Narrative Host-directed Therapy with COVID-19, Tuberculosis, and AIDS

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Abstract. The emergence of COVID-19 and the ongoing menace posed by infectious diseases such as tuberculosis, malaria, influenza, and HIV/AIDS underscore the profound impact infections continue to exert on public health. While vaccines stand out as highly effective protective measures, the development of vaccines for some of these diseases has proven challenging despite decades of research. Similarly, creating drugs and immunotherapies directly targeting pathogens presents formidable obstacles, with the added concern of potential resistance. An alternative strategy lies in host-directed therapies, which intervene in essential host cellular processes for pathogen survival or replication. These therapies may also target the host immune response (immunotherapies) to enhance immunity or mitigate immunopathology. In this article, we offer a historical overview of host-directed immunotherapeutic interventions addressing viral and bacterial infections. Subsequently, our attention turns to SARS-CoV-2 and Mycobacterium tuberculosis, prominent human pathogens in the contemporary landscape. The objective is to illuminate essential insights gleaned from these experiences, discussing potential immunotherapeutic approaches, with a specific emphasis on drugs presently undergoing clinical trials.

Keywords: Vaccine, immunotherapy, host-directed therapy.

1. Introduction

The clinical observation of fatal cases involving otherwise healthy young individuals implies a potential contribution of host genetics to both the susceptibility and severity of the disease. Various international collaborations, such as the COVID-19 Host Genetics Initiative and the COVID Human Genetic Effort, have explored genetic susceptibility through comprehensive approaches like genome-wide association studies (GWASs) and whole genome sequencing (WGS). It has been suggested that signaling pathways previously associated with susceptibility to other viral infections might also be relevant to COVID-19. An initial GWAS conducted in Spain and Italy pinpointed a gene cluster on chromosome 3 as a genetic susceptibility locus in COVID-19 patients experiencing respiratory failure. Subsequent validation by the COVID-19 Host Genetics Initiative and the Genetics of Mortality in Critical Care (GenOMICC) GWAS confirmed these findings. The chromosome 3 locus associated with COVID-19 risk encompasses immune-related genes, including CCR9, CXCR6, XCR1, CCR1, and CCR2. Comparative genomics strongly indicate that this COVID-19 risk locus is inherited from Neanderthals, present in approximately 50% of individuals in South Asia and 16% in Europe. CCR1, a receptor for various chemokines, has been identified within this locus, and its knockout in mice suggests a protective role against excessive inflammatory responses, reducing susceptibility to viruses and fungi. The GenOMICC study proposed a genetic association between critical illness in COVID-19 and variations in IFNAR2 and OAS2, two genes involved in antiviral defense mechanisms, along with DPP9, TYK2, and CCR2, previously linked to host-driven inflammatory lung injury. Transcriptome-wide association studies also highlighted the relevance of IFNAR2, DPP9, and CCR2. However, it is crucial to note that these GWASs have not established causative relationships, and the observed odds ratios are relatively low, indicating a minor influence of genetics at these loci.

2. The Role of B Cells in HIV Infection

In the assessment of individuals diagnosed during the primary stage of HIV infection, monitoring seroconversion constitutes a crucial aspect of clinical evaluation [1]. The origin of these early antibodies at the cellular level has not garnered significant attention, possibly due to their non-

neutralizing nature [2]. Moreover, studying patients with acute HIV infection poses challenges, as they are often inaccessible for research until the acute phase has subsided. Nevertheless, drawing on insights from other infectious diseases, it is plausible that short-lived plasmablasts, activated before germinal center (GC) formation and T-cell assistance, serve as the primary source of the initial antibody response [3]. This aligns with the detection of HIV-specific IgM within the initial weeks of infection. Furthermore, early responses to HIV involve an increase in IgG3 antibodies [4], believed to result from GC-independent class switching of B cells without affinity maturation [5-7]. Such early responses may also signify insufficient T-cell support due to the rapid deterioration of the lymphoid tissue environment crucial for B-T-cell interactions [8]. Notably, these early HIV-specific IgG3 antibodies experience a rapid decline in individuals with early HIV infection and post-vaccination in the RV144 trial. This decline is more likely attributed to a short in vivo half-life than factors directly related to HIV itself [9]. Nonetheless, IgG3 remains a compelling IgG isotype in the context of HIV, particularly due to its robust association with protection in the RV144 trial and its Fc-mediated effector function [10-11].

In the realm of responses to vaccination or self-contained infections, the maturation of T-cell-dependent B cells hinges critically on the dynamic interplay between antigen-specific B cells and T follicular helper (Tfh) cells within the GC reactions of secondary lymphoid tissues [12]. In this context, the intricate mechanisms underlying the selection of B cells possessing the utmost affinity for the antigen remain partially elucidated. This intricate process entails the orchestrated cycling of B cells between the GC light zone, where positive signals are received from Tfh cells contingent upon the BCR affinity for the antigen, and the dark zone, where proliferation and hypermutation occur, potentially guided by the intensity of signals received in the light zone [13]. The intricate evolution of the process involved in selecting B cells exhibiting optimal affinity for a cognate antigen within the framework of a persistent pathogen like HIV remains considerably obscure.

3. Use of B Cells and T Cells in Vaccines

The classical approach to vaccine design revolves around the priming of antigen-specific naive B and T cells, aiming to generate memory B and T cells. These memory cells play a crucial role in triggering a swift and potent immune response upon encountering the same pathogen, thereby establishing enduring protection against initial infection or disease. The specificity of B and T cells relies on the somatic rearrangement of genes responsible for coding receptors that identify specific epitopes and distinguish between self and non-self[14]. Because B cell activation depends on the presence of stimulatory T helper cells, the spleen and lymph nodes provide an optimal environment for T cell and B cell interactions. B cells have a unique B cell antigen receptor (BCR) on their cell surface. The BCR has two roles in B cell activation. The B-cell receptor (BCR) first binds to its specific antigen. Then, it transmits the cellular message from the binding site through the cell to the nucleus and intracellular sites. After that, the cell takes up and internalizes the antigen through receptor-mediated endocytosis. When presented with their corresponding antigen in the appropriate cytokine environment, naive lymphocytes undergo activation and clonal expansion, exponentially increasing the population of antigen-specific cells over several days. Throughout the priming process, the transcriptional profiles of B and T cells undergo epigenetic modulation, guiding their differentiation into effector and memory cells [15]. Activated B cells engage in immunoglobulin class switching and somatic hypermutation, yielding high-affinity antibodies with diverse effector functions. Meanwhile, activated T cells rapidly produce effector molecules, such as cytokines and cytotoxic mediators [16], and undergo metabolic reprogramming [17]. Changes in gene expression induced by activation also influence the expression of surface molecules that facilitate homing to lymphoid and peripheral tissues, where pathogens are most likely to be encountered. Effector T cells migrate to infected tissues to control the infection, subsequently contracting and leaving behind a smaller pool of long-lived memory cells, primarily located in the bone marrow (BM) or lymphoid tissues. Upon encountering the same pathogen again, antigen-specific memory cells exhibit a faster

and more efficient response compared to the primary infection. Less differentiated T cells, including memory stem cells [18] and central memory cells[19], maintain a high proliferative capacity, contributing to long-term anamnestic responses after vaccination [20]. On the other hand, more differentiated T cells, such as circulating effector and tissue-resident memory T cells, showcase robust effector functions crucial for immediate protection against pathogens [21]. Achieving a balanced induction of T cells with both long-term memory and the ability to rapidly migrate to the lung parenchyma is pivotal for T cell–mediated protection against TB [22].

Antigen-presenting cells, the amplification of the response facilitated by costimulatory molecules, and the strength of the T cell receptor signal collectively play pivotal roles in orchestrating the differentiation and functional polarization of T and B cells during priming [23, 24]. Nevertheless, T cells exhibit a remarkable degree of plasticity in both function and differentiation, demonstrated by their ability to modulate the expression of lineage-regulating transcription factors [25] and undergo dedifferentiation [26]. The formulation and delivery of vaccines intricately shape the distinct characteristics of adaptive immune responses, with the specificity and breadth of vaccine-induced immune responses hinging on antigen selection. Although immunodominant antigens are typically incorporated into vaccines, the process of antigen selection for tuberculosis (TB) vaccines has proven to be intricate. Mycobacterium tuberculosis (Mtb) harbors approximately 4000 genes [27], many of which undergo distinct expression patterns during infection [28]. The conservation of T cell epitopes in Mtb suggests an evolutionary advantage for T cell recognition, potentially contributing to lung tissue damage and TB transmission. However, T cell recognition might also confer protection, as the majority of individuals do not develop TB following exposure. Notably, mechanisms such as the export of mycobacterial antigens from infected cells [29] serve as decoy strategies, diverting T cell recognition to favor bacterial persistence. The development of MTBVAC, a live attenuated vaccine retaining the majority of antigens present in virulent Mtb, thus represents a revolutionary approach to circumvent biased antigen selection [30].

Oxidative stress stands out as a consequential outcome of M. tuberculosis infection, exerting its influence on both necrotic tissue damage and the dissemination of bacteria. This impact is, in part, attributed to the damage inflicted on host cell membranes through lipid peroxidation. Consequently, it emerges as a strategic focal point for host-directed therapy aimed at mitigating immunopathological effects. N-acetylcysteine, acting by replenishing cellular levels of the reduced form of glutathione—an integral antioxidant safeguarding cells against oxidative harm—has exhibited a capacity to diminish lung pathology and the bacterial load of M. tuberculosis in numerous animal model investigations. Furthermore, it has demonstrated an inhibitory effect on tolerance to the antibiotic isoniazid in vitro. In parallel research, ferrostatin, functioning as a radical-trapping antioxidant that impedes lipid peroxidation-induced membrane damage and cellular demise, has proven effective in reducing pulmonary necrosis and bacterial burden in mice infected with M. tuberculosis [31].

4. COVID-19

Coronaviruses are recognized for their capacity to induce disorders in both humans and animals. Among these, four strains (namely, human coronaviruses 229E, NL63, OC43, and HKU1) predominantly target the upper respiratory tract, resulting in comparatively mild symptoms. Nonetheless, three coronaviruses, namely severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2, have the ability to reproduce within the lower respiratory tract, leading to pneumonia with potentially lethal consequences. SARS-CoV-2 falls within the betacoronavirus genus and shares its closest genetic affinity with SARS-CoV, demonstrating a 79% similarity. Notably, within the spectrum of known coronavirus sequences, SARS-CoV-2 exhibits the highest resemblance to bat coronavirus RaTG13, with a staggering 98% similarity [32], while sequences found in pangolins, a scaly anteater, also manifest significant concordance [33]. Similar to other respiratory coronaviruses, SARS-CoV-2 primarily disseminates through respiratory droplets, with a conjectured, yet unconfirmed, fecal-oral

transmission route. Upon infection, the median incubation period spans approximately 4-5 days before the onset of symptoms [34-37], and a noteworthy 97.5% of symptomatic individuals exhibit signs within 11.5 days. Upon hospital admission, patients diagnosed with COVID-19 typically present with a fever and dry cough.

The immune responses against SARS-CoV-2 encompass both T and B cells, becoming discernible in the bloodstream approximately one week following the initiation of COVID-19 symptoms. CD8+ T cells play a pivotal role in the direct elimination of virus-infected cells, while CD4+ T cells are essential for priming both CD8+ T cells and B cells. Additionally, CD4+ T cells are responsible for generating cytokines that facilitate the recruitment of immune cells. The initial postmortem analysis of a COVID-19 patient unveiled an accumulation of mononuclear cells, likely monocytes and T cells, in the lungs, accompanied by diminished levels of hyperactive T cells in the peripheral blood [38]. These observations, coupled with reports of lymphopenia and reduced peripheral T cell counts in patients [39, 40], imply a migration of T cells from the bloodstream to the infected site for effective viral control. In individuals with COVID-19, an augmented T cell exhaustion and diminished functional diversity are indicative of severe disease[41]. Despite the compromised response, individuals who successfully recovered from SARS-CoV infection manifested the development of coronavirus-specific memory T cells, persisting for up to two years post-recovery. The immune system's response after vaccination typically doesn't last long, and its strength varies based on the person's immune system. Boosters are commonly given to enhance vaccine effectiveness in a significant portion of people by activating existing memory cells. A second reaction's greater size and length enhances memory formation enough to provide adequate protection.

B-cell responses in individuals with COVID-19 coincide with T follicular helper cell responses, emerging approximately one week after the onset of symptoms [42]. In cases of SARS-CoV infection, B-cell responses typically initiate against the nucleocapsid (N) protein. Within 4–8 days after the onset of symptoms, antibody responses to the S protein become detectable [43]. Neutralizing antibody responses, primarily directed at the S protein, commence around the second week, with the majority of patients developing neutralizing antibodies by the end of that week [44, 45]. Given the earlier peak in viral titers for SARS-CoV-2 compared to SARS-CoV [46-48], antibody responses may also initiate earlier. It appears that a subset of patients may not generate enduring antibodies to SARS-CoV-2, and whether these individuals are susceptible to reinfection remains unknown, with sporadic reports suggesting such a possibility. Even though the group that first noticed this new viral pneumonia quickly identified the SARS-CoV-2 genome and developed many precise diagnostic tools, efforts to combat the disease are hindered by the absence of immediate solutions to control its spread or lessen its impact. Antibodies are likely to be efficacious against SARS-CoV-2, as convalescent serum samples have demonstrated apparent clinical efficacy in treating COVID-19 and have previously shown success in treating SARS.

The unprecedented global ramifications of COVID-19 have thrust it into the forefront of extensive original research and critical examination [49, 50], offering an opportunity to scrutinize the current perspectives on immunotherapeutic approaches that have evolved across a broad spectrum of infectious and non-infectious diseases. The invasion of a virus initiates a unified immune response involving innate and adaptive processes that determine the course of the illness. Some patients exhibit an increased immune response, causing a "cytokine storm" with excessive production of pro-inflammatory cytokines. This excessive response may lead to serious lung damage and dysfunction of other organs in the body. One important factor in the development of SARS-CoV-2 is its ability to control the host's immune system. In the fight against COVID-19, treatment options include antiviral drugs and advanced regulators of the immune system. As the virus progresses in its evolution, enhancing its genetic arsenal, our immune response must be constantly monitored for its dynamism. It is essential to adapt and innovate therapeutic approaches. The contemporary understanding of SARS-CoV-2 pathogenesis in humans delineates two distinct phases: an initial phase characterized by heightened viral replication and compromised or negligible immune responsiveness, followed by a subsequent phase wherein this equilibrium undergoes a reversal. Immunotherapeutic strategies can

be strategically deployed to address both phases-either by enhancing immunity during the initial phase or mitigating immunopathology during the latter (Fig. 1). Two pivotal insights gleaned from historical experiences have promptly informed treatment design: firstly, the therapeutic window for antiviral immune intervention may be brief and necessitates early initiation; and secondly, cytokines possess dual attributes of both benefit and harm, prompting the consideration that cytokine responses might require inhibition to curtail immunopathology.

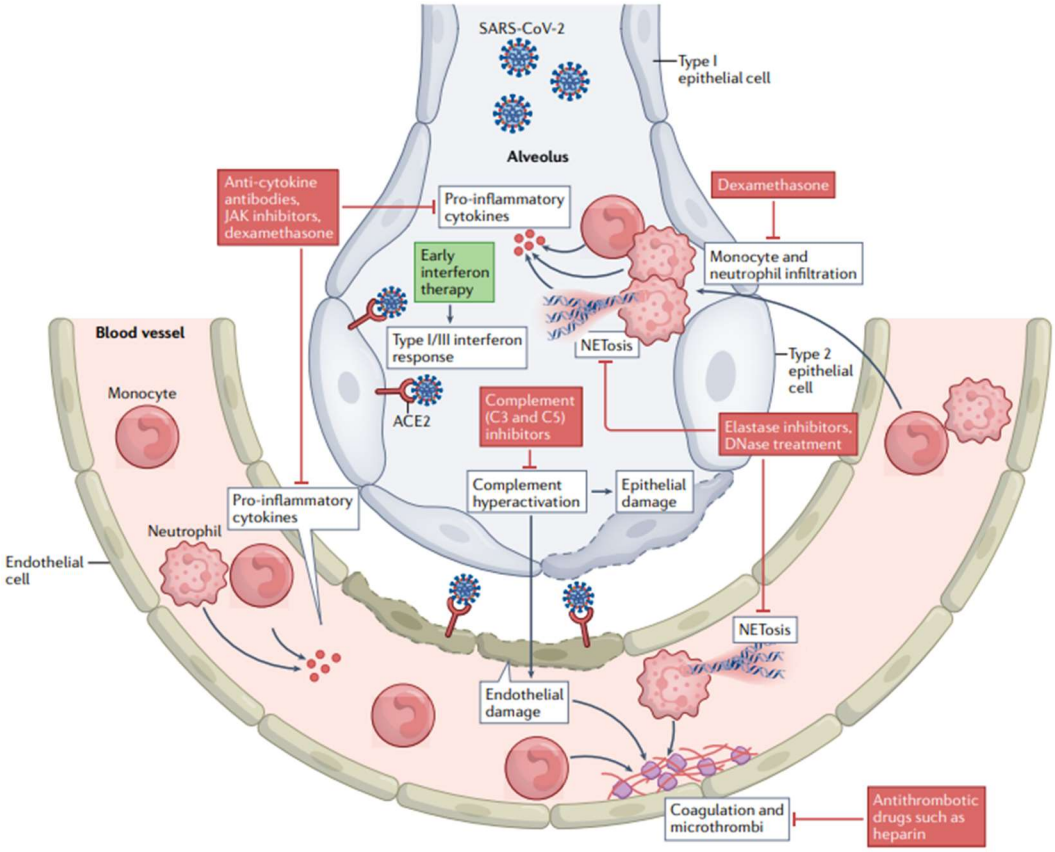

Figure 1. Host-directed immunotherapeutic intervention points for severe COVID-19

5. Perspectives

Numerous insights have surfaced through both historical and contemporary investigations into infection immunotherapy. Firstly, a notable trend reveals a higher degree of success in mitigating immunopathology across a diverse spectrum of infecting organisms compared to the enhancement of immunity. This phenomenon is, in part, indicative of the critical role played by the timing of intervention. The effectiveness of bolstering anti-pathogen responses during the “early” phase of acute infections, when promising outcomes are plausible, may diminish by the onset of symptoms. Nevertheless, untapped possibilities may exist for the implementation of early cytokine therapy in latent TB infection cases, particularly among household contacts of TB index cases. The potential benefit of employing immunotherapy to fortify immunity in this context lies in the fact that knowledge of microbial drug susceptibility becomes unnecessary. Furthermore, the relatively low pathogen burden may mitigate the risk of triggering immunopathological responses.

6. Conclusion

This review describes the pathogenesis of COVID, tuberculosis and HIV, and how to deal with it. Because it is difficult to develop targeted vaccines, host-directed approaches are used as an alternative. Managing the inflammatory response could be just as crucial as directly addressing the virus.

Approaches that not only hinder viral infection but also regulate malfunctioning immune reactions may collaborate to impede disease progression at various stages. Simultaneously, the link between immune dysfunction and the severity of COVID-19 outcomes in patients should be a warning sign in the development and assessment of vaccines. It is imperative to delve deeper into understanding the host's immune reaction to SARS-CoV-2, conducting thorough investigations into the factors distinguishing healthy outcomes from dysfunctional ones. These endeavors will not only aid in pinpointing biomarkers for defining immune indicators of protection and disease severity but also facilitate the efficient triaging of patients.

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