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EDITORIAL

Seeking and destroying the evils from the inside-translating cancer immunity to fight COVID-19

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Facing the current COVID-19 pandemic around the world, we are eagerly looking for protection and cure for this infectious disease. Certain uncertainties we are facing are: (1) to what degree our immune system can provide efficient protection to control the actual infection of COVID-19 virus and to avoid fatal side effects of immune responses, like cytokine storm and tissue damage; (2) how we can handle the immunologic impacts of a latent COVID-19 if it becomes a seasonal disease, especially if the viruses hide and live within host cells without a symptom. Although the latter is a speculation for now, it is never too late for us to develop scientific strategies to prepare for the risk when this becomes real. In this regard, it is the right time for our experts in the field of cancer immunity to share the knowledge and technology that we have developed in cancer immunology and immunotherapy for prevention and treatment of COVID-19.

As for the first uncertainty, we do have some strategies based on humoral immunity and innate immunity. Our humoral immunity to COVID-19 virus will be achieved through the generation of virus-specific antibody that can neutralize the COVID-19 viruses when they are in our circulation (blood or body fluid), in either blocking virus' entry to host cells or marking viruses for destruction by NK cells or macrophages which are key effector cells in our innate immunity. To that end, the COVID-19 vaccine can be used to generate a neutralizing antibody providing long-term protection if possible, and a direct transfer of potential COVID-19 virus-specific antibody in the plasma isolated from recovered patients previously infected with COVID-19 virus can be used to stop viral infection. In this regard, our knowledge in cancer vaccine development and technology in therapeutic antibody (blockade antibody in particular) production would help optimize the vaccine formula for COVID-19 and mass production of neutralizing or blocking antibody for COVID-19 virus.

To the second uncertainty, we do not have promising strategies yet. As we know, for a short period after the viruses enter the host cells, they are dormant intracellularly, without symptoms in infected patients, but they can expand quickly inside host cells providing a shelter for virus to escape the recognition or attack of our immune system using a mechanism called immune tolerance (a self-protection mechanism in our body to avoid self-or auto-immune responses). Of note, it is still unclear whether a tiny number of COVID-19 viruses would remain in the host cells (especially in the deep organs that are not easily accessible for a test) after most of the virus are destroyed by antibody and immune cells in circulation and the virus cannot be detected in blood or surface tissues (i.e., nasal or throat). To that end, our cellular immunity (mainly T cells) will come to the stage using their specific detector (T cell receptor) to seek viral epitopes on the surface of infected host cells when these viral antigens are presented by antigen-presenting complex (MHC molecules). Once T cells find the target epitopes of viral antigens, and they will initiate their cytolytic function to destroy the infected cells in a way that not only destroy the entire infected cells (no more shelter for the virus), but also cut the genome of virus into very small fragments (to prevent the leaking of virus from infection of other healthy cells). However, in certain situations, even though T cells can detect the viral antigens in infected cells, they may not be able to mount an attack due to lack of enough co-stimulation signals or due to the presence of immune checkpoint molecules. It is unknown if any immune tolerance mechanisms may be identified in patients at their early stage of infection when the COVID-19 virus might reduce costimulatory signals or increase expression of immune checkpoint molecules in host cells at their entry site. In this regard, our tumor immunologists can provide vital expertise in development of T cell epitope vaccine to enhance the T cell recognition of viral infected cells, and provide tools to detect and

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block immune checkpoint molecules in infected host cells in order to enhance T cell responses to COVID-19 viruses once they hide inside of host cells.

Finally, the last but not least challenge in both cancer immunity and viral immunity, is how to balance immune attack (to destroy cancer cells and infected cells) and immune tolerance (to preserve normal cells). As we know, there are several fatal immunopathology caused by over-activated immune responses to COVID-19, i.e., cytokine storm or tissue damage in the lung or other crucial organs (heart or kidney). Given our knowledge of immune suppression with cancer, we would be able to provide new insight to understanding of the immunopathology caused by uncontrolled immune response during viral infection, and provide tools to reduce the damage. For example, the regimens we are using to prevent or reduce cytokine storms in cancer patients during CAR-T cell therapy could be applied to reduce the risk of the cytokine storms in patients with COVID-19, although an appropriate timing needs to be defined in due course. Our knowledge of immune checkpoint molecules and regulatory immune cells in control of local or systemic immune response may also contribute to prevention of tissue damages caused by over-activation of anti-viral immune responses.

As both malignant cancer cells and latent viruses know how to hide from immune attack and to manipulate our immune tolerance mechanism, they are evils inside our cells and our body and wait for a chance to take our life. Using our knowledge and technologies accumulated in cancer immunity, we have come to understand how to seek and destroy the evils from the inside, although not yet perfectly, and we are prepared to help the fight against COVID-19. During this battle with COVID-19, it is equally important for us to learn new knowledge and technology that can be translated back to our fight with cancer. Standing together makes us stronger in fighting these two wars!