World of Knowledge

The Third Way to Fight against Dengue

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Dengue has been spreading in the tropic and subtropical areas after World War II. The cases and numbers of countries with dengue-related diseases have dramatically increased in the past 50 years. 50-100 million individuals are estimated to be infected with dengue virus every year. Dengue virus infection of humans causes a spectrum of illness ranging from asymptomatic, to classical dengue fever (DF), severe dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS). Dengue is a mosquito-borne disease and *Aedes aegypti* is responsible for major dengue outbreaks worldwide. In Taiwan, *Aedes aegypti* is confined to southern part of the island, where also has frequent dengue endemics. Comparing with our neighboring countries, the dengue control in Taiwan is doing much better. The biggest dengue outbreak in Taiwan occurred in 2002, in which there were 5388 cases. For the rest of times, the dengue case numbers were controlled to a couple hundreds per year in Taiwan. However, for most of the South-East Asia countries, dengue case numbers exceed 10 thousands every year. With frequent travels between Taiwan and these epidemic countries, we are under great threat of dengue outbreaks, especially in areas infested with *Aedes aegypti*. Thus, dengue has becoming a big challenge and burden for our pubic health system.

Are there any good ways to control dengue? Basically, if there is no dengue vector, there will be no dengue fever; and if there is no dengue fever, there will be no severe DHF/DSS. However, it is rather difficult to eradicate mosquitoes. Researchers mainly focus on antiviral and vaccine development to fight against dengue virus. Vaccine development for dengue has been started since 70s, but a big hurdle is the potential risk of secondary infection on severe DHF/DSS. Dengue viruses can be divided into four serotypes and there is no cross neutralization between the serotypes. Thus, if one individual has been infected with one of the dengue serotypes, he/she will still be susceptible to the other three serotypes of dengue virus. Furthermore, the antibody induced by the primary infection not only cannot neutralize the subsequent dengue virus, but also might enhance the secondary infected dengue virus through its cross reactivity, a phenomenon known as antibody-dependent enhancement (ADE). The ADE hypothesis in severe DHF/DSS pathogenesis has cast a great concern for the safety and efficacy of dengue vaccine. The basic idea of vaccine is to immunize an individual by injection with attenuated or killed virus to induce antibodies and other immune components. Once the individual is infected with the virus, he/she will then mount a potent immunity against this virus quickly. However, in the case of dengue, preexisting antibody might be a risk factor for severe form of the disease, contradicting to the basic principle of vaccination. Another problem for dengue vaccine development is the lack of suitable animal model, making the progress of dengue vaccine very slow. Recently, tetravalent attenuated dengue vaccines against all

four serotypes have been developed and some promising results have been collected from the human clinical trials. Large scale phase II/III clinical trials are also under planning. However, there are still some safety concerns and a global usage of dengue vaccine might be hampered by the safety issues. Antiviral drug development is another choice and some pharmaceutical companies have been devoted to developing antivirals against dengue virus. High-throughput screening has been used to search for the lead compounds against dengue virus infection, and many more research works are still required in this field. One potential problem is that dengue virus replication occurs in the early phase of the disease. If dengue patients cannot be diagnosed and given the drug during the viral replication phase, the antiviral treatment will not have its beneficial effect for the patients. Since many diseases have similar early symptoms such as fever and headache etc, it might restrict the potential usefulness of antivirals against dengue diseases.

The biggest concern for dengue diseases is the severe forms of DHF and DSS. If we can avoid death on dengue patients, the threat of dengue on humans will be greatly reduced. How to prevent the severe dengue has been an important subject for dengue researches, but the progress is rather slow. Besides the secondary infection mentioned above, other factors such as virus strains and host factors may be also involved. It is generally believed that in severe patients more virus replication and more immune activation have occurred, and the excess abnormal immune factors lead to hemorrhage and shock. The current treatments for severe dengue are mostly supportive and symptomatic cares by intravenous fluid therapy. The case fatality rate for DHF/DSS can be controlled to around 1% in experienced countries, but the fatality rate in Taiwan is around 10% in recent years. It might be due to that most of our dengue cases are adults with underlying diseases, in contract to the children cases in South-East Asia. However, the dengue management in our hospitals still needs to be further improved. Besides, if we understand the pathogenesis mechanism for severe DHF/DSS, we may be able to develop specific therapy for better treatment. Apparently, in dengue patients there is some “good” immunity to fight against dengue virus and some “bad” immunity that causes symptoms. Is there a way to just turn off the “bad” immunity without blocking the “good” one in dengue patients? Administration of immune suppressors such as corticosteroids might block both the good and bad immune responses. Neutralization of the downstream immune factors might be incomplete and cannot achieve an overall beneficial effect. Thus, if we could found the “switch” that triggers the bad immunity in dengue patients and specifically turn off this switch, it might then provide a better treatment to fight against dengue diseases.

This idea has been made possible in a recent study. Dr Shie-Liang Hsieh of National Yang-Ming University, who holds a joint appointment at the Genomics Research Center, Academia Sinica, has been collaborating with several groups in Taiwan including our president Dr. Chi-Huey Wong and writer of this article, Dr. Yi-Ling Lin in the Institute of Biomedical Sciences. We found that dengue virus binds to a human macrophage surface lectin receptor called CLEC5A and stimulates proinflammatory cytokines release. Blockage of CLEC5A-dengue virus interaction suppresses the secretion of proinflammatory cytokines without affecting the antiviral interferon

release. Moreover, anti-CLEC5A monoclonal antibodies inhibit dengue virus-induced plasma leakage, as well as subcutaneous and vital organ hemorrhaging, and reduce the mortality of dengue virus infection by ~50% in a Stat1-deficient mouse model. The observation that blockage of CLEC5A-mediated signaling attenuates the production of proinflammatory cytokines by macrophages infected with dengue virus (either alone or complexed with an enhancing antibody) offers a promising strategy for alleviating tissue damage and increasing the survival of patients suffering from DHF/DSS. The next step will be to humanize the murine anti-CLEC5A antibody and to plan for the human clinical trial. Other means to block the CLEC5A-dengue virus signaling cascade may also be explored. Hopefully, a new treatment option besides vaccine and antiviral drug for dengue victims would be available in a couple of years from now.

Reference:

1. Chen ST, Lin YL, Huang MT, Wu MF, Cheng SC, Lei HY, Lee CK, Chiou TW, Wong CH, and Hsieh SL. 2008. CLEC5A is critical for dengue-virus-induced lethal disease. **Nature** 453: 672-676.