excellent clock stability, the characterization of the frequency uncertainty in the clock transition is the next step to realizing a fully operational optical-tweezer clock. For example, the method used to form the tweezer array causes frequency shifts across the array that must be controlled.

These two studies impressively demonstrate how quantum-technology developments and precision metrology benefit each other. For optical clocks, sophisticated tools and platforms are now at hand. And in turn, squeezed ensembles of individually detectable clock atoms constitute exciting systems for further applications in the fields of quantum simulation and quantum information.

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Immunology

Engineered antibodies to combat viral threats

Xiaojie Yu & Mark S. Cragg

As the COVID-19 pandemic rages globally, interest in antiviral treatments has never been higher. Antibodies are key defence components, and engineering them to better exploit their natural functions might boost therapeutic options. **See p.485**

The use of antibodies to combat human disease dates back to the 1890s. At that time, the physiologist Emil von Behring used blood extracts from rabbits infected with the bacterium that causes diphtheria to tackle that infection. It was discovered only later that antibodies targeting the bacterium were the active ingredient. Amazingly, such serum therapy is still practised today. For example, blood (described as convalescent plasma) donated by people who have recovered from COVID-19, which contains antibodies targeting the SARS-CoV-2 virus, is used as a treatment for people with coronavirus infection. On page 485, Bournazos *et al.*[1] report progress in efforts to aid antiviral responses by engineering human antibodies to enhance their antiviral activity.

Antibodies are a key component of what is called the adaptive branch of the immune system. They can recognize a part of a foreign molecule called an antigen and mobilize various immune processes to neutralize the threat posed by the disease-causing agent. From the work in this area since von Behring's discovery, punctuated by multiple Nobel prizes, we have learnt much about the regulation, structure and function of antibodies, and their use in the clinic has grown exponentially (see go.nature.com/3kltoq7) . Nevertheless, efforts to manipulate, engineer and improve antibodies remain highly topical.

The Fab domain and the Fc domain (Fig. 1) are the two evolutionarily conserved structural components of antibodies. The Fab domain has a variable antigen-binding region, which is different in every antibody, whereas the Fc domain is a constant structure that is largely similar in different antibodies. The Fc domain engages with other elements of the immune system, including a family of what are called Fc receptors, found on a range of immune and non-immune cells[2]. A type of antibody known as IgG engages a subfamily of Fc receptors called the FcγRs. The FcγRs fall into two main classes: activating FcγRs (including the proteins FcγRI, FcγRIIa and FcγRIIIa) and the sole inhibitory FcγR, FcγRIIb. FcγR engagement stimulates or inhibits immune cells, respectively, and the balance of activating to inhibitory engagement determines the responses of cell types that have both activating and inhibitory FcγRs[2].

> **"Efforts to manipulate, engineer and improve antibodies remain highly topical."**

Although antibodies first entered the clinic for use against infection, so far, it has been mainly in combating cancer and autoimmunity that monoclonal antibodies (those with specificity for a single antigen) have had their greatest medical impact. Blockbuster drugs such as trastuzumab (Herceptin; for the treatment of breast cancer), rituximab (for autoimmune diseases and blood cancers) and adalimumab (Humira; for rheumatoid arthritis) have transformed patient outcomes. These advances have been followed by the use of antibodies called immune-checkpoint blockers, which help to unleash immune responses against tumour cells. Such successes have resulted in seven of the top ten global bestselling drugs in 2019 being antibodies[3].

These clinical achievements have fuelled efforts to learn more about the mechanisms underlying antibody action. This led to the rapid realization that FcγRs have pivotal roles in many IgG-mediated functions. Yet it soon became clear that not all patients respond optimally, and there is a need to develop more-effective antibodies for therapeutic purposes. This ushered in the era of Fc engineering, in which key amino-acid residues and sugars in the Fc domain were identified and modified to selectively enhance or reduce their interaction with different FcγRs[4,5].

As the use of monoclonal antibodies has grown, it has been found that different classes of monoclonal antibody require engagement with different FcγRs for optimal activity. For example, antibodies that target tumour cells directly for deletion require activating FcγRs on tumour-killing immune cells, whereas immunostimulatory antibodies that are often directed to receptors of the TNF receptor family on immune cells require inhibitory FcγRs[6]. Yet other types of antibody work optimally without FcγR interaction. In the realm of cancer, this knowledge has guided the development of next-generation antibodies that carry modified Fc domains, such as the antibody drugs atezolizumab and durvalumab, which are engineered for minimal engagement with FcγRs, and the drugs mogamulizumab and obinutuzumab, in which the Fc domain is engineered to increase its binding affinity for FcγRIIIa (ref. 4).

By contrast, the role of FcγRs in affecting antiviral antibody therapies remains relatively under-examined[7]. Indeed, for many researchers, the drive has been to optimize the Fab domain — developing it to serve as a way to tag the virus and prevent its entry into the cell, thus halting transmission and viral replication. However, studies using different viral models have shown that the Fc domain is needed for optimal antiviral therapy[7]. Bournazos *et al.* used mice in which the mouse FcγR was replaced with human FcγR. They found that anti-influenza antibodies directed to bind to various antigens on the viral surface provide an enhanced antiviral therapy if the Fc domain

can bind to FcγRs, and, in particular, if they are engineered to engage with FcγRIIa more tightly than normal.

FcγRIIa is expressed on a type of immune-cell lineage that can present antigens to other immune cells during the process that triggers further adaptive defence responses, including those by immune cells called T cells. Interestingly, if Bournazos and colleagues' anti-flu antibody was engineered so that its Fc domain selectively engaged another activating receptor, FcγRIIIa, which is thought to mediate the activity of many tumour-targeting monoclonal antibodies (although all activating FcγRs probably contribute to tumour-cell deletion *in vivo*[8]), it failed to exhibit increased therapeutic activity compared with wild-type anti-flu IgG that had a non-engineered Fc domain. This suggests that antitumour and antiviral antibodies use distinct mechanisms to mediate their activity, and thus that distinct Fc-engineering approaches are needed to optimize the use of such antibodies.

The authors found that, compared with wild-type anti-flu IgG that had a non-engineered Fc domain, the antibody engineered to have enhanced FcγRIIa binding induced greater maturation of antigen-presenting cells called dendritic cells, and a greater response *in vivo* by immune cells called CD8 T cells, which can kill unwanted cells such as those harbouring virus (Fig. 1). This implies that the engagement of activating FcγRs on antigen-presenting cells enhances their antigen-presenting capability, and therefore puts FcγRIIa in the spotlight as a key receptor for antibody-mediated antiviral defences.

It is possible that such FcγRIIa-optimized antibodies would also augment other antiviral immune responses. However, the mice that received the engineered antibodies showed no modulation of the natural antibody response to the virus that is mediated by immune cells called B cells. This indicates that the T-cell and B-cell responses are probably regulated independently in this infection model. In the absence of an augmented natural-antibody response, adding other monoclonal-antibody therapeutics, such as immunostimulatory antibodies (themselves targeting alternative FcγRs), might further boost antiviral responses compared with using this engineered antibody alone.

There are concerns about augmenting antibody activity because it might trigger unwanted consequences; after all, evolution has fine-tuned antibody activity over eons. One phenomenon observed with viral infections such as dengue is antibody-dependent enhancement, whereby antibody-coated viruses gain entry to cells through IgG–FcγR interactions, which can exacerbate the disease in some people[9]. Bournazos *et al*. found that, in their influenza model, which, like SARS-CoV-2, targets the lung, the FcγRIIa-enhanced antibody did not result in higher than normal inflammation (indicative of potential toxicity) or other evidence of antibody-dependent enhancement, such as an increase in viral infectivity. This suggests that such an approach is safe in this context.

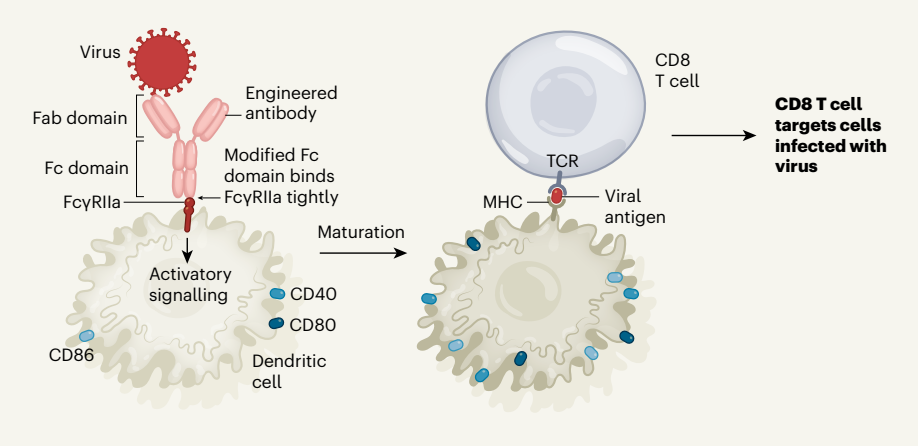

Figure 1 | Boosting antibody-mediated antiviral responses. Antibodies consist of Fab domains, which bind to disease-causing agents such as viruses, and an Fc domain, which enlists other defence components. Bournazos *et al*.[1] engineered an antiviral antibody to have an Fc domain that had an enhanced ability to bind to the receptor protein FcγRIIa. This receptor is found on immune cells such as dendritic cells (which express the defence-boosting proteins CD40, CD80 and CD86). Antibody binding to FcγRIIa triggers signalling that drives dendritic-cell maturation, as indicated by a rise in the expression of CD40, CD80 and CD86. The MHC receptor on dendritic cells can present a viral fragment called an antigen. When the TCR protein of an immune cell called a CD8 T cell recognizes viral antigen, it causes the T cell to kill cells infected with the virus. Consistent with this model, the authors report that mice exposed to influenza virus were better protected from disease if they received the engineered anti-flu antibody than were animals that received a version of the antibody that did not have enhanced binding to FcγRIIa.

The possibility of such a problem remains for other viruses. For example, it is unclear whether antibody-dependent enhancement occurs in people who have COVID-19, in which excessive inflammation has been a feature of severe disease. If so, Fc-enhanced antibodies that drive inflammation could make their use counter-productive as a treatment for COVID-19. However, the success of convalescent plasma in treating COVID-19 indicates that this is probably not the case.

We should be cautious about drawing conclusions regarding human disease on the basis of mouse studies. Although these animals were engineered to express human rather than mouse FcγR, they do not recapitulate the full spectrum of human FcγR expression patterns and genetic variation[10]. Of note, there are multiple human variants of FcγR that have different binding affinities for IgG, and whether FcγRIIa-optimized monoclonal antibodies would be equally effective in treating people who have these variants is unclear.

Nevertheless, Fc-domain engineering for antiviral therapy is a promising avenue to pursue, and Bournazos and colleagues' results support the continued development of such reagents for testing in the clinic. As the Northern Hemisphere moves into winter, with the dual hazards of seasonal influenza and the ongoing COVID-19 pandemic, the need for better treatments for both of these viral threats will become increasingly clear.

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