Immune receptor thought to be linked to hearing loss in child cancer survivors confirmed in new study

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Permanent hearing loss triggered by a common chemotherapy drug in half of children being treated for cancer may occur through a well-studied immune receptor, according to University of Alberta research.

The study confirms a long-held belief and sets the stage for the development of safe doses tailored to each child's genetic makeup.

For the study, recently posted in bioRxiv, Ghazal Babolmorad, a Ph.D. student in the Faculty of Medicine & Dentistry, focused her research on the immune response children with cancer have to cisplatin, a platinum-based chemotherapy drug that is highly effective in fighting the disease, but leads to serious side effects in 90 percent of patients. These side effects include kidney and heart damage as well as permanent hearing loss in upwards of 60 percent of children.

"If we're able make cisplatin, an otherwise invaluable chemotherapeutic tool, safe for everyone—not just low-risk patients—it could be a game-changer for the quality of life of the children using cisplatin as their cancer therapy," said Babolmorad.

The platinum atom at the center of cisplatin is responsible for killing cancer cells, but can also activate an immune receptor in the cell membrane, known as TLR4, that experts have long thought plays a role in inflammation. Immune receptors are proteins that detect the presence of a pathogen—or something wrong, like a cancer cell—and generate a signal to combat the pathogen.

The inflammation caused by the immune receptor that Babolmorad and her supervisor Amit Bhavsar were interested in occurs in the cochlea and results in damage to the auditory cells and, ultimately, hearing loss.

To better understand the mechanism behind this inflammation, th team treated two groups of auditory hair cell lines—similar to the ones found in human ears responsible for perceiving sound—that were essentially identical, except one of them lacked the TLR4 immune receptor, with platinum.

"As expected, we only saw signals arise in the cells with TLR4," said Babolmorad. "Basically, platinum, and cisplatin by extension, can activate the TLR4 immune receptor, which causes a response in the immune system—like inflammation in the cochlea."

However, thanks to genetic variation, there are people who express a low level of this immune receptor, which means their immune system isn't activated and they have a low risk of developing hearing loss, said Babolmorad.

Babolmorad is now working with other U of A

researchers, including groups led by chemistry professor Fred West and biology professor Ted Allison, to examine potential synthetic inhibitors that can block the TLR4 receptors.

More information: Ghazal Babolmorad et al. Toll-like receptor 4 is activated by platinum and contributes to cisplatin-induced ototoxicity, (2020). DOI: 10.1101/2020.06.19.162057

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