The light chain subunits of therapeutic antibodies impact drug performance and yield

November 29 2017

Antibody-based drugs have long been a mainstay of treatment for many conditions, especially cancer and autoimmune diseases, but there may still be room for improving these therapies. An A*STAR study has found that changes to a part of the antibodies that's often overlooked by protein engineers and drug companies can have dramatic effects on target binding and manufacturing yield.

An antibody is made up of four polypeptide chains: two 'heavy' chains form the Y shape of the molecule, and two 'light' chains sit alongside them. To date, most of the modification techniques in therapeutic antibody design have focused on the heavy chains. The light chains were generally considered less important, even though it has been demonstrated that they're also involved in binding target molecules, and that the 'framework' regions of light chains provide structural support to allow target contact.

To evaluate the importance of the light chain in antibody performance, a team led by Samuel Ken-En Gan from the A*STAR Bioinformatics Institute and the p53 Laboratory deleted two amino acids in the framework region of the light chain of trastuzumab, an antibody drug for treating breast cancer, sold under the brand name Herceptin. Either deletion on its own, the researchers found, led to a reduction in antibody secretion from a recombinant cell culture system, although it did not severely affect the ability of trastuzumab to bind its target, a protein

called human epidermal growth factor receptor 2 (Her2). Delete both amino acids, however, and both antibody production and Her2 binding decreased significantly.

Structural modeling and experiments conducted by members of Gan's Antibody Product and Development lab, including co-first authors Chinh Tran-To Su and Wei-Li Ling, revealed that the deletions impaired the interaction between trastuzumab and a protein used for antibody purification. That explains the yield reduction, while decreased affinity for Her2 explains why the deletions also obstruct antibody performance.

"This study shows that the light chain and its framework regions can impact key factors of a good therapeutic antibody, even at sites that are not known to be directly involved in binding or purification," he says.

Although these initial findings demonstrate only the negative consequences of altering an antibody's light chain, Gan and his team, in work not yet published, have also found ways to enhance both production and target binding through other light chain modifications. "This is only the first in a series of papers from my lab to show that we need to consider the antibody as a whole and not just as a sum of different parts," Gan says.

More information: Chinh Tran-To Su et al. The role of Antibody Vκ Framework 3 region towards Antigen binding: Effects on recombinant production and Protein L binding, *Scientific Reports* (2017). DOI: 10.1038/s41598-017-02756-3

Provided by Agency for Science, Technology and Research (A*STAR), Singapore