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Convalescent Memory T Cell Immunity in Individuals with Mild or Asymptomatic SARS-CoV-2 Infection May Result from an Evolutionarily Adapted Immune Response to Coronavirus and the ‘Common Cold’

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Data Collection B

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Data Interpretation D

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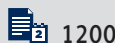
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Recent studies have shown a significant level of T cell immunity to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in convalescent coronavirus disease 2019 (COVID-19) patients and unexposed healthy individuals. Also, SARS-CoV-2-reactive T memory cells occur in unexposed healthy individuals from endemic coronaviruses that cause the ‘common cold.’ The finding of the expression of adaptive SARS-CoV-2-reactive T memory cells in unexposed healthy individuals may be due to multiple cross-reactive viral protein targets following previous exposure to endemic human coronavirus infections. The opinion of the authors is that determination of protein sequence homologies across seemingly disparate viral protein libraries may provide epitope-matching data that link SARS-CoV-2-reactive T memory cell signatures to prior administration of cross-reacting vaccines to common viral pathogens. Exposure to SARS-CoV-2 initiates diverse cellular immune responses, including the associated ‘cytokine storm’. Therefore, it is possible that the intact virus possesses a required degree of conformational matching, or stereoselectivity, to effectively target its receptor on multiple cell types. Therefore, conformational matching may be viewed as an evolving mechanism of viral infection and viral replication by an evolutionary modification of the angiotensin-converting enzyme 2 (ACE2) receptor required for SARS-CoV-2 binding and host cell entry. The authors propose that convalescent memory T cell immunity in individuals with mild or asymptomatic SARS-CoV-2 infection may result from an evolutionarily adapted immune response to coronavirus and the ‘common cold’.

MeSH Keywords: **Common Cold • Coronavirus • COVID-19 • Peptidyl-Dipeptidase A**

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Recent studies have provided empirical evidence of T cell immunity to SARS-CoV-2 infection in COVID-19 patients and unexposed healthy individuals [1–4]. Braun et al. recently identified reactive CD4⁺ T cells in 83% of COVID-19 patients and in 35% of unexposed healthy donors, which was confirmed by negative reverse transcription polymerase chain reaction (RT-PCR) and serological screening, following *in vitro* stimulation of peripheral blood mononuclear cells by S-I and S-II peptide pools corresponding to predicted HLA class II epitopes within the NH₂- and COOH- terminals of the SARS-CoV-2 spike glycoprotein [1]. More than 80% of reactive CD4⁺ T cells from healthy donors were derived from stimulation trials utilizing S-II peptide pools corresponding to COOH-terminal epitopes [1]. These epitopes were independently determined to share a higher degree of sequence homology to spike glycoproteins of the endemic ‘common cold’ coronaviruses, including 229E and OC43, and the spike glycoprotein of SARS-CoV-2 [1]. Also, SII-reactive CD4⁺ T cells from COVID-19 patients and healthy donors were predominantly of a TH1 memory phenotype [1]. These data support that the existence of SARS-CoV-2-reactive T memory cells in unexposed healthy individuals originated from previous immune responses to endemic coronaviruses that cause the ‘common cold’ in humans [1].

Grifoni and coworkers further studied SARS-CoV-2-reactive T memory cells in COVID-19 patients and unexposed healthy individuals to include CD4⁺ and CD8⁺ T cells responsive to predicted HLA class I epitopes [2]. Following stimulation with peptides corresponding to predicted HLA class I and class II epitopes, SARS-CoV-2-reactive CD8⁺ and CD4⁺ T cells were identified in between 70% and 100% of COVID-19 convalescent patients [2]. Also, reactive CD4⁺ T cells from COVID-19 patients were responsive to HLA class II epitope pools corresponding to the complete sequence of the SARS-CoV-2 spike glycoprotein and those contained within the sequences of highly-expressed SARS-CoV-2 M and N proteins [2]. Small but significant CD4⁺ T cell responses were observed following stimulation by HLA class II epitope pools corresponding to minor protein species expressed from SARS-CoV-2 open reading frames (ORFs), including nsp3, nsp4, ORF3a, and ORF8 [2]. There was also a diverse pattern of SARS-CoV-2-specific CD4⁺ T cell reactivity in COVID-19 patients that correlated with predicted concentrations of viral protein expression in infected cells [2]. The spectrum of SARS-CoV-2-specific CD8⁺ T cell reactivity from COVID-19 patients appeared to be more evenly distributed across targeted protein species, including spike protein, N and M proteins, nsp6, ORF8, and ORF3a. Importantly, SARS-CoV-2-specific CD8⁺ T cells were detected in at least 4 different healthy donors, but with a narrower distribution of targeted SARS-CoV-2 protein species compared with reactive CD4⁺ T cells [2]. The patterns of SARS-CoV-2-specific CD4⁺ and CD8⁺ T cells responsive to HLA class I and class II epitopes found in multiple species of viral proteins were observed in a significant

number of unexposed healthy donors [2]. These findings suggest a more extensive and more pervasive expression of SARS-CoV-2-reactive T memory cells in unexposed healthy individuals than previously believed [1–3]. These findings might possibly be due to multiple cross-reactive viral protein targets following previous exposure to circulating human endemic ‘common cold’ coronaviruses [1–3].

From a different perspective, a recent bioinformatics analysis of a large medical records database selectively correlated decreased SARS-CoV-2 infection rates in individuals who recently received non-COVID-19 vaccinations [5]. Specifically, prior administration of vaccines to polio virus, *Hemophilus influenzae* type-B (HIB), measles-mumps-rubella (MMR), varicella zoster, the pneumococcal conjugate (PCV13), influenza, hepatitis A, and hepatitis B (HepA-HepB) during 1, 2, and 5 years were associated with reduced SARS-CoV-2 infection rates, after elimination of potential confounders [5]. However, whether SARS-CoV-2-reactive T memory cells originated from previous immune responses to cross-reactive epitopes in human endemic ‘common cold’ coronaviruses remains to be determined. Importantly, supporting evidence is required for the possibility of involvement of similar immunologic mechanisms on a much broader scale. Accordingly, determination of protein sequence homologies across seemingly disparate viral protein libraries may provide invaluable epitope-matching data linking SARS-CoV-2-reactive T memory cell signatures to prior administration of cross-reacting vaccines directed against other common viral pathogens.

Given that exposure to SARS-CoV-2 initiates profound and diverse cellular immune mechanisms, it is possible to speculate that the intact viral particle possesses a required degree of conformational matching, or stereoselectivity, to effectively target the ACE2 receptor on multiple cell types. However, this complementary communication phenomenon is, by nature, restrictive and selective [6,7]. In living organisms, several compounds and processes emerge from genetic information through temporally determined evolutionary processes. Genetic processes are driven by change and adaptation, and the evolution of interactive regulatory mechanisms of gene evolution result in major molecular strategies that preserve and protect this information. Therefore, it may be expected that biochemicals, pharmacological agents, and organisms, including viruses, can both positively and negatively interact because of these commonalities. In this regard, all that is needed to influence other systems and organisms is the complementary matching of critical biochemical components, making them extremely compatible or partially compatible. Also, host ‘target’ processes that promote both viral and bacterial infection and replication tend to be conserved during evolution, probably due to requisite stereoselective aspects of these systems. Therefore, there are so many conformational matching steps

in an entirely integrated organism or system it would be impossible to invent an entirely new system. It is both efficient and economical to merely add tolerated favorable mutations that benefit survival. Furthermore, this conserved core information is relatively stationary in time, allowing for the presence of chance pathological ‘bullets’ that include viruses and bacteria, which periodically result in a conformational match that both alters the host systems and may use it for existential propagation [8]. In most instances, these external assaults may result in host death because of the host’s overall informational mismatching. Conformational matching as an evolving mechanism of viral infection and replication has been shown by a recent study of the angiotensin-converting enzyme 2 (ACE2) receptor, which is required for SARS-CoV-2 binding and host cell entry [9]. Braun et al. undertook a systematic analysis of the ACE2 conservation and coevolution of an interactive protein network across 1671 eukaryotes [1]. They identified potential therapeutic targets responsive to widely used drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and vasodilators [1]. Therefore, the prevention of SARS-CoV-2 binding to the ACE2 receptor is predicted to exert profound effects on viral infectivity and disease progression in COVID-19.

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Conclusions

The primary host immune strategies for survival, which include immune memory, may also be susceptible to disruption, as shown by the significance of host immune defense processes. Furthermore, this commonality may provide a strategy for therapeutic intervention, especially if pre-exposure to a prior infective agent containing homologous sequences in matched protein epitopes confers a significant degree of immunity. The evolutionarily adapted immune response to coronavirus that is the cause of the ‘common cold’ may represent a vulnerability in the host defense system. Individuals who are asymptomatic or unexposed to SARS-CoV-2 infection may benefit from prior exposure to cross-reactive endemic coronaviruses containing homologous epitopes distributed across viral proteins. Increasing awareness of the role of this evolutionarily adapted immune response to coronavirus may be both important and save time during the current urgent need to understand and develop biochemical and immunological strategies to treat, control, and prevent infection during the SARS-CoV-2 pandemic.

Conflict of interest

None.