How our immune system acquires tolerance to malaria and helped us survive COVID-19

Malaria and COVID-19 are two of the most devastating infectious diseases that have impacted public health globally. While they are caused by two entirely different pathogens, their clinical manifestations overlap significantly, and these similarities mirror the immunological mechanisms that determine disease outcomes. In this lecture, the biology of the two pathogens, as well as the human immune responses to infections by these pathogens will be discussed. In addition, the lecture will discuss science capacity building in Africa, and the impact of the West African Centre for Cell Biology of Infectious Pathogens (WACCBIP) in developing science leadership on the continent.

One of the most remarkable phenomena observed during the COVID-19 pandemic was the relatively low mortality in sub-Saharan Africa, despite various ominous predictions of devastation of the continent. Data will be presented to demonstrate how frequent exposure to malaria trained the human immune system to tolerate further infections. Furthermore, the data will show that the malaria-induced reprogramming of the immune system was beneficial to people living in malaria endemic areas during the COVID-19 pandemic by protecting them from severe disease and death.

Malaria is caused by a parasite known as Plasmodium, and the specific type that causes the most disease and death in humans is called *Plasmodium falciparum*. This parasite is transmitted from one human to another through the bite of an infected Anopheles mosquito. Although the parasites go to the liver first, they eventually enter the blood where they repeatedly invade, grow and burst out of red blood cells. During each cycle, when the parasites burst out, large quantities of parasite products are released into the blood, which stimulate the immune system, and cause symptoms such as fever. The immediate reaction of the immune system is an inflammatory response, characterized by the release of mediators including cytokines such as interleukin-12 (IL-12), Tumor necrosis factor alpha (TNF-α) and reactive nitrogen and oxygen species, which help kill the parasites. However, excessive production of these pro-inflammatory mediators can be deleterious to human tissues and organs, and therefore needs to be carefully regulated to prevent exacerbation of disease pathogenesis.

In individuals living in malaria-endemic countries such as Ghana and the rest of sub-Saharan Africa, exposure to malaria begins early in childhood, with immunity (resistance) being acquired after repeated infections by Plasmodium. This acquired resistance to malaria appears to be two-fold: anti-parasite immunity and anti-disease immunity. While anti-parasite immunity is mediated by the development of specific antibodies targeting *P. falciparum*, which act to suppress parasite multiplication, our data demonstrate that anti-disease immunity is mediated by controlling excessive inflammation and thereby

minimizing clinical symptoms without necessarily clearing the parasites. In that sense, anti-disease immunity is essentially clinical immunity, which can be achieved by 'tolerating' the parasites. Recent research indicates that the blunting of inflammatory responses that confers tolerance to malaria parasites is mediated by epigenetic (on-top-of genetics) mechanisms, which involve reprograming of immune cells to prevent them from responding to inflammatory stimuli. Therefore, the anti-disease effects of malaria-induced tolerance appears to extend beyond Plasmodium stimulation to other inflammatory stimuli, including other pro-inflammatory pathogens such as certain bacteria and viruses.

COVID-19 is caused by the Novel Coronavirus called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which is highly contagious and transmitted through the oral and nasopharyngeal routes. Although SARS-CoV-2 is a much smaller and less complex pathogen than Plasmodium, COVID-19 shares several symptoms with malaria, including fever/chills, headaches, malaise, vomiting etc. As observed in malaria, COVID-19 pathogenesis is characterized by the increased release of pro-inflammatory cytokines, the so-called 'cytokine storm', which if unchecked could cause multi-organ damage in the patients. Furthermore, the majority of SARS-CoV-2 infections are asymptomatic (without clinical symptoms), which mirrors the situation in malaria-endemic areas, where the majority of Plasmodium-infected individuals show no symptoms of disease. Given these curious similarities between COVID-19 and Malaria, and the general trend of less COVID-19 severity in sub-Saharan Africa, it was of interest to investigate the possible interactions between the two diseases. Therefore, we investigated the production of cytokines in SARS-CoV-2-infected individuals in Ghana who were either asymptomatic or had mild to severe symptoms of COVID-19. Our data show clearly that asymptomatic infections were associated with a distinct lack of inflammatory responses while individuals showing symptoms had significantly increased levels of pro-inflammatory cytokines in their blood. Of significant interest, we also observed that evidence of high previous exposure to malaria was associated with a blunted inflammatory response and protection from clinical disease following a SARS-CoV-2 infection, indicating the impact of malaria-induced tolerance to inflammatory stimuli.

Taken together, the evidence from our research establishes that our immune system learnt how to tolerate malaria parasites after repeated infections by inhibiting our cells from responding to further stimulation. Further, our work extended to COVID-19 and showed that the immune cell reprogramming that was acquired from living in a malaria-endemic area protected us against development of severe disease during infections by SARS-CoV-2. These findings contribute to a better understanding of the global dynamics of COVID-19 infections and mortality.

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