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Letter

Is Immunological Memory a Burden in Times of COVID-19?

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In a recent TrendsTalk in *Trends in Immunology*, Ger Rijkers [1] concluded that 'In times of COVID-19, it would seem as if loss of memory is the key to survival'. We are witnessing the emergence of a new disease caused by a novel virus (severe acute respiratory syndrome coronavirus 2; SARS-CoV-2), and the mechanisms used by the human immune system to eliminate the infection in individuals recovering from the disease are yet unknown. Thus, the field is open to speculation. Nonetheless, various considerations make it difficult to visualize immunological memory as a factor contributing to coronavirus disease 2019 (COVID-19) mortality.

Rijkers proposes that, in the present COVID-19 pandemic, adults are less capable of surviving SARS-CoV2 infection because their immune system is too weak to eliminate the virus, because it is 'clogged' with memory cells that are useless for this infection, hindering a fast and adequate primary immune response. He derives his argument from the question 'Why do we need immunological memory?' raised by Rolf Zinkernagel [2], who arrived at this question from a seemingly simple reasoning: if our defense system is able to eliminate a first infection caused by a given pathogen, why would it not be as capable of surviving a second encounter with the same pathogen? Arguments for why immunological memory is an important feature of adaptive immunity were given by both Zinkernagel himself in the same article, and soon after by Davenport [3]. In principle, in the absence of immunological memory, having survived an encounter with a specific pathogen cannot guarantee that a second infection might be defeated, because many variables might influence the outcome of second or subsequent infections; namely, the infective dose, and the overall shape of the defense system, which might be affected by different factors, such as nutrition, stressors, aging, hormonal concentrations, concomitant disease, and so on.

Immunological memory provides an increased chance of surviving subsequent infections by the same pathogen, with either milder symptoms, or (more often than not) no symptoms at all. It also allows at least some level of cross-protection against similar pathogens, or against new strains of a pathogen. In the present COVID-19 pandemic, it is not yet known whether previous infections with common coronaviruses provide any level of cross-protection, but it is noteworthy that T cell responses to SARS-CoV2 have been recently found in individuals not exposed to the virus [4,5]. Moreover, while it is true so far that most young children infected with SARS-CoV-2 appear to suffer a milder form of the disease, the assumption that adults are more likely to develop severe disease because they might harbor a higher number of memory cells relative to children, ignores the fact that a significant number of infected adults have been asymptomatic, or have coursed with only mild symptoms. There is no reason to believe that the pool of memory cells in these adults is lower than that of adults experiencing severe disease.

The formation and persistence of a pool of memory cells can have functional consequences other than surviving a second infection with the same pathogen, as suggested by the fact that lymphocytes with memory phenotypes are generated from naïve cells, even in the absence of antigen stimulation, to maintain a defined pool of memory cells (reviewed in [6,7]).

Finally, Rijkers proposes that, from an evolutionary point of view, it makes sense that the youngest members of a population have a better chance of surviving infection by a new virus. However, it appears unlikely that immunological memory is a mechanism that evolution adopted in order to renew populations of a species by increasing the susceptibility of older individuals to an emerging infectious disease. Immunological memory is a mechanism that contributes to rendering the lifespan of individuals longer. Given that adaptive immunity (including specific memory cells) evolved from defense systems with limited or absent mechanisms of specific immune memory at the individual level, one can consider that, if vertebrates do have immunological memory, it is because, from an evolutionary perspective, it is better for them to have immunological memory than to not.

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