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Technique to generate antibodies for natural immune responses to cancer and leukemia

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The artificial enhancement of the body's natural immune defenses is a potential weapon in the battle against diseases such as leukemia. A*STAR researchers are honing methods to boost the interactions between antibodies and natural killer (NK) cells, which will increase the ability of the immune system to attack and destroy cancer cells.

Recombinant therapeutic antibodies are commonly produced in Chinese hamster ovary (CHO) cells and some of these antibodies are used to treat cancer patients by killing cancer cells. It is the job of these antibodies (usually human immunoglobulin G1 or IgG1) to bind to target antigens on cancer cells; the antibody then acts as a bridge to recruit natural killer (NK) cells by binding to its receptor, FcγRIII, on the NK cells, before the NK cells trigger cancer cell death using a mechanism known as antibody-dependent cellular cytotoxicity (ADCC).

It is widely accepted that the removal of the sugar, fucose, from IgG1 antibodies can increase their affinity with FcγRIII, dramatically enhancing ADCC activity.

Now, Zhiwei Song at the A*STAR Bioprocessing Technology Institute and co-workers have successfully created fucose-free IgG1 antibodies by inactivating a key fucose-transporting gene (Slc35cl) in CHO cells. These fucose-free antibodies have the potential to be used in therapies to treat breast cancer and leukemia patients.

"Other methods exist to generate fucose-free antibodies, but some

simply reduce the level of fucose rather than eliminating it," explains Song. "Earlier studies investigated the removal of a different gene involved in transferring fucose to IgG1, for example. Our new technique provides a feasible strategy for creating fucose-free antibodies, and cell lines can be produced in less than two months."

The team faced two main challenges when it came to mutating genes in mammalian cells. Firstly, they needed to create a mutation at the target site on the chromosome; to achieve this they used three different gene editing techniques and compared their effectiveness. Secondly, they had to find a way to quickly and efficiently identify and isolate the cells that carry the mutated genes of interest, and used fluorescent cell-sorting for this purpose.

Although all three gene editing techniques successfully inactivated Slc35cl to produce fucose-free antibodies, one method—CRISPR-Cas9—proved easy and quick compared with the other two. Most importantly, Song and his team found that inactivating Slc35cl did not affect cell growth, cell density or antibody productivity.

"Our hope is to collaborate with biotechnology companies to generate anti cancer antibodies on a larger scale in future," says Song.

More information: Kah Fai Chan et al. Inactivation of GDP-fucose transporter gene ( ) in CHO cells by ZFNs, TALENs and CRISPR-Cas9 for production of fucose-free antibodies , *Biotechnology Journal* (2016). DOI: 10.1002/biot.201500331

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