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Viewpoint

Breathing more breadth into COVID-19 T cell responses

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SUMMARY

Innate and adaptive heterologous immunity confers resistance to pathogens. However, its impact on resistance and the course of human infection have remained largely elusive, hampering the use of this phenomenon to enhance vaccine efficacy. In this issue of *Med*, Mysore et al. show that T cell responses elicited by SARS-CoV-2 infection or vaccination correlate with those induced by MMR and Tdap immunization, revealing the transcriptomic basis of these correlations and find that heterologous adaptive immunity contributes to a better prognosis of COVID-19 disease.[1]

Adaptive immune responses elicited by T and B cells are crucial for the control of viral infections. Antigen presenting cells (APC) such as dendritic cells (DC) process incoming antigens and present them to $CD4^+$ or $CD8^+$ T cells, inducing their activation, clonal selection, and subsequent proliferation.[2] During viral infection, restricting viral replication and spread is essential to host survival and to limit disease severity. T cells have been indicated to be indispensable for limiting viral replication. During this process, $CD4^+$ T helper T cell populations (Th) which support the generation of antibody producing B cells and secrete pro-inflammatory cytokines, such as interferon gamma (IFNγ), promoting clearance of the infection, increase. In parallel, a pool of heterogenous antigen-specific long-lasting memory $CD4^+$ and $CD8^+$ T cells is generated. Among those $CD4^+$ and $CD8^+$ memory T cells, effector memory re-expressing CD45RA (T_{EMRA}) T cells have recently been identified to be major contributors to tissue-resident immunity to viruses, in particular SARS-CoV-2.[3] Within the tissue, T_{EMRA} cells provide a rapidly activated, antigen-specific, long-lasting first barrier to reinfection and induction of T_{EMRA} cells by vaccination often correlates with enhanced protection.

During early infection, SARS-CoV-2 induces antigen-specific $CD4^+$ and $CD8^+$ T cells, which exhibit a prototypical antiviral phenotype (i.e., $IFN\gamma^+$, $IL\text{-}2^+$) and are detectable even during convalescence.[4] Several studies have reported a positive correlation between the magnitude and timing of T cell responses with antibody production and disease severity.[4] Recently, it was discovered that in spite of the high specificity of T cell responses conferred by the T cell receptor (TCR), cross-reactive memory T cells can be found in humans and in experimental mouse models and were shown to exhibit reactivity to different influenza A virus strains in naive donors or to induce cross-protection to Zika Virus in patients seropositive for Dengue virus, a phenomenon termed heterologous immunity. Similarly, T cells reactive to SARS-CoV-2 peptides have been isolated from patients who were infected with SARS-CoV more than 10 years ago or from healthy donors exposed to other coronaviruses causing the common cold [5].

Vaccines, such as BCG, the measles-mumps-rubella (MMR) and tetanus-diphtheria-pertussis (Tdap) have been shown to induce adaptive heterologous immunity,[6] but the biological significance of such heterologous immunity remains unclear although it could potentially inform the design of more efficient vaccines (Figure 1).

To shed further light on the molecular processes underlying heterologous adaptive immunity in response to SARS-CoV-2, Mysore and colleagues[1] developed a refined approach to study antigen-specific T cell responses and reported the identification of a heterologous T cell pool sharing responsiveness to SARS-CoV-2 and the antigens of two of the most used vaccines in humans, MMR and Tdap. In this study the authors use highly activated SARS-CoV-2 or MMR/Tdap vaccine antigen pulsed neutrophils or monocyte-derived DCs from the blood of SARS-CoV-2 infected patients or healthy donors, to allow physiological antigen processing, and subsequently co-culture those APCs with autologous T cells to evaluate T cell reactivity.

Interestingly the authors not only observed strong memory T cell activation specific to nucleocapsid and the S1 spike protein of SARS-CoV-2, but also reactivation of memory T cells toward antigen contained within the MMR and Tdap vaccines. These recall responses were higher in infected individuals than in healthy ones and in contrast to IgG antibodies, they were readily detected early during infection. An increase of memory T cells reactive to the S1 spike but also to MMR and Tdap antigens was observed in samples from individuals who received the Moderna mRNA-1273 COVID-19 vaccine 2.5 months after the second dose, confirming cross-reactivity to other antigens induced by vaccination. A

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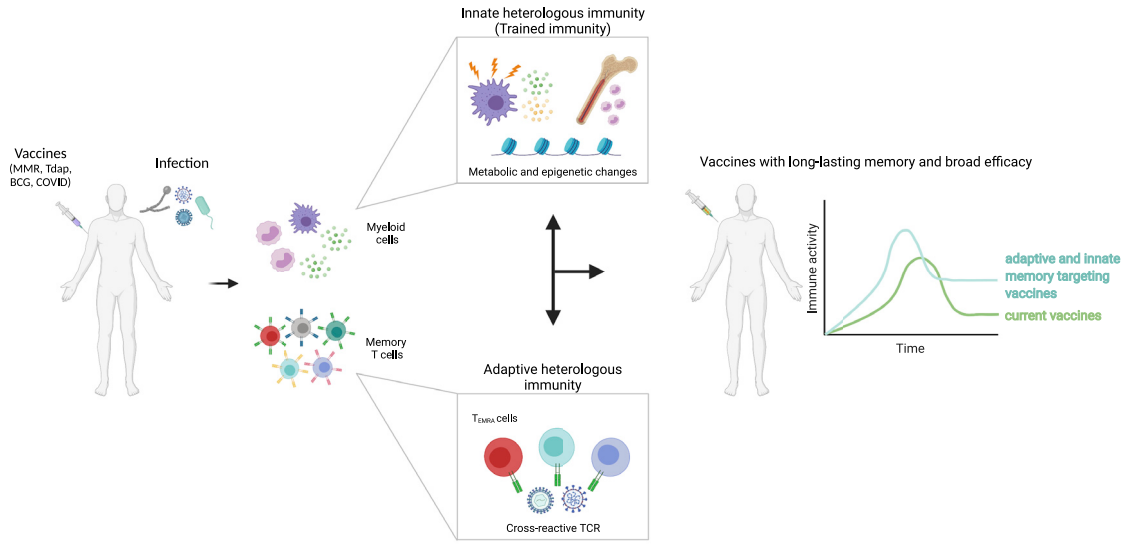

Figure 1. Origin and mechanisms of innate and adaptive heterologous immunity

Vaccination and infection events along a person's lifetime generate immune memory to confer long-lasting protection. Cross-reactive memory $CD4^+$ and $CD8^+$ T_{EMRA} cells are persistent and can react to different antigens creating a broader barrier, as shown by a recent publication exploring the effect of MMR and Tdap vaccines on the adaptive immune responses to SARS-CoV-2.[1] Other vaccines, such as BCG are also capable of inducing similar heterologous responses by priming myeloid cells, which undergo metabolic and epigenetic changes that trigger broad and persistent protection. Both mechanisms of heterologous immunity should be considered to improve vaccine efficacy and prolong protection.

phenotypic characterization of the heterologous reactive T cells revealed a prevalent and overlapping population of $CD4^+$ T_{EMRA}, expressing $IFN\gamma^+$, $GPR56^+$, and $CX3CR1^+$, providing them with the molecular toolbox to enter peripheral tissues and to provide adaptive first line defense. $CD8^+$ T_{EMRA} were also reactive to all antigens, although they were lower in COVID-19-vaccinated individuals than in convalescent ones. To reveal the underlying molecular mechanisms of heterologous immunity in the identified T_{EMRA} populations, single-cell mRNA sequencing together with TCR sequencing was performed and identified more than 10,000 TCR clonotypes. Among those 10,000 clonotypes, 90 heterologous clonotypes were found, of which 30 were shared across all assessed donors. The authors also confirmed their identity as cytotoxic T_{EMRA} cells according to their transcriptomic profile.

To extend these findings and assess if heterologous immunity to SARS-CoV-2, MMR, and Tdap antigens contributed to the breadth of severity seen during SARS-CoV-2 infection, the authors retrospectively investigated a cohort of 11,483 and 36,793 infected patients previously vaccinated with MMR or Tdap, respectively. After adjusting for several demographic traits and risk factors, the authors observed a 38% or 23% decrease of COVID-19 severity in individuals who were previously immunized against MMR or Tdap, respectively. This suggests that previous events, such as vaccination or infection, enhance the immune response to SARS-CoV-2.

Although previous *ex vivo* studies had shown that pre-existent memory T cells exist and recognize antigenic peptides related to SARS-CoV-2,[5,7] the existence of heterologous T cell clones recognizing physiologically processed antigen remained elusive. Here, the authors combined physiological processing of SARS-CoV-2 with a single-cell resolution characterization of TCR specificity and diversity, generating a detailed helpful resource to understand the transcriptional basis of heterologous T cell responses and to utilize such knowledge designing more efficient vaccines.[1]

Convalescent and COVID-19 mRNA vaccinated individuals exhibited a significant increase of MMR- and Tdap-specific T_{EMRA} cells corroborating the efficacy of vaccines in triggering a heterologous adaptive response to SARS-CoV-2.[1] $CD8^+$ T_{EMRA} cells have been shown to be essential for viral control and as a central cornerstone for the control of reinfection. Intriguingly, a subtle difference between SARS-CoV-2 and vaccination with COVID-19 mRNA vaccines was described. Here, vaccines were shown to exhibit a lower amount of activated $CD8^+$ T_{EMRA} cells post vaccination. Therefore, studies comparing the effect of vector-based and mRNA vaccines regarding induction of heterologous $CD8^+$ T_{EMRA} are necessary to evaluate novel vaccination designs and schemes.

Viral- and bacterial-derived antigens have been shown to induce heterologous adaptive immunity, converging on a similar repertoire of memory T cells that

are cross-reactive to SARS-CoV-2 peptides. Additionally, BCG, the world's most used vaccine, confers some protection toward infection with Yellow Fever Virus (YFV) and other types of pathogens *in vivo*.[8,9] Recently, YFV itself has been linked with the induction of heterologous innate immunity, also termed trained immunity, in humans. Both induction of trained immunity by BCG and YFV have been linked to a reprogramming of myeloid cell progenitors and effector cells, inducing a marked metabolic and secretory switch, enhancing the amplitude and duration of inflammatory responses, allowing for an increased first line defense against invading pathogens.[8,9] Mechanisms of the induction of adaptive heterologous immune responses remain elusive, except for the notion that shared TCR specificities are triggered by antigenic similarity. However, the mechanisms by which T_{EMRA} cells are preferentially generated, and there is a strict licensing dependency toward interleukin 15, remain unknown. Further studies elucidating the transcriptional networks active in heterologous T cells are urgently needed (Figure 1).

The clinical benefits of BCG-induced trained immunity are currently evaluated in first-line health care workers in regards to protection and severity of COVID-19 (NCT04659941, NCT04648800, NCT04384549, NCT04348370).[10] Here the effect of MMR and Tdap vaccination was retrospectively evaluated and a reduction of severe COVID-19 was found and attributed to the induction of heterologous adaptive immune response.[1] However, effects of the innate immune system cannot be ruled out in this retrospective analysis as MMR and Tdap have been shown before to induce trained immunity in humans.

Collectively, robust, specific, and long-lasting T cell responses are essential to protect against viral infection, especially in the absence of efficient antibody responses as it occurs in elderly. Here, the authors highlight that heterologous adaptive immunity, inducing efficient T_{EMRA} effector cells, might prove a novel avenue to increase overall immunity against viruses and other pathogens. Therefore, these data build a foundation to incorporate the benefits of heterologous adaptive and innate immunity into the design and development of novel vaccine toolboxes and vaccination schemes to counteract the current ongoing SARS-CoV-2 pandemic and to increase preparedness toward new and as of now unknow pathogens with pandemic potential (Figure 1).

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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