose prevalence preceded the disease.

The microbiome composition largely recovered about two months after the end of treatment, supporting the view that there is an early "window of opportunity" when microbial diversity is crucial for immune development.

Further experiments showed that antibiotic treatment triggered changes in expression of the genes involved in immune development and function as well as in metabolic pathways weeks before the diabetes became apparent.

STUDY DESIGN AND METHODS:

The study used mice that are genetically susceptible to T1D, known as non-obese diabetic (NOD) mice and which are commonly used in research. The researchers monitored if giving pups antibiotics during infancy led them to become diabetic sooner than untreated pups. Two drug regimens were tested: a continuous low-dose and three separate doses akin to those used to treat infections in young children. After initially failing to detect changes in disease onset in female pups, which are known to be more prone to T1D, the team focused the rest of the study on the males.

To investigate the microbiome composition, the researchers sifted through the pups' stools to collect and sequence pieces of bacterial DNA that revealed which species were present. They also measured gene activity in the gut and liver to glean insights into any antibiotic-related changes in immune development and metabolism.

IMPLICATIONS:

The study confirms previous findings that antibiotics, at doses used to treat childhood infections, disrupt the balance of microbial communities in the gut at the expense of protective bacteria. It brings into question the widespread use of antibiotics, especially among children that may be genetically susceptible to T1D and other autoimmune diseases. If a diagnostic model, based on the rise of bacterial communities that herald the disease, can be established in humans, this could help identify children at a greater risk of T1D before the disease develops. Further, study data on gene expression could help tease out cellular pathways that drugs could target to delay or prevent T1D development.

However, as the authors also note, there are other studies that did not found a link between antibiotic use and T1D and the effect is likely to depend on the type of drug, dose given, and age when given as well as sex and environmental factors.

REFERENCE:

Livanos et al. (2016) Antibiotic-mediated gut microbiome perturbation accelerates development of type 1 diabetes in mice. *Nature Microbiology* 1(11):16140.

HUMANS & THE MICROBIOME:

Microbes represent a significant unexplored link to human health, development and evolution. The Humans & the Microbiome program at CIFAR brings together biologists, anthropologists and historians to shape a new, unified understanding of the relationship between the microbiome and humans. Learn more at **www.cifar.ca/research/humans-the-microbiome.**

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