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Review Article

The Role of Memory T-Cell Mediated Immunity in Long-term COVID-19: Effects of Vaccination Status

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Abstract

T-cell-mediated immunity is essential for controlling severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, preventing severe disease, and potentially reducing the risk of long-term coronavirus disease (COVID). This study investigated the impact of natural infection, vaccination, and hybrid immunity on T-cell responses, with a particular emphasis on the role of memory T-cells in long-term COVID-19. The present study reviewed current literature on T-cell responses, including memory T-cell development, in individuals with natural SARS-CoV-2 infection, those vaccinated with messenger RNA (mRNA) vaccines, and those with hybrid immunity. It examined studies that compared T-cell activity, immune regulation, and the prevalence of long-term COVID-19 across these groups. Natural infection induces variable T-cell responses, with severe cases showing stronger but sometimes dysregulated immunological activity, which may contribute to prolonged COVID-19. Vaccination, particularly with mRNA vaccines, elicits targeted and consistent T-cell responses, including memory T-cells, reducing disease severity, and the incidence of long-term COVID-19. Hybrid immunity combines natural infection and vaccination, provides the most robust protection, enhanceds memory T-cell responses, and reduces the risk of long-term COVID-19 through balanced immune regulation. Memory T-cells play a critical role in mitigating long-term COVID-19. Vaccination significantly enhances T-cell-mediated immunity, minimizing the risk of chronic symptoms compared to natural infection alone. Hybrid immunity provides the most effective defense, emphasizing the importance of vaccination, even after natural infection, to prevent long-term COVID-19.

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What's Known

- T-cell-mediated immunity plays a vital role in combating SARS-CoV-2 by regulating viral replication and preventing severe outcomes. CD8+ cytotoxic T-cells directly attack infected cells, while CD4+ helper T-cells aid B cells produce antibodies.
- Long-term COVID-19 can cause immune dysregulation, chronic inflammation, and potentially incomplete viral clearance.

What's New

- Vaccination, especially with messenger RNA (mRNA) vaccines and booster doses, enhances T-cell responses, reducing the risk and severity of long-term COVID-19.
- Hybrid immunity, which combines natural infection with vaccination, provides stronger protection than natural infection or vaccination alone by broadening T-cell responses and reducing the risk of long-term COVID-19 infection.

Introduction

T-cell-mediated immunity plays a critical role in the body's defense against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), particularly in controlling viral spread, preventing severe outcomes, and providing long-term protection.[1] T-cells

play a central role in recognizing and eliminating infected cells, with cluster of differentiation 8+ (CD8+) cytotoxic T-cells directly attacking infected cells, and CD4+ helper T-cells assisting in the activation of other immune cells, including B cells that produce antibodies.[2, 3]

Long-term coronavirus disease (COVID), defined as a set of persistent symptoms that continue for weeks to months after the acute phase of infection, has been associated with ongoing immunological dysregulation.[4] Emerging research suggested that T-cell immunity could play an important role in managing or mitigating these prolonged symptoms.[5] Dysregulated immunological responses, chronic inflammation, and probably viral persistence have all been implicated in long-term COVID-19,[6] and the ability of T-cells to effectively remove the virus might influence the development of this syndrome.[7, 8]

One hypothesis is that a robust T-cell response might enhance viral clearance, reducing the likelihood of prolonged viral persistence, which could contribute to long-term COVID-19.[9] Furthermore, the ability of memory T-cells to respond quickly to reinfections or viral reactivations could also play a role in preventing chronic symptoms.[10] Previous studies indicated that individuals with stronger T-cell responses during the acute phase of COVID-19 had better long-term outcomes, including a lower incidence of severe disease and lingering symptoms.[11, 12]

However, the exact mechanisms by which T-cell-mediated immunity impacts long-term COVID-19 are still being investigated. Variability in individual immune responses, the role of different T-cell subsets, and the long-term behavior of memory T-cells are all areas of ongoing research. Understanding these factors will be critical for developing strategies to prevent and treat long-term COVID-19, particularly in populations with diverse immunization statuses. This study aimed to investigate the role of T-cell-mediated immunity in long-term COVID-19 and to assess how vaccination status affects T-cell response and long-term outcomes.

T-Cell Responses in Natural Infection vs. Vaccination

Natural Infection and T-Cell Responses: T-cell responses in individuals who contract COVID-19 through natural infection differ based on the severity of the illness.[11] Severe infections generally induce more robust and long-lasting T-cell responses than mild or asymptomatic cases.[13] This is because a higher viral load and more intense immunological activation during severe disease can lead to stronger and broader T-cell activation.[14] CD8+ cytotoxic T-cells, which directly target infected cells, are frequently more abundant and persistent in individuals with severe illness.[15] Similarly, CD4+ helper T-cells, which help produce antibodies and coordinate immunological responses, tend to be more active.[16]

However, the same robust immune response that contributes to longer-lasting immunity can also contribute to the development of long-term COVID-19.[17] In some cases, a heightened and prolonged immune activation can lead to chronic inflammation, which has been implicated in the persistence of symptoms in long-term COVID-19.[6] The balance between protective immunity and chronic inflammation is delicate, and when it is dysregulated, it may contribute to the prolonged symptoms experienced by some individuals after acute infection.[18]

Cross-reactivity of Coronaviruses in Natural Infection Before Vaccination

Cross-reactivity refers to the ability of immune cells to recognize and respond to antigens from related pathogens due to prior exposure.[19] In the context of SARS-CoV-2, some individuals who were previously exposed to other coronaviruses, such as those causing the common cold (e.g., HCoV-OC43, HCoV-229E), might exhibit pre-existing immune responses.[20, 21] Studies suggested that earlier exposure to these endemic coronaviruses can activate memory T-cells, which may offer partial protection against SARS-CoV-2 infection.[22, 23]

T-cells derived from previous coronavirus infections can recognize conserved regions across different coronaviruses, particularly within the spike protein and other structural proteins.[24] This cross-reactive immunity could potentially modulate the severity of initial SARS-CoV-2 infection, as these memory T-cells are primed to react faster to viral antigens.[25] Research suggested that individuals with cross-reactive T-cells might have a milder course of COVID-19. However, this is highly variable and depends on the individual's immunological profile and the specific coronavirus exposure.[26]

However, while cross-reactivity may provide some early immunological advantages, it does not replace the targeted immunity induced by vaccination.[27] Vaccines, particularly mRNA vaccines, are intended to stimulate a strong and specific T-cell response against the SARS-CoV-2 spike protein, providing more robust and long-lasting protection.[28, 29] Furthermore, vaccination after natural infection (hybrid immunity) enhances the immune system's ability to respond to SARS-CoV-2 and its variants, minimizing the risks of severe disease and prolonged COVID-19.[30]

Memory T-cells and Their Role in Long COVID-19

Memory T-cells play a critical role in the immune system's ability to recognize and respond to SARS-CoV-2 during acute infection as well as the long-term resistance against reinfection.[11] Following the initial immune response to SARS-CoV-2, a subset of T-cells, both CD4+ helper and CD8+ cytotoxic T-cells, differentiate into memory T-cells.[31] These cells are essential for providing long-lasting immunity by quickly recognizing and responding to the virus during subsequent exposures or viral reactivations.[14]

In the context of long-term COVID-19, viral persistence or reactivation of the virus might pose a challenge to the immune system.[32, 33] On the other hand, memory T-cells can swiftly reactivate and mount a response, potentially mitigating prolonged symptoms.[34] According to previous research, individuals with a robust pool of memory T-cells were less likely to experience severe long-term COVID-19, as these cells help control viral replication and preserve immune homeostasis, preventing chronic inflammation.[11]

Furthermore, vaccination enhances the formation and function of memory T-cells, providing better protection against long-term COVID-19.[35] Vaccinated people are more likely to have an efficient memory T-cell response, reducing the risk of viral persistence or immunological dysregulation.[31] This is particularly noticeable with booster doses, which reinforce the memory T-cell pool, thereby sustaining long-term immunity and reducing the risk of prolonged symptoms.[36]

Vaccination and T-Cell Responses

COVID-19 vaccines, particularly mRNA vaccines, such as Pfizer-BioNTech (Pfizer Inc., USA; BioNTech SE, Germany) and Moderna (Moderna, Inc., USA), are specifically designed to elicit strong T-cell responses in addition to antibody production.[37] These vaccines generate a targeted T-cell response against the spike protein of SARS-CoV-2, which was shown to be effective against multiple variants of concern.[38] The T-cell response induced by vaccination is crucial for preventing severe disease, as it helps control viral replication early in the infection.[39] This early intervention is critical in minimizing viral spread within the body and reducing the overall inflammatory response.[9]

Vaccination has also been associated with a reduction in the incidence of long-term COVID-19 symptoms.[40] A previous study suggested that individuals who were vaccinated before contracting SARS-CoV-2 were less likely to develop prolonged COVID-19 than unvaccinated individuals.[41] This protective effect is assumed to be caused by a primed T-cell response, which lowers the severity of the initial infection and helps prevent the immune dysregulation associated with long-term COVID-19.[11] Moreover, booster doses further enhance T-cell responses, providing additional protection against variants and reducing the risk of developing long-term COVID-19 by maintaining a more balanced and controlled immune response.[31, 42]

Comparative Analysis: Vaccinated vs. Unvaccinated Individuals

Vaccinated Individuals: Vaccinated individuals typically exhibit more consistent and robust T-cell responses, particularly after receiving booster doses.[43] COVID-19 vaccines, particularly mRNA vaccines such as Pfizer-BioNTech and Moderna, induce strong T-cell responses against the spike protein of the SARS-CoV-2 virus.[44] These T-cells are effective in controlling viral replication by targeting and destroying infected cells, which reduces the severity of acute infection and prevents complications such as long-term COVID-19.[45]

A previous study indicated that vaccinated individuals were less likely to develop persistent symptoms associated with long-term COVID-19.[40] This is most likely due to the modulation of the immune response by vaccination, which aids in preventing the chronic inflammation found in long-term COVID-19.[46] By priming the immune system, vaccines allow for a quicker and more effective T-cell response upon encountering the virus, minimizing the risk of immune dysregulation.[47]

Moreover, booster doses not only reinforce antibody levels but also maintain T-cell activity, providing enhanced protection against new variants of concern and long-term COVID-19.[48] This continuous immunological activity ensures better viral control and contributes to a lower likelihood of experiencing prolonged symptoms.[17]

***Unvaccinated Individuals*:** In contrast, unvaccinated individuals exhibit more variable T-cell responses, which can be less effective in controlling the virus.[49] The absence of vaccine-induced priming means that the T-cell response in unvaccinated individuals may take longer to activate during infection, allowing the virus more time to replicate and trigger inflammatory responses.[50] This slower and potentially less effective T-cell activation can lead to incomplete viral clearance, increasing the likelihood of chronic inflammation, and contributing to the development of long-term COVID-19.[32]

Unvaccinated individuals are at a higher risk of experiencing severe disease and prolonged symptoms, as their immune systems may fail to control the virus efficiently.[51] This ongoing immunological stimulation, along with a lack of targeted T-cell responses, may contribute to immune dysregulation, which is a hallmark of long-term COVID-19.[52] The variability in natural T-cell responses, influenced by factors such as disease severity, age, and underlying conditions, further complicates the immune response in unvaccinated individuals.[53]

In summary, vaccination enhances T-cell-mediated immunity, resulting in more consistent and effective viral control, reducing the risk of severe disease, and long-term COVID-19. Unvaccinated individuals face greater challenges in developing an efficient immune response, increasing their susceptibility to prolonged symptoms.

Impact of Hybrid Immunity

Hybrid immunity, which results from a combination of natural infection and vaccination, is now regarded as the most robust form of protection against SARS-CoV-2 and its variants.[54] Individuals with hybrid immunity benefit from both the broad, diverse T-cell responses, triggered by natural infection and the specific, targeted T-cell responses induced by vaccination, particularly against the spike protein of the virus.[55, 56]

Advantages of Hybrid Immunity

Broader T-Cell Response: Natural infection exposes the immune system to the entire virus, not just the spike protein, leading to a broader T-cell response.[57] This broad T-cell activation provides enhanced protection across different parts of the virus, including against variants that may partially evade spike protein-targeted immunity.[38]

Enhanced and Sustained Immunity: Research revealed that hybrid immunity resulted in a more durable and potent immune response than either natural infection or vaccination alone.[54] The synergy between natural infection and vaccination leads to higher antibody titers and better T-cell responses, which are more efficient in suppressing viral replication.[58] This enhanced immunity contributes to better long-term protection against severe disease and complications, such as long-term COVID-19.[11]

Reduction in Long-term COVID-19 Risk: Individuals with hybrid immunity also appear to have a lower risk of acquiring long-term COVID-19.[59] The combination of the natural immune response to the whole virus and the booster effect of vaccination promotes a more controlled and balanced immune response, reducing the likelihood of chronic inflammation, which can cause prolonged symptoms.[60]

Booster Effect: Vaccination after natural infection serves as a booster, further strengthening the immune system's ability to quickly and effectively respond to future exposures to SARS-CoV-2.[61] This booster effect also contributes to increased protection against variants of concern by maintaining higher levels of neutralizing antibodies and functional T-cells.[62]

Overall, hybrid immunity provides the most comprehensive defense against COVID-19 by combining the strengths of natural and vaccine-induced immunity, leading to better long-term outcomes and a lower vulnerability to long-term COVID-19.

Conclusion

T-cell-mediated immunity, particularly through the role of memory T-cells, is critical in protecting the body against SARS-CoV-2, preventing severe disease and chronic symptoms associated with long-term COVID-19. Robust memory T-cell responses reduce the likelihood of prolonged immune dysregulation, which is frequently associated with persistent inflammation in long-term COVID-19 cases. Vaccination enhances memory T-cell responses, reduces infection severity and long-term COVID-19 risk, with boosters offering additional protection against emerging variants. Hybrid immunity, which combines natural infection with vaccination, provides the most comprehensive defense, fostering strong memory T-cell responses, and providing long-term protection against both acute disease and chronic symptoms.

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Authors' Contribution

A.M and Y.B: led the literature search, synthesizing research findings, and drafting the manuscript with a focus on clinical implications of T-cell immunity and vaccination; S.K and K.K: Conceptualized the study and supervised the

sections on T-cell responses and immunological insights; S.U and Kh. K: Contributed to gathering and interpreting epidemiological data on long COVID and the role of vaccination. All authors contributed significantly to the development of this narrative review. All authors critically reviewed and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest: None declared.

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