Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

T helper type (Th1/Th2) responses to SARS-CoV-2 and influenza A (H1N1) virus: From cytokines produced to immune responses

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ABSTRACT

Cytokines produced by T helper cells (T_h cells) have essential roles in the body's defense against viruses. Type 1 T helper (Th1) cells are essential for the host defense toward intracellular pathogens while T helper type 2 (Th2) cells are considered to be critical for the helminthic parasites' elimination swine-origin influenza A (H1N1) virus, a disease led to an epidemic in 2009 and rapidly spread globally via human-to-human transmission. Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused a global pandemic in 2020 and is a serious threat to the public health. Pulmonary immunopathology is the leading cause of death during influenza and SARS-CoV-2 epidemics and pandemics. Influenza and SARS-CoV-2 cause high levels of cytokines in the lung. Both inadequate levels and high levels of specific cytokines can have side effects. In this literature review article, we want to compare the Th1 and Th2 cells responses in SARS-CoV-2 and H1N1.

1. Introduction

The immune environment heavily dictates the type and the magnitude of an antibody response. Particularly, the differentiation of naïve immature T cells into distinct lineages is thought to depend heavily on the local cytokine milieu and can greatly influence subsequent B-cell responses [1,2]. Cytokines signal via various STAT (signal transducers and activators of transcription) family protein members that induce master transcriptional regulators. Activation of genes, repression, or epigenetic modification occurs by binding several transcriptional factors to the effector cytokine gene [2–4]. $CD4^+$ helper T cells are a heterogeneous population, and to date, several subsets have been characterized, including Th1, Th2, Th17, and T follicular helper (T_{fh}) cells [5]. T_{fh} cells were initially described as a subset of $CD4^+$ cells found in human tonsils. They are localized within the B-cell follicle, particularly the germinal center. They have also been reported to express high levels of several cytokines such as Interleukin-21 (IL-21) and interleukin 4 (IL-4), critical in driving B-cell proliferation, survival, and isotype class switch.

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Since their initial identification, the fundamental role of T_{fh} cells in humoral immunity has been shown in infectious disease, vaccination, autoimmune disease, cancer, and immunodeficiencies [6]. Interleukin 12 (IL-12) and IL-4 are two other cytokines that, respectively, are recognized to signal the Th1 and Th2 cell differentiation induction. Th1 cells are essential for the host defense toward intracellular pathogens, while Th2 cells are considered critical for the helminthic parasites' elimination [7,8]. Naive T cells are immature. They can be differentiated after activation into various sub-sets of T cells. In this process, cytokines have an important role. They signal via various STAT family protein members that induce master transcriptional regulators. Activation of genes, repression, or epigenetic modification occurs by binding several transcriptional factors to the effector cytokine gene [1,9–12]. CD4 + T helper cells order the immune response and have a crucial role throughout infection, autoimmune disease, carcinogenesis, and chronic inflammatory disease. CD4 + T helper cells are classified into different subgroups, distinguished by a particular transcription regulator network and specific cytokine profiles: Th1 cells, expresses T-box expressed in T cells (T-bet) and secretes, Tumor necrosis factor alpha (TNF-α), Interferon gamma (IFN-γ) and Interleukin-2 (IL-2); Th2 cells express GATA Binding Protein 3 (GATA-3) and produce IL-4, Interleukin-5 (IL-5), and Interleukin-13 (IL-13) [13–15]. Wuhan city (capital city of Hubei province, China) experienced a massive epidemic in "December 2019" by a new coronavirus. The coronavirus 2 (SARS-CoV-2) was believed to cause this outbreak [16,17]. At the end of 2019, the SARS-CoV-2 pandemic recorded the third outbreak of an extremely pathogenic coronavirus that has threatened the human population over the last twenty years [18]. The World Health Organization (WHO), because of significant influenza cases of the strain H1N1 (2009) virus in the United States of America (USA) and Mexico, declared with a formal statement that it was a public health event with a global impact on April 25, 2009. Gradually, the scientific world went from Phase 3 to phase 6 of the pandemic vigilance, announcing the onset of the 2009 influenza pandemic. The 2009 flu epidemic, widely known as "swine influenza," or influenza A-subtype H1N1, mentioned to an influenza A because of a new "H1N1" strain, also known as swine-origin influenza virus A [19,20]. Human influenza viruses are usually divided into two strains (H1N1 and H3N2). Both are single-stranded RNA viruses. Human influenza A type A viruses bind to sialic acid and glycolipid receptors on glycoproteins and enter the cell, inducing their pathogenicity. The virus builds antigens to protect the host immune system; this phenomenon is called antigenic shift. Due to pulmonary and extra-pulmonary involvement of the SARS virus, 2 Angiotensin-converting enzyme 2 (ACE2) was proposed as the virus's first receptor [21–23]. There has been a lot of discussion about the possible consequences of the coming flu season on the current COVID-19 pandemic. It has been hypothesized that IAV infection may cause more severe disease, since secondary SARS-CoV-2 infection or co-infection with two viruses causes more severe disease [24,25]. The severity of the H1N1 and COVID-19 pandemic is systematically associated with increased production of pro-inflammatory cytokines (cytokine storm syndrome) [26–28]. Recently, some researchers have also suggested that immune depression, rather than profuse immune activation, is responsible for the clinical pathology of severe COVID-19 [29]. Therefore, evaluating the immune responses elicited through SARS-CoV-2 and H1N1 virus can be more helpful in figuring out unique immune mechanisms associated with morbidity and mortality in COVID-19. In this literature review article, we want to compare the Th1 T helper type 1 and Th2 cells 2 responses in to COVID-19 and H1N1. (See Figs. 1 and 2.)

2. T-cells: immune response

T lymphocytes are divided into different types of cells such as Th1, Th2, Th3, Th9, T Cytotoxic, and Regulatory T cells (Tregs). Each of these cells has a specific function in the immune system that is different from other lymphocytes. Regulatory T cells are considered effective cells in

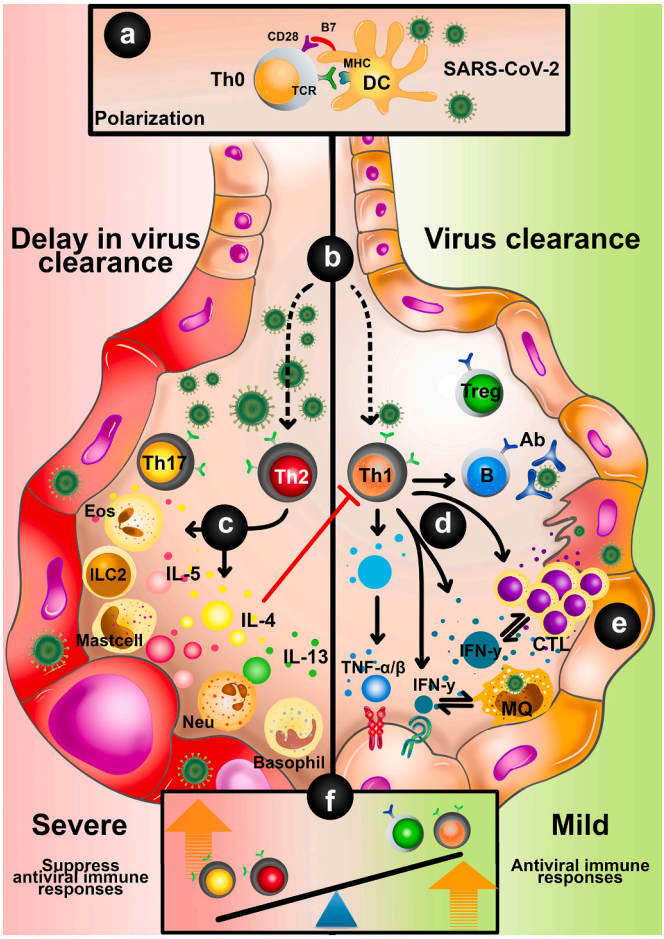

Fig. 1. Immune responses against SARS-CoV-2. In severe disease conditions, Th2 secrete cytokines such as IL-4, IL-5, IL-13, and IL-10, which inhibit antiviral responses and delay clearance of the virus. In mild disease conditions, the response of Th1 and the activation of macrophages, Tc, and B cells remove the reservoirs of the virus. In addition to the synergistic effect and activation of macrophages, TNF-α and IFN-γ induce antiviral responses directly through their receptors on the epithelial surfaces of the lung. DC, dendritic cell; MQ, macrophage; Tc, cytotoxic T cell; IFN, interferon; Eos, eosinophil; TCR, T cell receptor; MHC, major histocompatibility complex.

the immune system that play an important role in infectious diseases [30,31]. T cell activity is associated with less disease severity in SARS-CoV-2 infection, indicating that T cells play an essential role in controlling and treating primary SARS-CoV-2 infection [32]. T cells play a crucial role in harmonizing antiviral immune responses that cause the death of infected cells or mediate humoral responses. Current data emphasize that while not all patients can develop a protective humoral immune response, a sustained T-cell reaction develops.

Interestingly, data on SARS-CoV-1 infections have shown that antibodies often weaken 1–2 years after infection, while T-cell responses can last up to 17 years [33]. Peripheral T cell depletion is acutely associated with adults with COVID-19, the severity of which is positively correlated with disease severity, while asymptomatic patients and children tend to maintain peripheral T cell counts. It has been suggested that children may be protected by a diverse repertoire of naive T lymphocytes and that older adults are at greater risk due to the aging of the immune system [34,35]. In addition, existing cross-reactive T cells may accelerate virus clearance into SARS-CoV-2, but their relevance remains unclear. There is evidence that a balanced T-cell response may prevent or attenuate the course of COVID-19. In contrast, a delayed or insufficient response may lead to uncoordinated and ineffective viral control and, consequently, exacerbation of tissue damage [36–38]. Given a large

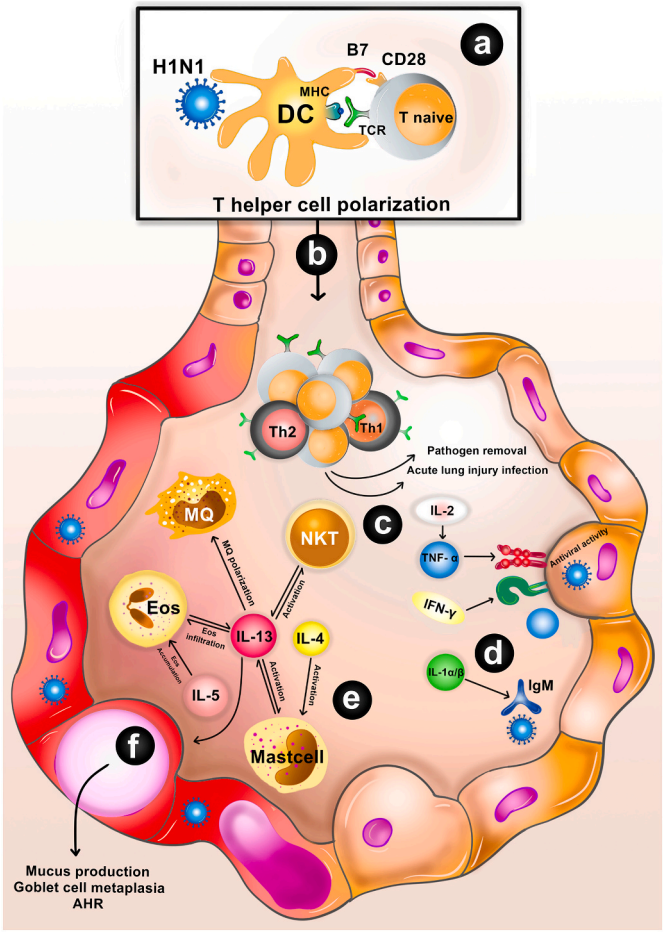

Fig. 2. Immune responses against H1N1. T helper cell polarization has a critical role in tissue damage, pathogen removal, and the inflammatory response processing the acute lung injury infection (ALI). TNF-α and IFN-γ induce antiviral responses directly through their receptors on the epithelial surfaces of the lung, and IL-1 increases IgM antibody feedbacks. IL-4 can suppress antiviral immune responses, and IL-5 causes the continuing accumulation of eosinophils in the lungs. Besides, IL-13 can activate NKT, eosinophil, macrophage, and mast cells. All mentioned cells, excluding macrophages, are able to also secrete IL-13, which is in charge of elevating eosinophil infiltration, causing changes to the contractile apparatus of ASM, macrophage polarization, following mucus production, and elevating AHR and goblet cell metaplasia. NKT, natural killer T cell.

number of Th1 lymphocytes and inflammatory monocytes in bronchoalveolar lavage and lung biopsies from critically ill COVID-19 patients, an excessive cellular immune response could significantly affect lung function by disrupting pulmonary function microcirculation. The cellular immune response to viral infection is mediated by interferon (IFN), in which type I IFN plays a significant role [39–42]. Host factors, for instance, comorbidities, can negatively affect IFN production. Although antibodies are sometimes undetectable in people who have recovered from mild COVID-19, T cell responses can often be identified [37]. T cells (CD4 + and CD8 +) respond within the first two weeks of symptom onset, usually by activating Th1 [43,44]. In the acute phase of infection, they show an activated cytotoxic phenotype. In the next phase of recovery, virus-specific T cells may change to the memory phenotype of CD4 +, as well as CD8 + T cells expressing IFNγ, interleukin2 (IL2), and/or TNFα [37]. Mobile response was critically important to clean the infection in animal models, testing of SARS-CoV-1 and Merscov infections [45–47]. Therefore, as SARS and MERS demonstrate, T-cell immunity to SARS-CoV-2 can occur in the absence of humoral immunity, perhaps even more frequently in some populations, may be more related to regeneration, and may serve as a more sensitive exposure biomarker [48,49].

3. T-Helper (Th) cell subset

Th lymphocytes are divided into the subgroups Th1, Th2, Th9, Th17, and follicular T helper lymphocytes, each of which plays a specific role in fighting infection [50]. The Th1 / Th2 balance in COVID-19 has been linked to the final outcome of the disease. Once a viral infection has been identified, an appropriate Th1 immune response can clear it. However, if this immune response is not correctly organized, the increased response leads to a cytokine storm that triggers Th2 cells, with a poor prognosis [50,51]. According to these results, it appears that Th cell activation plays an essential role in determining the severity of COVID-19, although the exact mechanism is still not fully understood. Gil-Etayo et al. [52] recorded a significant reduction in the number of Th1 and Th17 cells in COVID-19 patients compared to the control group with a higher-than-expected number of activated Th2 cells. Deceased patients have been found to have more senescent Th2 cells than survivors. COVID-19 patients had an overly reactive Th2 response to the virus. The percentage of senescent Th2 cells was an independent risk factor for death in association with total lymphocyte counts [52]. It is suspected that this may somehow explain the development of ARDS in patients with severe COVID-19. In addition, reducing the number of peripheral Tregs in COVID-19 cases may alter the balance between the regulatory and effector parts of the immune system. This imbalance can lead to massive proliferation and activation of neutrophils, macrophages, dendritic cells, mast cells, and Th17 cells, leading to uncontrolled inflammatory responses mediated by innate immune cells. This imbalance can also contribute to tissue breakdown [53].

4. Th1/Th2 cells and strengthening the immune response in viral infections SARS-CoV-2 and H1N1

Naive T-helper cells (Th0) have the ability to react to the new pathogens that the immune system has not previously encountered, such as the case of the SARS-CoV-2, is considered a positive sense of single-stranded RNA virus, which is the reason for the ongoing epidemic disease called COVID-19. Due to the infectious factors, Th0 polarizes the immune response into Th2, which is directed against non-phagocytosable pathogens located extracellular and mainly has effects on mastocytes, B cells, basophils, and eosinophils (humoral immunity) or into Th1, which are considered as the default response cells in immunocompetent subjects to phagocytosable or intracellular pathogens such as fungi, protozoa, bacteria, and viruses. Th1 cells are mediated by T-cytotoxic (Tc) cells and macrophages (cell-mediated immunity) [54–56]. Recovered COVID-19 patients, and the patients with milder disease, may lose considerable normal tissue activities because of persistent fibrosis and inflammation, causing the progress of chronic lung disease [57,58]. To obtain insights into the pathophysiologic mechanisms of COVID-19, McGregor et al. (2020), have analyzed the detail of single cell RNAseq (scRNAseq) from the peripheral blood mononuclear cells (PBMCs) and the bronchoalveolar lavage fluid (BALF) of the COVID-19 patients and healthy controls. Protective immunity to both Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome (SARS) is considered to be mediated by other cells, like IFN-γ, which produces airway memory CD4+ T helper (Th) cells [59]. The stimulation of Th1 responses is also considered a characteristic of SARS-CoV-2 in humans [38,60,61]. In addition, severe COVID-19 may be along with exacerbated and prolonged Th1 responses [62]. They have also focused on the scRNAseq datasets on CD4+ T cells and have specified the T cells within the scRNAseq of BALF. Due to the outcomes, the CD4+ T cells of BALF in the COVID-19 patients seemed to be polarized towards Th1 unlike the Th17 or Th2 lineages. Similar tests within scRNAseq of PBMC from healthy controls and the COVID-19 cases did not display any significant variations in the

expression of Th17, Th2, and Th1 lineage genes, proposing that expression of Th1 is a special characteristic of Th cells in the place of pulmonary inflammation. These sites are vital because of the concentration of T cells [59–64]. During McGregor et al. studies, on the COVID-19 pandemic, for many clinic-laboratory reasons, including MERS-like lymphopenia, they have found that in the patients with severe stages, the immune system can induce a Th2 response against SARS-CoV-2, rather than a Th1 response, which can control the infection by Tc cells and macrophages [59]. Additionally, they have presented documents that a life-threatening exacerbation from Th2 immune response to type 3 hypersensitivity in COVID-19 vasculitis happens. Subsequently, the inflamed smooth muscle cells in the blood vessels via IL-6 lead to cytokine storms [65–67]. Due to Yoon et al. (2009) research, pregnancy is known as a suppression for the immune system and polarized the cytokine profile toward the responses of Th2 [68]. PBMCs samples from pregnant women who responded to innate immune inductions less than those were isolated from the no pregnant women. In spite of the fact that pregnant women are thought to be at high risk of being infected with the influenza virus, there is no comprehensive information about its underlying mechanisms [68,69]. T helper cell polarization has a vital role in tissue damage, pathogen removal, and the inflammatory response processing the acute lung injury infection (ALI). However, the polarization of Th cell in bacterial- or viral-mediated ALI is not well understood. Lipopolysaccharide (LPS) and H1N1, an influenza virus, were selected to induce ALI in mice, and thus the outcomes of Th-cell polarization were defined [70]. In Ryu et al. (2016) article, CIA06 (A combination of dLOS and aluminum hydroxide) decreased the production of Th2-type cytokines and induced the response of Th1 to the influenza vaccine. Indeed, chemokine and cytokine gene expression and lung histology showed that the CIA06-adjuvanted vaccine reduced hypercytokinemia and hyperneutrophilia in the lungs after the natural infection [71]. While people with the (H1N1) pandemic also have elevated levels of some inflammatory mediators, they may have sufficient regulatory mechanisms to counteract the harmful effects of hyperinflammation. This is well illustrated by the higher levels of IL1RA observed here in patients with the H1N1 pandemic compared to patients with COVID-19 [72,73]. Moreover, this study confirms that the immune reaction in opposition to SARS-CoV-2 is absolutely distinct from in opposition to pandemic H1N1. This look confirmed that TNFα degrees had been decreased withinside the serum of COVID-19 sufferers compared to H1N1 pandemic sufferers [73]. At the equal time, an exacerbated polyfunctional immune reaction is dominant withinside the remedy of COVID-19 patients. This reaction is characterized with the aid of using better ranges of Th1 and Th2 cytokines in comparison to H1N1 pandemic patients. Conversely, despite the fact that people with the H1N1 pandemic additionally show off increased levels of positive inflammatory mediators, those people can also additionally have enough regulatory mechanisms to counteract the damaging results of hyper inflammation [72–74]. In a study by Choreño-Parra et al. (2021), the results confirmed that severely ill COVID-19 sufferers had accelerated levels of IL1β, IL1RA, IL6, IL9, and CXCL10, and decrease levels of IL2 and IL17A in comparison to healthy volunteer donors. These results are consistent with the immune profiles reported in Chinese COVID-19 patients [72–74]. The levels of pro-inflammatory (IFNγ, IL1β, IL6, IL9, IL12p70, CCL11) and anti-inflammatory (IL4, IL5, IL10, IL13) and VEGF cytokines were higher in critically ill patients with COVID-19 compared to the H1N1 pandemic. Item [29,73,75]. In contrast, levels of IL1RA, IL2, TNFα, CCL3, and GCSF were more elevated among patients with the H1N1 pandemic. These serum cytokine profiles indicate that, further to expanded production of pro-inflammatory and Th1 cytokines, SARS-CoV-2, however not H1N1 contamination, caused Th2 responses in parallel. This may also imply that the lack of enough regulation and stability of the sort of immune reaction elicited after SARS-CoV-2 contamination may also make a contribution to the immune disorder suggested in the course of COVID-19 [73,76]. In addition, higher levels of Th2 cytokines, especially IL4 and IL5, can inhibit protective Th1 antiviral responses in COVID-19 patients. Thus, an immune imbalance of the effector response type is another important determinant of the breakdown of the host's protective immunity to SARS-CoV-2. This displaced Th2 response can generate interstitial infiltrates of Th2 cells, neutrophils, eosinophils and type 2 innate lymphoid cells, mediating pneumonia and tissue damage. In fact, critically ill COVID-19 patients typically have interstitial lung infiltrates, some of which resemble several forms of progressive interstitial lung disease, such as cryptogenic organizing pneumonia and nonspecific interstitial pneumonia [77–79].

5. The role of Th2-derived cytokines in viral infections

Classically the defensive mechanisms of the body against viral infections have been called Cellular immunity. The evolution of humoral or cellular immune reactions hangs on a repertory of cytokines manufactured by various cells, such as CD8 and CD4 T cells. Depending on the cytokine types they synthesize, these T lymphocytes are divided into two subsets called Th1 and Th2 [80]. Cytokines function as the immune response molecules with numerous physiological roles and control the immunological, reparative and inflammatory host reactions, and monocytes and lymphocytes mostly release these. T cells which are derived by cytokines are necessary for the host immune responses [81,82]. Cytokines produced by Th1 cells, especially gamma interferon, develop the production of cell-mediated immunity, Th2 cells, and cytokines secreted by them such as IL-4, IL-5, IL-10, and IL-13 seem to operate in rehabilitation from in antibody responses and parasitic infections. The sequels of the main Th2 cytokine (IL-4) on immunity to viral infections have been examined. The examination on mice with IL-4 led to a highly notable delay in virus clearance. Consequently, IL-4 can suppress both secondary and primary antiviral immune reactions [83]. In respiratory viral infections, like influenza infection, eosinophils and IL-5 are not assessed to have a crucial function in host defense. IL-5 is secreted following influenza infection and causes the continuing accumulation of eosinophils in the lungs [84]. Results of clinical researches in animals and humans have also associated the high systemic amounts of IL-6 with the provocation of clinical outcomes including viral pathogens. As such, elevated levels of IL-6 has been seen in human cases chronically infected with influenza [85], Andes [86], Hepatitis C [87], Chikungunya virus (CHIKV) [88], hepatitis B virus) HBV([89], Human immunodeficiency viruses (HIV) [90], and Crimean-Congo hemorrhagic fever virus (CCHF) [91]. IL- 6 over secretion can likely be a supporting tool for the stability of some viruses. Likewise, in HIV-infected patients, elevated IL-6 levels are associated with amounts of persisting viremia, but IL-6 remaining was associated with increased HIV-1 transcriptional quantities in ectocervical tissues [92]. In short, numerous proofs are reassuring a significant function of IL-6 in viral infections [93]. IL-13 also has a major role in the engaging and activating a suite of cells, like T cells, natural helper cell, natural killer T (NKT) cell, eosinophil, macrophage and mast cell. All mentioned cells, excluding macrophages, are able to also secrete IL-13, which is in charge for elevating eosinophil infiltration, causing changes to the contractile apparatus of airway smooth muscle (ASM), macrophage polarization, following mucus production and elevating hyper responsiveness of airway (AHR) and goblet cell metaplasia [94]. Studies show that IL-1α/β moderate severe inflammatory pulmonary pathology and increase survival from influenza viral infections. IL-1α/β seem to not affect destroying of cells infected with virus but to increase Immunoglobulin M (IgM) antibody feedbacks and attract CD4+ T cells infection site [95].

6. Th1 and Th2 cells and humoral immunity

Helper T cells are almost the primary cells in adaptive immunity because they are needed for nearly all adaptive immune reactions. They assist the activation of B cells to release antibodies and macrophages to kill absorbed microbes. Besides they assist in activating cytotoxic T cells to destroy infected target cells [96–98]. Th1 secreted cytokines tend to

manufacture the pro-inflammatory reactions that destroy intra-cellular parasites and maintain autoimmune reactions. Interferon-gamma is the most critical Th1 secreted cytokine. Extreme pro-inflammatory responses may cause uninhibited damage to tissues; therefore, mechanism is required to prevent this. The Th2 cytokines involve IL-4, IL-5, and IL-13, which are connected to the increasing Immunoglobulin E (IgE) and eosinophilic reactions in atopy, and also IL-10 that often has an anti-inflammatory function. Moreover, reactions performed by Th2 can inhibit the moderate antimicrobial action of Th1. Moderate microbicide functions. The ideal situation would likely be manufacturing a properly balanced Th2 and Th1 reactions, adjusted to the immune challenges [98–101]. Simple T cells need two signals at the minimum for being activated. The two signals are supplied by an antigen-presenting cell, usually a dendritic cell: MHC-peptide complexes sticking with T cell receptors provide signal 1, and signal 2 is supplied mainly by B7 co-stimulatory proteins sticking with CD28 on the surface of the T cells. When a helper T cell is at first activated on a dendritic cell, it can be transformed into Th2 or Th1 effector cells, that depends on the cytokines in their environs: Th1-cells activate B cells, macrophages, and cytotoxic T cells, and Th2-cell mostly cause the activation of B cells [97,98]. Since the beginning of the pandemic, the behavior of T cells has been observed; however, some studies have reported that the reduction of CD4 is more significant than CD8. In response to the spike protein of the virus, Th1 releases a specific class of cytokines, thereby activating the immune system. Shreds of evidence have shown that these cells usually increase in the early and acute stages of the disease and act more in moderate conditions than severe. On the other hand, little information is available about the behavior of Th2 in severe conditions and the high viral load, and it seems that these cells act properly in the mild form of the disease and low viral load [102–104].

7. The role of Th1-derived cytokines in viral infections

Th-1 cells release IL-2, IFN-γ, and TNF-α/β, which promote the activation of macrophages, production of nitric oxide, and proliferation of cytotoxic T lymphocytes and thus lead to microbial pathogens destruction and phagocytosis [105,106]. As a pleiotropic cytokine, IFN-γ modulates both adaptive and innate immune networks and is known as the most potent macrophage activator. Also, IFN-γ is the signature cytokine of the activated T lymphocytes. It is now known to exert various roles in modulating the immune system and defense against a broad spectrum of pathogens. IFN-γ was first discovered as a secretory factor that interfered with the replication of viruses. Moreover, it has a unique position in the antiviral defense system [107]. Antiviral activities of the TNF-α have been reported. Accordingly, its robust effects against the Influenza virus have been evidenced in the Lung Epithelial Cells [108]. IFN-γ and TNF-α may bind to their specific surface receptors on the infected cells. Thus, they trigger intracellular antiviral pathways. Also, it is believed IL-2 modulated different aspects of the immune response, including paracrine or autocrine upregulation of TNF-α and IFN-γ [109]. Both cellular and humoral responses show Th1-influenced immunity, caused by MeVvac2-SARS2-S(H) [110]. The T helper phenotypes of T cells produced by vaccines are linked to the preservation they effectuate. Less acute SARS cases were related to the advanced inductance of Th1 cellular responses [111]. Still, responses of Th2 cells were related to lung disease improvement, succeeding infection in clients vaccinated parenterally with viral SARS-CoV vaccines which were inactivated [112,113]. Therefore, tissue-resident memory T cells (TRM) produced by COVID-19 must have a phenotype similar to Th1 cells [114]. Since acute COVID-19 cases have dysregulated immune responses, we assume that T-regs might have therapeutic potentialities. An adoptive way of transferring ex-vivo polyclonal expanded T-regs has been utilized lately to treat inflammatory and autoimmune illnesses [115]. A further method is to stimulate T-regs in vivo. IL-2 in low doses is employed to precisely induce T-reg development in-vivo [77,116]. Other studies have shown that patients suffering from acute COVID-19 have higher levels of IL-2 [117]. and despite having increased IL-2 levels, T-regs were decreased in acute COVID-19 cases [118]. Therapy using T-reg-originated immuno-regulatory molecules, particularly CTLA-4, may have the ability to control the inflammations in acute COVID-19 cases. Co-stimulatory T-cell signals are decreased by CTLA-4 [119]. The recombinant abatacept Fc-fused CTLA-4 protein is utilized for many years to cure systematic autoimmune illnesses [120,121] .early clinical trials mostly attended to manage 'cytokine storm' and particularly, the function of IL-1-beta and IL-6. findings about T-regs in COVID-19 cases were lacking at the initial periods of COVID-19 pandemic. These facts can explain the reason why abatacept has not yet been counted for managing COVID-19 cases [122].

8. Vaccination and immune response

Vaccination is one of the best ways to prevent the spread of emerging infectious diseases; the COVID-19 pandemic prompted scientists to design and produce vaccines in addition to available therapeutic methods. There are various methods for designing vaccines, resulting in the production of inactivated, live-attenuated, messenger RNA, polysaccharide or conjugate, and viral vector vaccines [123,124]. Vaccination in humans induces Ki67 + CD38 + CD4 and CD8 T cells approximately 1–2 weeks after immunization; this activated, proliferating subset comprises antigen-binding T cells. As previously reported, the Ki67 + CD38 + CD4 T cell population was induced after the first dose of vaccine in healthy controls, peaking at T2 and then returning to baseline. While neutralizing antibodies are, in all likelihood, crucial for vaccine-precipitated protection, the precise correlates of immunity are not absolutely defined, and the recent evidence additionally factors to a function for T cells [125–130]. Due to the structural and functional similarity of SARS-CoV and SARS-CoV-2, the scientists used past information to design the vaccine platforms. At the time of writing, only three types of mRNA, protein subunit, and vector vaccines have been authorized and recommended for emergency use in the United States [125,131]. Vaccines are used to prevent COVID-19 activate the immune system in several ways. One of the primary mechanisms is based on virus-neutralizing antibodies. In this method, stimulation of B-cells and the production of antibodies prevent the virus from connecting to the host cell. Another way to immunize is to stimulate T cells. It counteracts the virus-infected cells by stimulating and producing CD4 and CD8 cells. HLA molecules are presented to T cells by antigen-presenting cells; this identifies the cytotoxic CD8 T cells relative to the viral peptides synthesized on the infected cell's surface [132,133]. One of the disadvantages of this scheme is the slow performance of CD4 T-helper cells in providing antigen, which can be detected by low serum IFNγ level [134,135]. published the study of the BNT162b1 vaccine, a type of lipid nanoparticle-formed nucleoside-modified mRNA in which results show acceptable levels of IFNγ, IL-2, and IL-12p70. Still, IL-4 or IL-5 is found negligible on the opposite side, indicating Th1 efficiency and the absence of Th2, which can be harmful in the safety process [134]. Animal studies have also clearly shown the COVID-19 vaccine responses to be Th1 type. Assessment of researchers on the mRNA-1273 vaccine against COVID-19 in nonhuman primates, showed that vaccination-induced Th1–biased CD4 T-cell responses and low or undetectable Th2 or CD8 T-cell responses [136]. Another study by Liang et al. (2021), described S-Trimer, a native-like trimeric subunit vaccine candidate for COVID-19 based on Trimer-Tag technology. This study also reported that immunization of S-Trimer with either CpG 1018 (TLR9 agonist) or AS03 (oil-in-water emulsion) plus alum adjuvants induced high-level of neutralizing antibodies and Th1-biased cellular immune responses in animal models [137]. In study published by Seo et al., a candidate for the SARS-CoV-2 spike (S) soluble vaccine, a DNA-based vaccine, GX-19, has been tested. These researchers observed that immunization with GX-19 in mice, in a dose-dependent manner, elicited specific systemic and pulmonary antibody responses to S and T cell responses with Th1-biased orientation. Nonhuman primates vaccinated with "GX-19"

seroconverted quickly and exhibited multifunctional CD4+ and CD8+ T cell responses as well as a detectable neutralizing antibody response [108]. Numerous articles have recently been presented on how SARS-CoV-2 vaccines interact with T cells. S-protein or its receptor-binding domain is the target of these vaccines. In most volunteers in clinical trials, the serum level of neutralizing antibodies (nAB) was more significant than or equal to those recovering [135,138–140]. T cell responses varied among volunteers for the vaccine so that when levels of CD4 and CD8 T cells were examined, differences in their levels were found in the peripheral blood. A chimpanzee adenovirus-based vaccine that targets the S protein triggers the response of S-specific T cells, which in many people lasts at least 56 days [140,141]. However, after 28 days, 90% of individuals who had received the human adenovirus-based vaccination had more restricted T cells than the virus had generated [142,143]. RBD-specific CD8 T cell responses and T4 cell responses, as well as greater memory response to CMV, EBV, and influenza in >80% of individuals after 29 days of treatment with an mRNA vaccine targeting RBD, were observed in the majority of participants, which varies with nAB titles and among individuals [138,144]. As an alternative, vaccination with the identical CD4 T cell generation technique generates a particular protein S with Th1 defect in most persons after 43 days. Still, it elicits a modest CD8 T cell response [139,145]. While vaccination safety depends largely on the production of antibodies, the vaccines produced for SARS-CoV-2 can greatly benefit the T cell response. T_{fh} cells are the most important regulators, germinal cells, and affinity-matured Ab maturation responses between CD4 T cells. CD4 T cells, on the other hand, have other subsets that may play an important role, thereby facilitating the optimal response of CD8 T cells. Finally, pathogen-infected cells are killed by cytotoxic CD8 T cells by releasing molecules such as granzyme and perforin. Granzyme and perforin are important proteins that can be produced by vaccination if protective Abs fails to prevent productive viral infection [146–148]. in addition, vaccine-induced T cell responses can sometimes be associated with protective responses [149]. Studies in patients with agammaglobulinemia, a primary immunodeficiency disorder, have shown that some other cell types (including T cells) can die if the B cell does not function properly and the antibody responds. The SARS-CoV-2 infection leads to mild to moderate disease [150,151]. as demonstrated by the production of IL4, IL5, and IL13, mice inoculated with the recombinant S2P protein recondensed in alum showed a tendency to correspond to the Th2 deviation. The mRNA-LNP vaccine generates potent production of Th1-induced cytokines (including IFN, TNF, and IL2) [152–154]. After ex vivo stimulation, the rhesus monkeys immunized with the BNT162b2 and mRNA1273 vaccines secreted Th1 cytokines but not Th2, suggesting that the total CD4 T lymphocytes are strongly biased towards T-helper 1 [152,155]. T_{fh} cells are functionally different. Different diseases or vaccination platforms can modify their functional profile. Therefore, it is interesting to observe which characteristics of T_{fh} cells are affected by mmRNA vaccines and how they differ. in a recently published study [156], Mice immunized with SARS-CoV-2 mRNA were tested for the quality of the T_{fh} cell response. T_{fh} cells were polarized towards Th1 or Th2 after in vitro restimulation with the SARS-CoV-2 peptide pool. Vaccination with mRNALNP changed the phenotype of T_{fh} cells towards Th1 using the (S Furin) immunogen or the RBD immunogen. on the other hand, rRBD-AddaVax was generating T_{fh} cells from Th2 bias. in mice, Th2 shifted responses are associated with IgG1 production; so, it was the expected outcome [157,158]. on the other hand, polarized Th1 responses are associated with the production of IgG2 antibodies. They did not test the T_{fh} cell responses, but identical IgG1 to IgG2a ratios were observed when comparing mRNA1273-induced IgG responses with the S2P protein preparations in mice [153].

9. Conclusion

There are several types of functional CD4 + T cells in humans, namely Th1, Th2, and Th17, T_{fh}, and Treg; these cells play an important role in acquired immunity. These subsets of T Cells produce cytokines like IL-1, IL-6, IL-12, IFN-γ, and TNF-α, critical in SARS-CoV-2 infection. Increased cytokine expression at appropriate levels protects the host against influenza and SARS-CoV-2 and effectively controls viral replication. However, their excessive production often lead to pulmonary immunopathology and adverse tissue damage. T cell activity is associated with less disease severity in SARS-CoV-2 infection, indicating that T cells play an important role in controlling and treating primary SARS-CoV-2 infection. The difference in the Th1/Th2 balance in COVID-19 development has been linked to the distinct outcomes. Once a viral infection has been identified, an effective Th1-type immune response can clear it. However, if the immune response is excessive with an increased production of cytokines, this cytokine storm triggers Th2-type response with poor COVID-19 prognosis. This situation may be further aggravated by the high circulation of pandemic H1N1. In this regard, the influenza A virus may circulate concurrently with the SARS-CoV-2 virus, perhaps resulting in more severe respiratory infections in the winter. Bao et al. [159]; demonstrated the establishment of systematic models of H1N1 and SARS-CoV-2 co-infection, which significantly exacerbated pneumonia in ferrets and mice, as well as suggesting concurrent vaccination against H1N1 and SARS-CoV-2 may be an effective winter preventative method. Moreover, Greco et al. [160]; indicated that gender and age are important predictors of hospitalization among COVID-19 patients, however it appears that age is the most important risk factor for short-term mortality among those who had influenza vaccine. Therefore, a better understanding of the clinical and immunopathological features that distinguish the two diseases is still needed to define specific therapeutic approaches. This is an obstacle to setting targets for drug and vaccine development. The inevitable co-circulation of influenza and SARS-CoV-2 viruses, as well as potential viral co-infection scenarios, may additionally mean a worsening of morbidity and mortality due to COVID-19.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or fal-sification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Authors' contributions

Molavi B, Mokhtari M, Deravi N, Fathi M, Fazel T, Mohebalizadeh M, Koochaki P, Shobeiri P, prepared the initial draft; Aleebrahim-Dehkordi E, study design, supervised the project, writing-final draft and editing; Hasanpour-Dehkordi A, supervised the project, review and editing the manuscript.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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