Engineering a safer antibody drug

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An innovative approach to protein engineering could help make antibody-based drug therapies less toxic and more effective.

Working with two antibody drugs taken by thousands of women with breast cancer each year, A*STAR researchers have shown the possibility of transforming these agents —which normally circulate in the bloodstream—but can also harm healthy heart tissue) into alternative forms that may have more localized tissue distribution. This tweak should result in fewer side-effects, while potentially reducing the dosage needed, which could help lower the cost of treatment.

"It's proof-of-concept that such antibody modification can be undertaken," says Samuel Gan, head of the Antibody and Product Development group at the Bioinformatics Institute and the p53 Laboratory at A*STAR.

Antibodies are also known as immunoglobulins, and they come in five main different 'isotypes': IgA, IgD, IgE, IgG and IgM. Most therapeutic antibody drugs are of the IgG isotype that circulate in the bloodstream, but Gan's team showed they could remodel IgG antibodies into some of the other isotypes that may have greater tissue precision.

Their finding lays the groundwork for future antibody therapies that can be safer for patients without compromising yield or potency.

The researchers worked with trastuzumab and pertuzumab, two antibody drugs marketed under the brand names Herceptin and Perjeta, that

selectively bind to different parts of human epidermal growth factor receptor 2 (HER2), a protein that is implicated in approximately 20 per cent of all breast cancer cases. They transformed these IgG antibodies into all five human isotypes and the four subtypes, and examined what impact that change had on drug production and binding to the HER2 target.

IgD versions of the antibody drugs proved inferior, both in terms of yield and HER2-targeting, but IgE and IgA versions both generally retained the effectiveness of the original therapies—which raises the possibility of developing safer versions of trastuzumab and pertuzumab based on these alternate isotypes. Most interestingly, the findings also show that constant regions in antibodies can influence in the antibody's ability to bind, a finding that is often not noticed and often neglected in antibody research.

As Gan points out, both IgE and IgA antibodies are likely to be more active in the ductal tissues of the breast, where HER2-expressing tumor cells are also found, and they could be combined with low doses of blood-targeting IgG antibodies to guard against circulating metastatic cells while lowering the risk of other side-effects such as cardiac toxicity.

Additionally, Gan suggests that immunotherapies could be developed with IgA and IgE antibodies to better guard against mucosal infections such as influenza or AIDS. "There is a whole range of possibilities to using more localized antibodies as prophylactics," he says.

More information: Wai-Heng Lua et al. The effects of Antibody Engineering CH and CL in Trastuzumab and Pertuzumab recombinant models: Impact on antibody production and antigen-binding, *Scientific Reports* (2018). DOI: 10.1038/s41598-017-18892-9