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Can antibiotics cause autoimmunity?

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The code for every gene includes a message at the end of it that signals the translation machinery to stop. Some diseases, such as cystic fibrosis and Duchenne muscular dystrophy, can result from mutations that insert this stop signal into the middle of an essential gene, causing the resulting protein to be truncated. Some antibiotics cause the cell's translation machinery to ignore the stop codons and are therefore being explored as a potential therapy for these diseases. But new research reported online in *Proceedings of the National Academy of Sciences* (the week of March 31st) shows that this approach could come with the price of triggering autoimmune disease.

"It's worth thinking about this as a potential mechanism for autoimmunity," says co-lead investigator, Laurence Eisenlohr, Ph.D., a professor in the department of Microbiology and Immunology at Thomas Jefferson University.

Autoimmune diseases such as Crohn's disease, eczema, or lupus are caused by an immune system that attacks normal components of various tissues of the body. The immune system attacks these normal tissues just as it would attack tissue infected by a bacteria or virus. What causes the immune system to malfunction in some people but not others, however, has been a puzzle. "Often, the trigger happens years before the disease has been diagnosed," says Dr. Eisenlohr.

The researchers looked at a class of antibiotics that includes gentamicin because these antibiotics have the unique property of inducing cells to read through stop codons in the genetic code – producing a longer

protein product. This mechanism can help save the translation of mutated genes whose processing is interrupted by aberrant stop codons, such as in cystic fibrosis. However, when cellular machinery reads through normal stop codons, it could create abnormally elongated proteins in the cell. Pieces of these abnormal proteins may be presented to the immune system as a part of normal protein processing, where they could be detected by the immune system. At least, that's the theory.

To test this theory, Eisenlohr's team, in collaboration with a translation biology group at the University of Utah led by Michael Howard, Ph.D., used a gene that they knew would get presented to the immune system and added a stop codon in the middle of it. They then inserted this gene into a mammalian cell line. Because the stop codon truncates the gene, normal cells did not produce the protein. However, when the researchers treated the cells with gentamicin, they began to detect the protein on the surface of cells.

While a very low number of these proteins were produced – too little to detect by normal biochemical tests – the T cells of the immune system are sensitive enough to pick up these miniscule amounts. Indeed, the group showed that the immune cells could detect the protein produced by gentamicin-treated cells, even at low quantities.

To test whether this process was active even in normal cells that weren't expressing an experimental gene, first author Elliot Goodenough exposed the HeLa human cell line to gentamicin and then searched for novel peptides presented on the surface of the cells. He identified 17 peptides that hadn't been characterized before in cells treated with gentamicin and showed that the peptides were presentable to the immune system. "The results suggest that gentamicin can cause cells to display novel protein fragments to the immune system," says Goodenough. In other words, "what may be garbage biologically may be important immunologically," says Eisenlohr.

However, presenting an antigen to the immune system does not guarantee that it will activate the kind of immune response that initiates autoimmunity. But because gentamicin is usually used to treat infections, "all of the right conditions are in place to potentially initiate autoimmunity," says Eisenlohr. The inflammation associated with bacterial diseases gives a signal to immune cells that the peptides they encounter are dangerous. So even as gentamicin fights the bacteria causing the infection, it also causes normal cells to produce abnormal proteins that are presented to the immune system and have a potential of initiating an autoimmune reaction.

"A number of autoimmune diseases are thought to be triggered by infections," says Eisenlohr. "The results of this study suggest that certain antibiotics used to treat those infections may also contribute to that trigger."

The next steps, says Eisenlohr, could be to look at population data to see whether use of gentamicin correlates with higher rates of autoimmune diseases, as well as testing whether the peptides generated during gentamicin treatment actually do cause autoimmunity in a mouse model of the disease.

More information: E Goodenough et al., "Cryptic Q:1 MHC class I-binding peptides are revealed by aminoglycoside-induced stop codon read-through into the 3' UTR," *PNAS*, DOI: 10.1073/pnas. 1402670111 , 2014.

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