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REVIEW

Cytokine Storm-Induced Thyroid Dysfunction in COVID-19: Insights into Pathogenesis and Therapeutic Approaches

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Abstract: Angiotensin-converting enzyme 2 receptors (ACE2R) are requisite to enter the host cells for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). ACE2R is constitutive and functions as a type I transmembrane metallo-carboxypeptidase in the renin-angiotensin system (RAS). On thyroid follicular cells, ACE2R allows SARS-CoV-2 to invade the thyroid gland, impose cytopathic effects and produce endocrine abnormalities, including stiff back, neck pain, muscle ache, lethargy, and enlarged, inflamed thyroid gland in COVID-19 patients. Further damage is perpetuated by the sudden bursts of pro-inflammatory cytokines, which is suggestive of a life-threatening syndrome known as a "cytokine storm". IL-1β, IL-6, IFN-γ, and TNF-α are identified as the key orchestrators of the cytokine storm. These inflammatory mediators upregulate transcriptional turnover of nuclear factor-kappa B (NF-κB), Janus kinase/signal transducer and activator of transcription (JAK/STAT), and mitogen-activated protein kinase (MAPK), paving the pathway for cytokine storm-induced thyroid dysfunctions including euthyroid sick syndrome, autoimmune thyroid diseases, and thyrotoxicosis in COVID-19 patients. Targeted therapies with corticosteroids (dexamethasone), JAK inhibitor (baricitinib), nucleotide analogue (remdesivir) and N-acetyl-cysteine have demonstrated effectiveness in terms of attenuating the severity and frequency of cytokine storm-induced thyroid dysfunctions, morbidity and mortality in severe COVID-19 patients. Here, we review the pathogenesis of cytokine storms and the mechanisms and pathways that establish the connection between thyroid disorder and COVID-19. Moreover, cross-talk interactions of signalling pathways and therapeutic strategies to address COVID-19-associated thyroid diseases are also discussed herein.

Keywords: COVID-19, cytokine storm, signalling pathways, inflammation, thyroid disorders, cross talks

Introduction

In the initial stages of COVID-19, the patient exhibits anosmia, dyspnoea, non-productive cough, intermittent fever, and obstructive sleep apnoea.[1] However, as the disease progresses, patients experience delirium, depression, ageusia, epigastric distress, thromboembolism, metabolic irregularities and acute respiratory distress syndrome (ARDS).[2,3] Angiotensin-converting enzyme 2 (ACE2) receptors are requisite for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) to enter the host cells. It is worth mentioning that ACE2 receptors are constitutive and function as type I transmembrane metallo-carboxypeptidase in the renin-angiotensin system (RAS). Detail transcriptome analyses have identified ACE2 expressions on multiple organs, including pulmonary epithelium, kidney vasculature, myocardium and thyroid follicular cells, vindicating the plethora of pulmonary and extra-pulmonary manifestations in advanced COVID-19 patients.[4]

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Studies suggest that ACE2 receptor interaction in COVID-19 involves structural binding with SARS-CoV-2 spike proteins, modulation by glycans, and post-infection regulation affecting immune response.[5,6] ACE2 receptors on thyroid follicular cells allow SARS-CoV-2 to invade the thyroid gland, impose cytopathic effects and produce endocrine abnormalities. Clinical data suggest that COVID-19 patients experience various thyroid complications such as subacute thyroiditis,[7,8] autoimmune thyroiditis,[9,10] and abnormal thyroid function,[11,12] with symptoms such as stiff back, neck pain, fever, muscle ache, lethargy, enlarged and inflamed thyroid gland.[12–14] Further damage is perpetuated by the sudden burst of pro-inflammatory cytokines in the infected cell, which suggests a life-threatening syndrome known as a "cytokine storm".[15] Numerous immune effector proteins such as interleukins (ILs), interferons (IFNs), tumour necrosis factor (TNF), chemokines orchestrate the cytokine storm by upregulating the transcriptional activities of Janus kinase (JAK), signal transducer and activator of transcription (STAT), nuclear factor-kappa-B (NF-κB) and mitogen-activated protein kinase (MAPK). Upon activation, these transcriptional factors momentously increase the plasma level of the inflammatory mediators, which hastens the disease progression by promoting systemic inflammation and multi-organ damage.[16]

SARS-CoV-2 infection induces thyroid follicular cell damage and hypothyroidism akin to its predecessor, SARS-CoV-1.[11,17] According to recent studies, COVID-19 have the potential to actuate euthyroid sick syndrome (ESS), Hashimoto thyroiditis (HT), and Graves' disease (GD) in patients with no previous history of thyroid disorders.[18] Clausen, Rasmussen et al[19] recently reviewed the similarities between inflammatory thyroid illness and COVID-19-induced hyper-inflammation. It is suggested that elevated IL-6 concentration perturbates the production and functionality of thyroid-stimulating hormone (TSH), which paves the pathogenesis of thyrotoxicosis in COVID-19.[20]

According to a recent epidemiological study by Ashrafi, Hatami, Bidhendi-Yarandi, Panahi,[21] thyroid dysfunction is frequently observed in patients with COVID-19, characterised by a notable prevalence of non-thyroidal illness syndrome (NTIS) and thyrotoxicosis. It is worth mentioning that a significant prevalence of 26% and 10% of NTIS and thyrotoxicosis has been reported among COVID-19 patients, respectively.[21] Nonetheless, the diagnostic challenges of COVID-19 patients with thyroid complications are multifaceted. Subacute thyroiditis and alterations in thyroid function can mimic or exacerbate COVID-19 symptoms, complicating the patient diagnosis and prognosis.[22–24]

Moreover, diagnosing COVID-19 patients with thyroid complications is challenging due to overlapping symptoms and laboratory findings. Pre-existing thyroid conditions can worsen COVID-19 outcomes, requiring careful management.[23,25,26] Thyroid complications in COVID-19 patients have significant knowledge gaps, particularly in the variability of prevalence rates and the underlying mechanisms of thyroid disorders.[21,27] There is also a need for greater awareness among the public and healthcare providers regarding the link between COVID-19 and thyroid issues and improved clinical management protocols for affected patients.[21,28,29] Here, we review the pathogenesis of cytokine storms and the mechanisms and pathways that establish the connection between thyroid disorder and COVID-19. Moreover, cross-talk interactions of signalling pathways and therapeutic strategies to address COVID-19-associated thyroid diseases are also discussed herein.

SARS-COV-2 and Cytokine Storm

The SARS-COV-2 contains four (4) structural proteins, including spike (S), membrane (M), envelope (E) and nucleocapsid (N).[30] The S protein facilitates the viral attachment to host receptors (Figure 1). The SARS-CoV-2 requires S protein proteolytic processing and degradation to initiate the endocytic pathway.[31] The S protein has two functional units, namely S1 and S2. The S1 subunit binds to the host cell receptor, whereas the S2 subunit fuses the virus with the host cellular membrane.[32] The M protein defines the virion's shape and allows the virus to interact with the N protein. The N protein consists of the N-terminal domain (NTD) and C-terminal domain (CTD), both of which interact with the viral RNA genome and encapsulate the genome into virions during the replication phase by interacting with non-structural protein (nsp) 3.[33,34] The E protein arranges the viral assembly, initiates the release and plays a definitive role in the virulency and COVID-19 progression. The SARS-CoV-2 employs a receptor cognition process similar to its predecessor, SARS-CoV. SARS-CoV and SARS-CoV-2 utilise ACE2 as a receptor to enter its target cells.[35] However, Shang, Wan et al[36] suggested that SARS-CoV-2 requires the transmembrane protease serine protease 2 (TMPRSS2), cathepsin L, and furin to gain entry into the host cells. It is noteworthy that ACE2 is co-expressed with TMPRSS2 in many tissues, including nasal epithelial cells, lungs, and bronchial branches, suggesting the tissue tropism of SARS-CoV-2.[37]

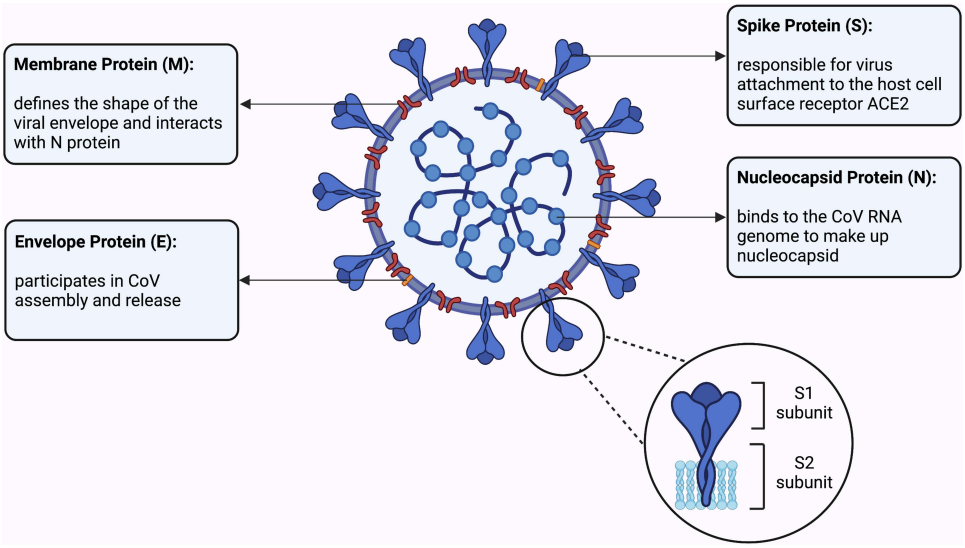

Figure 1 SARS-CoV-2 virus structure.

The furin cleavage site formation in S protein subunits facilitates S-glycoprotein binding with the ACE2 receptor of SARS-CoV-2.[38] The protease enzyme binds to the ACE2 receptor, cleaving the S protein into S1 and S2 subunits. This cleavage brings out irreversible conformational changes in the S protein, significantly increasing its affinity towards the ACE2 receptor.[39] Zhou, Yang et al[40] indicated that the rapid transmission, replication and infectivity of the SARS-CoV-2 results from the furin cleavage and the receptor-binding sites of the modified S1 subunit as the viral genomic messenger RNA (mRNA) enter the host cell cytoplasm together with the nucleocapsid. The E, M, and S proteins and several other accessory proteins are produced by translating this genomic mRNA.[41] These proteins are inserted into the rough endoplasmic reticulum (RER) and transported to the endoplasmic reticulum-golgi intermediate compartment (ERGIC). The nucleocapsids prepared by N protein and genomic RNA fuse into ERGIC, allowing the infected cell to release the virus-containing vesicles through exocytosis or simply fusing with the plasma membrane.[42] The receptor-binding domain (RBD) of the S1 subunit significantly contributes to the pathogenicity of COVID-19. The RBD S1 subunit on the S protein binds to the ACE2 receptors, which can be found abundantly in type-2 pneumocytes. Upon binding, the RBD S1 subunit downregulates ACE2 receptors and conversely upregulates the production of angiotensin-2 (AT2), which is well-known for its vasodilatory activity.[43] As the AT2 production jacks up, it leads to tissue injury by increasing pulmonary vascular permeability.[44] The SARS-CoV-2 comprises antigen-presenting cells (APC) that adhere to the host dendritic cells. Their interaction activates macrophages and other immune cells to bolster the production and release of pro-inflammatory cytokines. Excessive and uncontrolled production of cytokines and chemokines, including TNF-α, IL-1α, IL-6, IL-7, IL-8, IL-9, IL-10, G-CSF, GM-CSF, IFN- γ, IP-10, MCP-1, MIP-1β, PDGF and VEGF alter the cellular function, damages visceral tissues and create a perfect environment for systemic inflammation, which is suggestive of a life-threatening syndrome known as "cytokine storm".[45]

Hypothalamic-Pituitary-Thyroid (HPT) Axis and COVID-19

While COVID-19 patients primarily exhibit pulmonary manifestations, the involvement and damage to other organs, including cardiovascular, lymphatic and endocrine systems, are translated as extrapulmonary manifestations.[46] Of interest, the thyroid gland exhibits higher levels of ACE2 and TMPRSS2 expression than the pulmonary airways, which invariably allows the SARS-CoV-2 to quickly gain excess, target and pose direct cytopathic damage to the thyroid gland and the entire hypothalamic-pituitary-thyroid (HPT) axis. The said damage is often translated into thyroid dysregulations, including hypothyroidism, thyrotoxicosis, and non-thyroidal illness syndrome.[3,15] Autoimmune thyroid disorders such as Graves' disease have been reported in patients with no previous medical or family history of thyroid abnormalities.[47] It is worth

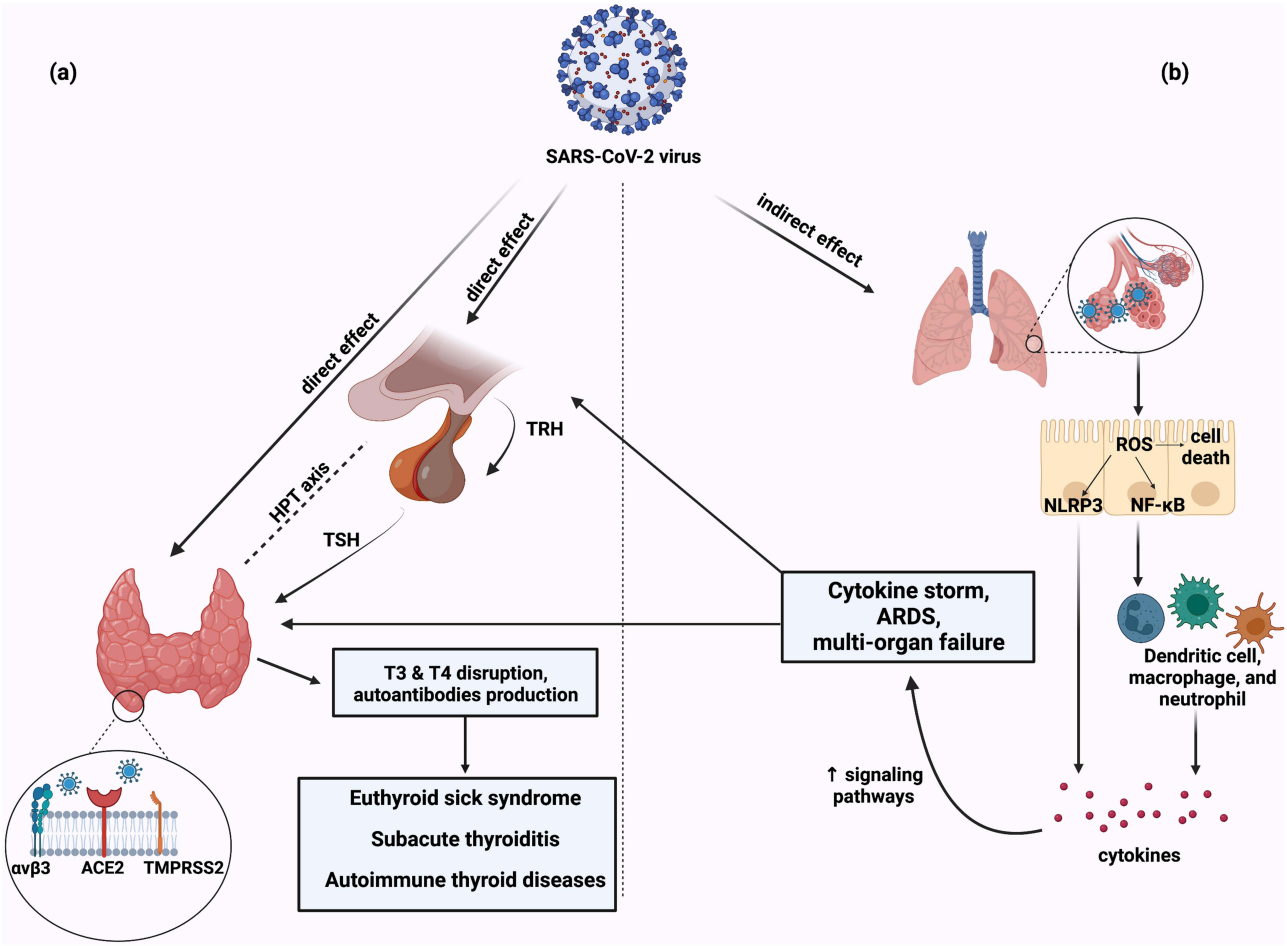

Figure 2 SARS-CoV-2-induced thyroid dysregulations. (**a**) The diagram illustrates the potential path of thyroid gland infection. ACE2, TMPRSS2, and αvβ3 integrin have been identified at all hypothalamic-pituitary-thyroid (HPT) axis levels. The SARS-CoV-2 enters thyrocytes and the HPT axis by binding to these receptors and facilitates direct viral attack to thyroid cells, thus causing thyroid dysfunctions. (**b**) The host lung-mediated infection triggers hyper-inflammatory immune responses that lead to the formation of reactive oxygen species (ROS) in epithelial cells. ROS promotes NLR pyrin domain containing 3 (NLRP3) and nuclear factor-kappa B (NF-κB) activation, which raises the number of cytokines and, thus, activates various signalling pathways in the cells. These immunological responses result in clinically significant conditions like cytokine storm and acute respiratory distress syndrome (ARDS). These affect thyroid cells and the HPT axis and induce thyroid diseases.

mentioning that spontaneous bursts of IL-1, IL-6 and TNF-α are mainly responsible for the development of thyrotoxicosis in critical care COVID-19 patients.[48]

SARS-CoV- and MERS-CoV-associated thyroid dysfunctions provide valuable insight into the SARS-CoV-2-induced HPT pathogenesis (Figure 2).[49] Endocrine abnormalities are mainly due to aberrated pituitary-hypothalamus functions and insufficient thyroid-stimulating hormone (TSH) production and release. A substantial amount of neurons have also been found in the hypothalamus with cytoplasmic SARS genome sequences.[50] Additionally, the number of TSH-positive cells reduces significantly in the pituitary region of SARS patients. The lower TSH levels are possibly linked to the alterations in TSH-secreting cells in the pituitary, leading to the interruption of the pituitary endocrine axis feedback loop.[51] It is further suggested that COVID-19 patients experienced low TSH levels, and the degree of reduction is linked with COVID-19 disease severity.[52] When comparing the serum TSH levels in COVID-19 and non-COVID-19 pneumonia patients with a similar degree of severity, the former showed a lower value of TSH, assuming that COVID-19 disease has a specific impact on the TSH-secreting cells. Few studies have suggested that it may have resulted from the direct cytopathic effect of SARS-CoV-2 on the pituitary gland and indirect damage by the induced cytokine storm.

Cytokine Storm and Signal Transduction Pathways

Pattern-Recognition Receptor (PRR)

PRRs recognise the pathogens and damaged cells via interacting with pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), respectively.[53] They appear phylogenetically before the emergence of adaptive immunity and thus are recognised as an impotent effector molecule of innate immunity. Depending on protein domain homology, the PRRs are classified into toll-like receptors (TLRs), retinoic acid-inducible gene-1 (RIG)-like receptors (RLRs), nucleotide oligomerisation domain (NOD)-like receptors (NLRs), C-type lectin receptors (CLRs) and absent in melanoma-2 (AIM2)-like receptors (ALRs).[54,55]

The TLRs and CLRs are extracellular PRRs that recognise pathogens in the endosomal compartment, while the rest serve as intracellular PRRs. Due to the presence of tandem caspase recruitment domain (CARD) in the N-terminal region, RIG-1 actively participates in the production of IFN following viral infections.[56] The CARD reacts with the mitochondrial antiviral-signalling protein to recruit downstream signalling molecules such as TNF receptor-associated factor (TRAF) and inhibitors of NF-κB kinase (IκK), causing the IFN to be transcriptionally activated.[57] Moreover, TLRs induce the signal transduction pathways by recognising the respective PAMPs and DAMPs, which results in the activation of NF-κB and MAPKs via the myeloid differentiation primary response 88 (MYD88) [29]. The findings are previously supported by Medzhitov, Preston-Hurlburt, Janeway,[58] suggesting that the TLR4 activate NF-κB and CD80 expression, resulting in the release of numerous pro-inflammatory mediators such as cytokines, chemokines and reactive oxygen species (ROS).[59]

The thyrocyte functional PRRs, including TLRs and RLRs, are susceptible to PAMPs- or DAMPs- inducing cytokines and chemokines production.[60] Harii, Lewis et al[61] discovered that the PAMP induces adjuvant thyroid complications from detecting dsRNA by functional TLR3 in the human thyroid. The production of ILs, IFNs, and TNF inhibits thyroid function through MAPK and NF-κB activation. Furthermore, the innate immune response influences the thyrocytes to act as APCs, which recruit lymphocytes and provoke an autoimmune response, consequently developing hypothyroidism, ESS, GD and HT.[62]

Nuclear Factor-Kappa B (NF-κB)

NF-κB is an inducible transcription factor involved in various immuno-inflammatory processes. NF-κB signalling requires phosphorylation and degradation of inhibitory IκB kinase-β (IKKβ), which liberates the p50 and p65 dimers. These subunits are translocated into the nucleus, functioning as transcriptional factors and regulating the genes involved in the inflammatory processes.[63,64] Giuliani, Bucci, Napolitano[60] indicated that the PRR ligands, cytokines, T-cell and B-cell receptor signals, and MAPKs serve as NF-κB activating stimulus. Two signalling cascades activate NF-κB, namely canonical and non-canonical pathways. The canonical pathway is characterised by activating p50, p65, and c-Rel dimer transcription factors, encoding the expression of cytokines, chemokines, and adhesion molecules responsible for recruiting and activating inflammatory cells. The latter predominantly stimulates the p52/RelB transcription factor and upregulates the proteins required for B cell viability, function, and antigen presentation.[45,65]

Thyroid cells predominantly express TLRs and RLRs. Hence, it is unsurprising that NF-κB dysregulation plays a pivotal role in the pathogenesis of thyroid disorders. The constitutive activation of the NF-κB pathway results in aberrant cytokine gene expressions, especially IL-1β, IL-6, and TNF-α that act as the primary mediators of thyroid diseases, including ESS and autoimmune thyroid diseases (AITDs).[66] Downstream NF-κB) signalling converts pro-caspase-1 to active caspase-1 that cleaves pro-IL-1β. Subsequently, the IL-1β generates ROS intracellularly and causes thyroid cell apoptosis and hypothyroidism. Kwakkel, Wiersinga, Boelen[67] hypothesised that NF-κB-induced IL-1β leads to the degradation of TRβ1 mRNA and increases transcriptional repression of the TRβ1, causing D1 level to plunge in thyroid cells. Moreover, NF-κB-stimulated IL-6 production induces Th17 lineage transcription factor RAR-related orphan receptor-γ (RORγt) and differentiates Th0 lymphocytes into Th17 cells.[68] The Th17 cells intensify intracellular IL-17 production, enhancing SARS-CoV-2 and thyrocyte survival by preventing cytotoxic T cells from destroying target cells and paving the way for AITDs.[69] Regulatory T (Treg) cells are essential for immune responses to restrict chronic inflammation and autoimmunity.[70,71] Upon T-cell receptor (TCR) stimulation, c-Rel induces FoxP3 (master transcription factor for Treg), which indicates that NF-κB canonical signalling plays a significant role in mediating Treg cell development and regulation.[72]

Janus Kinase (JAK)/Signal Transducer and Activator of Transcription (STAT)

JAKs are non-receptor-associated tyrosine kinases, that consist of JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). They are essential in transmitting extracellular signals from cytokine activating the STAT pathway.[73] IL-6 and IL-23 stimulate STAT3 via JAK2, while IL-21 activates STAT1, STAT3 and STAT5 via JAK1 and JAK3.[74] The members included are STAT1, STAT2, STAT3, STAT4, STAT5 and STAT6. Each protein has different functions in innate and adaptive immunity.[75] STAT1 proteins are involved in producing vascular cell adhesion molecules (VCAM) and inducible nitric oxide synthase (iNOS).[76] Additionally, STAT1 and STAT2 mediate IFN signalling; STAT1 is associated with type I and II IFN signalling, whereas STAT2 is the type I IFN mediator.[77] STAT3 induces IL-6 and IL-10, whereas STAT4 and STAT6 are involved in adaptive immunity. STAT4 is utilised for T-helper (Th) 1 cell differentiation associated with autoimmune disorders. In contrast, STAT6 participates in Th2 cell differentiation, which causes an allergic reaction, namely airway hyper-responsiveness. Lastly, STAT5 regulates lymphoid proliferation, inhibiting apoptosis and inducing cytokines.[71,75] Recent studies have suggested a strong correlation between the STAT pathway and COVID-19 pathogenesis. STAT4-mediated Th1 response, cytotoxic effect in specific plays a pivotal role in SARS-CoV-2 immunity in moderate to severe conditions. This is further supported by the reports suggesting the presence of virus-specific $CD8^+$ T lymphocytes in approximately 70% of COVID-19 patients.[78]

The JAK/STAT is essential for mediating cytokine receptors' signalling cascades. Cytokine binding at the extracellular domain initiates the cross-phosphorylation of JAK, activating tyrosine residues at the corresponding receptor. The activated JAKs create a docking site for STAT molecules, which paves the way for the dissociation, dimerisation, and nuclear translocation of phosphorylated STAT molecules.[79] Among the family members, the function of STAT3 is underlined. IL-6-induced JAK/STAT3 activates the gp130/cytokine-specific receptor complex.[80] Activated receptor complexes with STAT3 mediate IL-6 and IL-23 signals, which allows TH17 cells to differentiate and function as effectors. Likewise, the Th0 lymphocyte differentiates into Th17, upregulating the IL-17 expression, an essential mediator of autoimmune diseases, including GD.[81] Kotkowska, Sewerynek, Domańska, Pastuszak-Lewandoska, Brzeziańska[82] support the involvement of STAT3 polymorphism in the development and progression of AITD.

Moreover, combining IL-6 and JAK/STAT3 is a prerequisite for fully activating NF-κB. The nuclear translocation of phosphorylated STAT3 invariably promotes cytokine storm by NF-κB activation and abrogating IFN-γ production.[66] NF-κB activation promotes IL-6 positive feedback loop mechanisms and IL-6 amplifier (IL-6 Amp) activation, which paves the way for major histocompatibility complex (MHC) class II-associated autoimmune disease, including GD.[83] Lee, Nakagiri et al[84] discussed that IL-6 Amp mainly targets C-C motif chemokine ligand 2 (CCL2), and the elevated concentration is apparent after IL-6 Amp activation. The increased CCL2 plasma level modulates macrophages' cellular adhesion and chemotaxis through β1 integrins and p38MAPK signalling pathways.[85]

Mitogen-Activated Protein Kinases (MAPKs)

MAPKs are essential in transducing the signals from the surface receptors to the transcriptional factors. It is activated by cytokines such as IL-1, IL-6, and TNF-α. The MAPK comprises three main groups: c-jun N-terminal kinase (JNK), p38, and extracellular signal-regulated kinases (ERKs).[86] p38 MAPK upregulates the expression of IL-1, IL-6, IFN-γ and TNF-α. In addition, the activated p38 MAPK in $CD4^+$ T cells has an essential role in Th17 cell function by regulating the production of IL-17.[87] The ERK MAPK governs the synthesis of IL-6, IL-12, IL-23 and TNF-α and induces thyroid cell damage by increasing pro-inflammatory cytokine production from macrophages.[88] It is worth mentioning that JNK MAPK activation has been associated with decreased TSH and increased T4 serum levels. It has been suggested that the upregulation of the DIO3 gene can be induced by MAPK activation and the TGFβ pathway, leading to reduced serum T3 and T4 levels.[89] Other than that, the production of ROS, specifically anion superoxide from TLR, increases the expression of intracellular adhesion molecule-1 (ICAM-1) by activating the MAPK pathway.[90,91] The ICAM-1 is expressed by IFN-γ through JAK/STAT signalling, resulting in the transmigration of leukocytes to the inflamed site and co-stimulation for T cell activation. Based on these studies, it is highly suggested that MAPK signalling pathways are essential to stimulate thyrocyte destruction, which plays a significant role in the pathogenesis of AITD.[92]

Key Orchestrators of Cytokine Storm-Related Thyroid Complications in COVID-19

Interleukins (IL)

ILs are a cytokine group that regulates cell growth, differentiation, and immune activation during inflammation and other immune responses. These proteins induce various cells and tissues by binding to high-affinity cell surface receptors.[65] The histo-biochemistry analysis of COVID-19 patients has revealed elevated levels of numerous cytokines (Table 1). In inflammation, IL-6 utilises cis- and trans-signalling to activate the JAK/STAT3 pathway.[93] In cis-signalling, the IL-6 binds to gp130 and membrane-bound IL-6 receptor (mIL-6R) and activates downstream signalling of JAK/STAT3 and MAPK. This signalling cascade promotes the differentiation of Th17, $CD8^+$ T and B cells and supports neutrophil migration. These actions further enhance IL-6 release and aggravate inflammation. In the trans-signalling, the circulating IL-6 binds to the soluble IL-6 receptor (sIL-6R) and induces JAK/STAT3 signalling in the cells lacking mIL-6R expressions, like endothelial cells and vascular smooth muscle cells (Table 1). The over-activation of JAK/STAT3 signalling triggers more mediators to be secreted, like IL-6 itself, thereby promoting C-reactive protein (CRP) in hepatocytes.[94] Croce, Gangemi et al[95] proposed that the elevated circulating IL-6 reduces Tg and T3 synthesis in thyroid follicular cells, leading to thyroid complications.

Table 1 Mechanism of Action and Functions of Soluble Inflammatory Mediators in COVID-19-Related Thyroid Disorders

Mediators	Mechanism of Action and Function (s)
Cytokines and growth factors	
IL-1β	Downregulates the expression of DIO1, decrease iodide and T3 uptake, induce Fas and MCP-1 mRNA levels in thyrocytes[67,95]
IL-2	Restricts EGF-stimulated thyroid follicular cell proliferation and induce thyroid autoantibodies production[96]
IL-4	Promotes Th2 cell differentiation and ameliorate Th1 response[96]
IL-5	Induce B cell proliferation[97]
IL-6	Downregulates TBG gene expression, decrease D1 and D2 activity by stimulating ROS, reduces T3 synthesis, rT3 clearance, and intracellular T4 to T3 conversion. Increase DIO3 gene and D3 activity and differentiate $CD4^+$ T cells into Th17 cells[74,98]
IL-8	Increase the neutrophils adherence to endothelial cells[99]
IL-10	Promote autoreactive B cell survival through Bcl-2 stimulation[100]
IL-12	Prime towards IFN-γ stimulation and Th1 response[101]
IL-13	Induce B cells to produce IgG[102]
IL-15	Promote anti-apoptotic activity and lymphocyte survival[103]
IL-17	Stimulate the release of IL-1β, TNF-α and chemokines Promote anti-apoptotic activity by interfering with the Fas/FasL pathway in thyrocytes[104]
IL-23	Induce Th0 differentiation to Th17[105]
IFN-α and IFN-β	Decrease iodine incorporation, TPO, and Tg gene expression in the thyrocytes[106]
IFN-γ	Decrease Tg expression and production in thyroid cells Upregulate MHC class II on thyroid follicular cells and induce Fas expression on thyrocytes[107]
TGF-β	Induces apoptosis and inhibit thyrocyte growth. Induce Th17 differentiation by stimulating IL-6 production[108]
TNF-α	Decrease D1 activity, and T4 to T3 conversion. Decrease TSH-stimulated TPO and Tg gene expression in thyrocytes. Induce TRAIL-mediated cell apoptosis[103]
Chemokines	
CXCL9 (MIG)	Recruitment of macrophages, Th1 cells, NK cells, dendritic cells and strengthen CXCL10 activity[104]
CXCL10 (IP-10)	Amplify Th1 immune responses and IFN-γ production[109]
CXCL11	Mimics the mechanism and actions of CXCL9[45]
CCL2 (MCP-1)	Th0 cells Polarisation to Th2 phenotype. Recruit monocytes and T cells at the inflamed thyroid gland[108]
CCL3 (MIP1α)	Chemotactic agent; selectively attract $CD8^+$ T cells[108]
CCL4 (MIP1β)	Chemotactic agent; selectively attract $CD4^+$ T cells[108]
CCL20	Activate IL-17 signalling and migrate Th17 cells to trigger a self-destructive immune response[110]

The IL-1 family upregulates T and B lymphocyte maturation, leukocyte adhesion and CRP production. The IL-1 affects nearly every tissue in the human body but selectively participates in thyroid-driven autoimmunity. IL-1 comprises two agonists: IL-1α and IL-1β. The latter is a well-studied member of this family owing to its pivotal role in autoimmunity.[111,112] The Fas ligand is generally expressed on thyroid follicular cells, which allows them to invade and eliminate Fas-sensitive target cells. As a result, IL-1β exposure induces thyroid follicular cell apoptosis, implying that IL-1β-induced Fas expression is critical for thyrocyte destruction and hypothyroidism.[113] Croce, Gangemi, Ancona, Liboà, Bendotti, Minelli, Chiovato[95] also reviewed the role of IL-1β in the pathogenesis of thyroid dysfunctions, proposing that IL-1β reduces T3 secretion and Tg mRNA expression in the thyroid cells. Macrophages primarily secrete the IL-1β through apoptosis and pyroptosis. Aside from the functions mentioned earlier, IL-1β is one of the dominant activators of IL-6 expression and the NF-κB pathway to establish positive feedback for its production.[94] Further, the inactivated IL-1β is cleaved by the NLR pyrin domain containing 3 (NLRP3) protein to initiate sustained inflammation, suggesting that the NLRP3-IL-1β signalling pathway is actively involved in the inception of cytokine storm in COVID-19 patients.[93]

Tumour Necrosis Factor (TNF)

TNF produced by macrophages plays a pivotal role in the pathogenesis of cytokine release syndrome. TNF is classified into TNF-α and -β based on functional variability (Table 1).[114] TNF-α primarily binds to TNFR1 and TNFR2. According to Yang, Wang, Brand, Zheng,[115] TNF-α and TNFR1 complex is infamous for modulating inflammatory pathways and promoting the adhesion and permeability of endothelial cells. TNF-α is a well-known inducer of NF-κB that initiates the immune cell hyper-activation in cytokine storm by inducing epithelial cell death and aggravating systemic inflammation.[45] The late study of Lee, Lombardi et al[116] on thyroid cell $CD40^+$ signalling contributed to a better understanding of NF-κB role in thyroid disorders. $CD40^+$, a TNF receptor expressed on the APCs and thyroid cells, is required for adaptive immune response.[117] The overexpression of $CD40^+$ on thyrocytes is associated with autoimmune disease. The activated $CD40^+$ upregulates p65 and p52 subunits to initiate the NF-κB canonical and non-canonical pathways.[60] The elevated plasma level of TNF-α decreases the DIO1 activity, T3 and Tg production, and TSH-stimulated TPO gene expression in the normal thyroid follicular cells, resulting in AITD.[95]

Chemokines

Chemokines are chemotactic cytokines essential for migrating and positioning immune cells in tissues. Chemokines can be divided into homeostatic and pro-inflammatory chemokines. The former controls the cell migration for normal tissue maintenance, while the latter directs the immune cells towards inflamed sites.[118] Studies have suggested that IFN-γ-induced chemokines like CXCL9, CXCL10 and CXCL11 provoke various thyroid disorders (Table 1).[109] Interestingly, all three chemokines bind to the same receptor, CXCR3. The CXCR3 is abundantly expressed by activated Th1 and $CD8^+$ lymphocytes and is hypothesised to have an active role in the recruitment of immune cells to sites of inflammation. It has three isoforms, CXCR3-A, CXCR3-B, and CXCR3-alternative (CXCR3-alt). The activated CXCR-3A results in cell proliferation, migration and invasion via MAPK/ERK and MAPK/JNK signalling. Meanwhile, the activation of CXCR-3B triggers cAMP formation and apoptosis through the MAPK/p38 pathway.[119] In addition, the attraction of high levels of CXCR3-expressing macrophages by CXCL10 promotes IL-6 production, which is responsible for the further deterioration of the thyroid cell.[120]

Interferons (INFs)

Infected cells produce IFNs as alarmins to stimulate intracellular defence against viral invasion. The IFN family can be categorised into IFN-α, IFN-β, and IFN-γ. IFN-α and IFN-β are considered type 1 IFN, whereas IFN-γ is called type 2 IFN. Their action on the neighbouring cells prevents virus replication and regulates immune response.[121] The role of IFN-γ is underlined in the COVID-19-related cytokine storm, which activates protective immunity against the virus via JAK/STAT1 signalling and downstream the STAT1-IFN-γ-activated site cascades (Table 1).[93] Of note, the IFNs are found to induce cytokine-related thyroid dysfunctions. For instance, the IFN-α restricts iodine incorporation and thyroid hormone release, as well as decreases thyroid peroxidase (TPO), sodium iodide symporter (NIS) and thyroglobulin

(Tg) gene expression in the thyrocytes.[106] In addition, IFN-γ upregulates ICAM-1 on the thyroid cells, establishing cell-cell interaction and boosting the inflammatory processes.

Signalling Cross-Talks and Thyroid Disorders

Euthyroid Sick Syndrome (ESS)

ESS is commonly known as non-thyroidal illness or low T3 syndrome. It is characterised by reduced triiodothyronine (T3) and thyroxine (T4) serum levels and elevated reverse T3 (rT3) with abnormally low serum TSH concentrations.[122] According to de Vries, Fliers, Boelen,[123] cytokines generated during viral infections can provoke ESS due to their potential to inflict numerous genes in thyroid hormone metabolism. Zou, Wu et al[124] revealed that 41 out of 149 (28%) were diagnosed with ESS in moderate to severe COVID-19 patients. As a result, it is conceivable that COVID-19 has the potential to induce ESS. In this context, the cytokines secreted profoundly as a generalised reaction to the infection have drawn particular interest. Available findings have suggested that IL-1β, IL-6, and TNF-α are the vital inflammatory mediators that play pivotal roles in ESS pathogenesis.

SARS-CoV-2 invades epithelial tissue and stimulates local innate immune cells, inducing the production of inflammatory cytokines (Figure 3). Specifically, IL-6 produced by monocytes, macrophages, and dendritic cells serves as a key activator of the JAK/STAT3 by utilising the cis-signalling pathway.[93] The IL-6 binds to mIL-6Rs expressed on immune cells and establishes an IL-6/IL-R/gp130 complex, initiating IL-6 signal transduction. Based on Wajner, Goemann, Bueno, Larsen, Maia[88] study, all three deiodinase mRNAs involved in the p38 and ERK MAPK pathways are upregulated by IL-6. Upon the formation of the receptor complex, JAK/STAT initiation leads to MAPK cascade activation, stimulating the deiodinase gene transcription inducer called cAMP response element-binding protein (CREB).[125] Kester, Kuiper, Versteeg, Visser[126] investigation revealed that cAMP is one of the main factors that induce D3 activity. All three deiodinases are selenocysteines, and thiols contain oxidoreductases, making them equally susceptible to redox reactions.

Interestingly, the elevated D3 function is directly associated with MAPK-induced DIO3 upregulation. On the contrary, DIO1 and DIO2 gene expressions remain unaffected due to the absence of catalytic position in D1 and D2. On the other hand, the presence of catalytic positing in D3 facilitates its easy access to extracellular glutathione (GSH) (Figure 3). In this scenario, if the intracellular concentration of GSH falls, D3 actions are not changed and remain unaffected.[127] Conclusively, augmented D3 activity lowers plasma T3 levels by increasing T3 and T4 clearance and elevating rT3 conversion from T4.

From another perspective, the ESS is characterised by oxidative stress imposed by the production of ROS and reactive nitrogen species (RNS). The patients frequently exhibit lower antioxidant molecules (GSH) and lower reactions of the antioxidant enzymatic system associated with ROS detoxification.[128] Wajner, Maia[98] proposed that the elevated serum IL-6 level is directly linked to oxidative stress. The IL-6 triggers an oxidative burst by increasing superoxide radical production via nicotine adenine dinucleotide phosphate (NADPH) oxidase pathway activation.[129,130] Consequently, intracellular GSH is depleted, and the GSH/GSSG ratio is lowered, affecting deiodinase functions when the intracellular redox state is perturbated (Figure 3).[131]

Deiodinases are oxidoreductases that facilitate iodine removal from the outer or inner ring of the thyroid hormones.[132] Protein cysteine residues are oxidised to produce inter-and intramolecular disulfide bonds and GSH-mixed disulfides, especially important for deiodinase activity.[133] Therefore, the raised ROS is expected to deplete putative thiol cofactors for D1 and D2, impairing catalytic reactions that demand a reductive intracellular environment. The IL-6-induced D1 depletion diminishes T3 synthesis and rT3 clearance. In contrast, the D2 shortage is complemented by disabling intracellular T4 to T3 conversion. Based on these reports, it is inferred that excessive IL-6 production results in decreased T3 plasma levels, which serve as a hallmark of ESS in COVID-19.

Furthermore, the ESS can be provoked through IL-1β and TNF-α activation during cytokine storm in COVID-19 patients.[124] At the early stages of SARS-CoV-2 infection, the NLRP3-mediated inflammasome is activated by utilising two separate events. The first phase is priming, which involves the viral RNA engaging TLRs. The myddosome complex is recruited, which transmits downstream signals to NF-κB and elevates the levels of NLRP3 and pro-IL (Figure 3). The

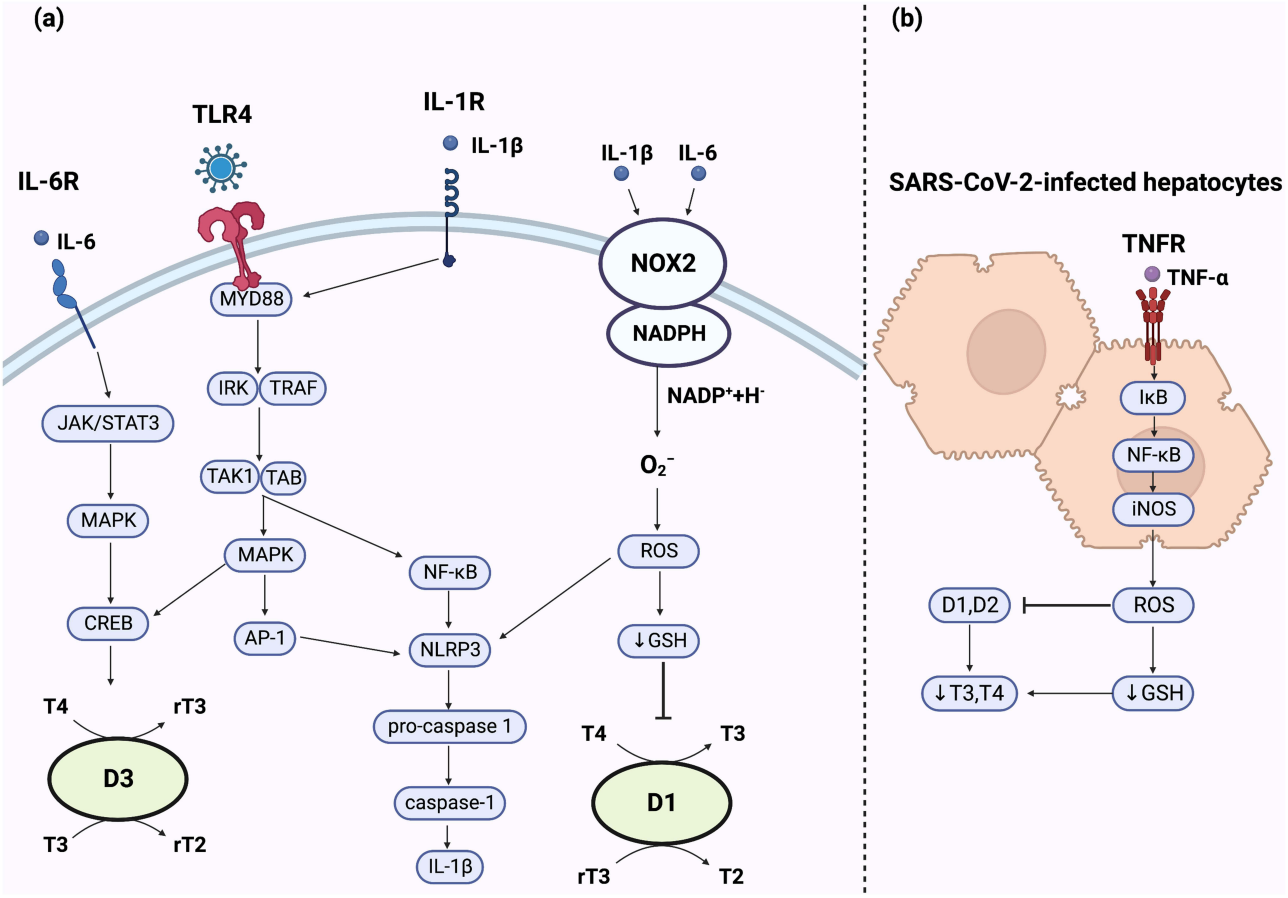

Figure 3 Proposed mechanism for the effects of cytokines on deiodinase function leading to euthyroid sick syndrome (ESS). (**a**) IL-6 binds to its receptor followed by the formation of the IL-6/mIL-6R/gp130 complex, initiates JAK/STAT3 pathway, p38 and ERK mitogen-activated protein kinase (MAPK) signalling. These MAPK cascades activate cAMP response element-binding protein (CREB) which induces DIO3 gene transcription. The increased D3 in thyrocytes further reduce plasma T3 and increase production of rT3 from T4. Additionally, TLR4/IL-1/MYD88-dependent pathway directs the downstream activation of transforming growth factor-β-activated kinase 1 (TAK1), stimulating IκB kinase (IKK) and MAPK signalling. This results in a synergistic increase in IL-1β by upregulating NLRP3 and pro-IL levels. The activation of NLRP3 cleaves pro-caspase-1 into active caspase-1 and causes pyroptosis, which leads to the secretion of IL-1β that can bind to IL-1R and stimulate MYD88 pathway. Hence, a vicious cycle of NLRP3 priming, activation, and pyroptosis that worsens ESS. Both excessive produced IL-1β and IL-6 also binds to NADPH oxidase 2 (NOX2) to generate ROS via the NADPH oxidase pathway. This process is catalysed by NADPH oxidase, which releases two electrons (e^-) to convert NADPH into $NADP^+$. The molecular oxygen (O^2) accepts the e^- and generates the ROS superoxide (O^{2-}). ROS itself promotes NLRP3 inflammasome activation and depletes intracellular glutathione (GSH) thereby diminishing D1 catalytic activity. (**b**) Excessive TNF-α production activates NF-κB signalling and increases intracellular nitric oxide synthase (iNOS) activity in the liver, thereby producing large amount of ROS and hepatic oxidative stress. Since conversion of T4 into T3 primarily occurs in the liver, oxidative stress and diminished GSH levels impair D1 and D2 function, resulting in decreased T4 to T3 conversion and rT3 clearance. Taken together, excessive cytokine production particularly IL-1β, IL-6, and TNF-α activates multiple signalling pathways to disrupt deiodinase functions by reducing T3 levels while elevating rT3 concentrations observed in the ESS.

following step is assembling the inflammasome proteins into a functionally active structure comprising several signal molecules, creating an intracellular ion imbalance and promoting ROS generation.[134] Typically, T3 regulates D1 mRNA expression by binding liganded thyroid hormone receptor (TR)-1 to the thyroid hormone response elements (TREs) in the DIO1 gene promoter region.

Meanwhile, the D1 mRNA activity is reduced due to the involvement of pro-inflammatory cytokines during illness. According to Kwakkel, Wiersinga, Boelen,[67] a decline of D1 and TRβ1 mRNA levels by IL-1β is related to the NF-κB activation. It is hypothesised that the TRβ1 mRNA degradation is augmented during inflammation and transcriptional repression of the TRβ1 (through NF-κB) is due to the competitive behaviours of common factors in limited quantities to activate NF-κB and TRβ1-mediated D1gene transcription.

The Phagocytic NADPH oxidase pathway facilitates the IL-1β-induced ROS production, which resembles oxidative burst situ to IL-6-induced-ESS.[135] TNF-α has been implicated in ESS due to its potent NF-κB activating potential. Nagaya, Fujieda et al[136] discussed that the TNF-α-mediated-NF-κB activation disrupts the T3-dependent induction of deiodinase by reducing D1 promoter action, leading to the ESS. Further, it was suggested that thyroid hormone action is

impaired in HepG2 cells since the liver is the primary site of T4 conversion to T3. These studies indicate that the cytokines, either alone or in combination, downregulate multiple TH production mechanisms, leading to lower T3 and T4 secretion from the thyroid gland.

Autoimmune Thyroid Disease (AITD)

AITD is known for its reactivity to self-thyroid antigens, resulting in destructive inflammatory reactions.[109] Few documented incidences have reported severe hypothyroidism or GD during and after COVID-19 disease.[47,137] Depending on the primary effector mechanism and type of cell implicated, it is classified as a T-cell or autoantibody-mediated disease. The T-cell infiltrates and destroys the target tissue, known as T-cell-mediated disorder, as seen in HT. In contrast, autoantibody-mediated disease is described as the disruption of function, as in GD.[138] The cytokine productions are stimulated by thyroid follicular cells and are initially induced by IL-1, IFN-γ and TNF-α. They upregulate the expression of MHC class I and II on the surface of thyroid follicular cells to recruit T cells. Therefore, it is indicated that COVID-19-induced hyper-inflammation predisposes individuals to autoimmune complications (Figure 4).

AITD patients have more $CD4^+$ T cells, exhibiting abnormal FoxP3 expression, a critical gene for developing Treg cells. The Treg suppresses lymphocyte differentiation into Th1 cells.[107] The reduced Treg activity enhanced follicular T helper cell function, and the DNA fragment release contributes to the initiation and perpetuation of HT.[139] The HT is characterised by a Th1 immune response that favours cell-mediated immunity and apoptosis in thyrocytes. The Th1 cytokines are synthesised from the naïve Th cells by TCR engagement. In addition, IFN-γ binds to its cognate receptor to initiate STAT1 signalling. This phosphorylated STAT1 stimulates the expression of the transcription factor T-bet, which leads to the differentiation of Th cells into Th1 cells by trans-activating IFN-γ and receptor for IL-12. Subsequently, the cell becomes responsive to IL-12, and the signalling through STAT4 further stabilises the Th1 phenotype. The Th1 cells secrete pro-inflammatory cytokines such as IFN-γ, TNF-α, and IL-1β, which activate the macrophages and cytotoxic effects.

The thyroid peroxidase (TPO) autoantibody levels represent MHC expression on thyrocytes and the degree of lymphocyte infiltration, which stimulates autoantibody production.[140] In patients with HT, anti-TPO antibodies depend on GSH levels, exhibiting an inverse correlation.[141] The IFN-α restricts iodine incorporation and decreases the thyrocytes' TPO and thyroglobulin (Tg) gene expression.[106] IFN-α receptor binding and JAK/STAT activation stimulate the interferon-stimulated genes (ISGs). As such, the TPO surface expression on thyroid cells is dramatically increased by IFN-α. Subsequently, hyper-expression of TPO as thyroid autoantigens leads to TPO autoantibodies formation, mainly when IFN-α causes a reduction in T suppressor cells and elevation of B cells. As expected, IFN-α boosts the MHC class I antigen expression on the thyrocytes, thus recruiting cytotoxic T lymphocytes and causing inflammatory responses.[142] Down the lane, TPO antibodies mediate thyroid cell damage by antibody-dependent cytotoxicity (ADCC). Autoantibodies attached to the thyrocytes recognise the Fc receptor on NK cells, which results in thyroid cell lysis.[143] Among the mechanisms of ADCC involving NK cells, the perforin/granzyme pathway has been widely studied. Self-reactive $CD4^+$ T cells attract $CD8^+$ cytotoxic T cells and stimulate the release of cytotoxic granules containing perforin and granzyme to induce cell necrosis.[144]

TNF, FasL, and TRAIL pro-apoptotic death ligands and receptors are significantly expressed in thyrocytes, which are normally inactive in healthy settings.[145] Interestingly, IL-1β, IFN-γ, and TNF-α activate the apoptotic pathways, typically inactive in thyroid cells. Mezosi, Wang et al[103] suggested that combining IL-1β and TNF-α promotes TRAIL-mediated cell death by increasing TRAIL receptors and procaspase expression and decreasing p44/p42 MAPK pathway activity. This pathway has been reported to have a dominant protecting role against apoptotic signalling from death receptors. At the same time, the activation kinetics were slowed in the IL-1β/TNF-α-treated cells.[146,147] Hence, declining p44/p42 MAPK signalling facilitates thyroid cell apoptosis. Mezosi, Wang et al[148] again suggested that the signalling pathways that include everything from the receptor to the apoptosis-inducing caspase enzymes undergo profound alterations when the thyrocytes are exposed to the IL-1β together with IFN-γ. Although the IFN-γ upregulates the Fas receptor expression, contrarily, it does not sensitise the thyrocytes but abrogates Bid concentration, which is crucial for cell apoptosis and hypothyroidism. The GD promotes Th2, and naïve T cells are differentiated via STAT6 activation. The STAT6 is phosphorylated when TCR engages with the IL-4 receptor, leading to the Th2 transcription factor GATA3 induction.

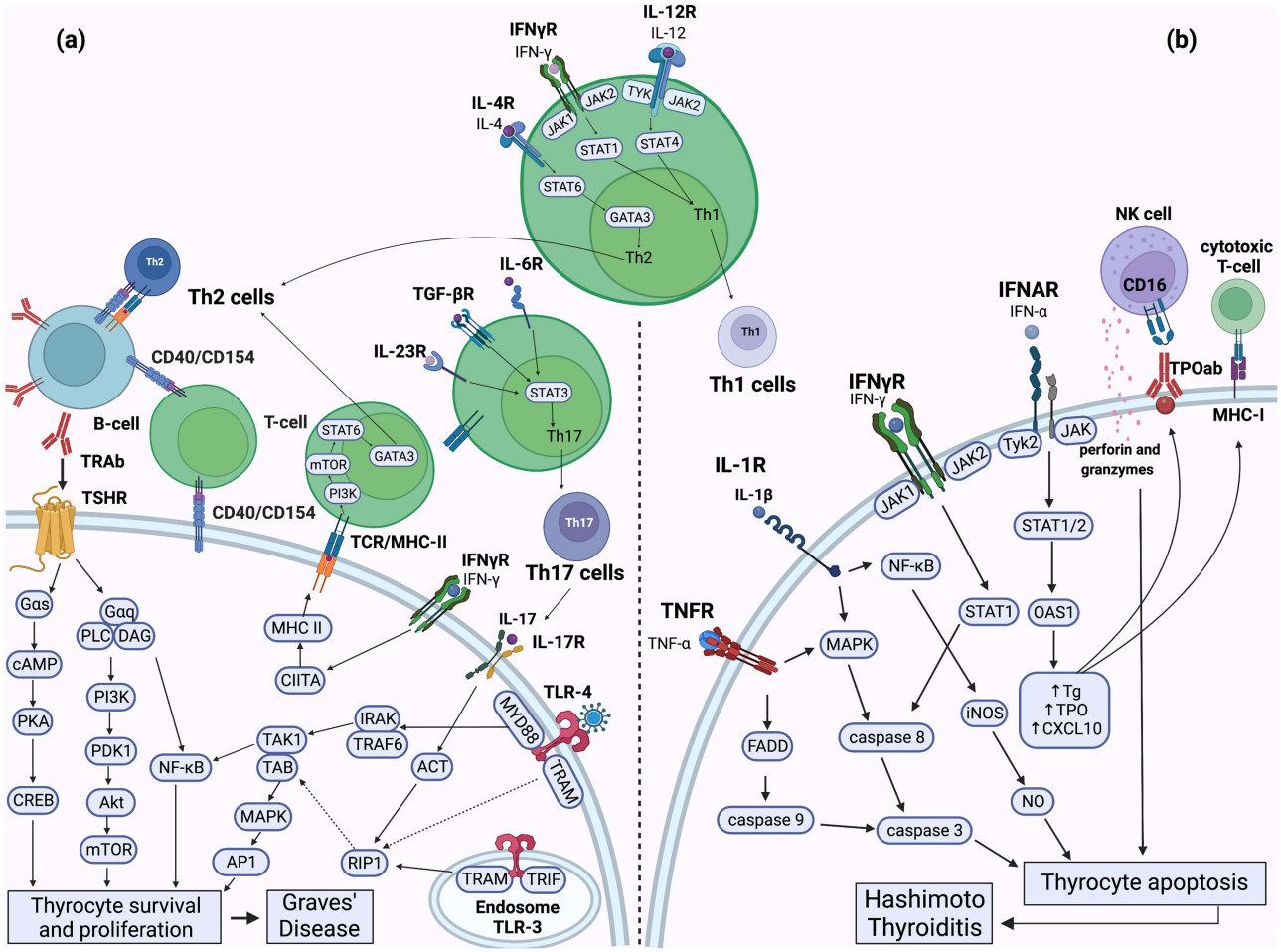

Figure 4 Proposed mechanism for COVID-19-associated cytokine storm-induce autoimmune thyroid diseases (AITDs), (**a**) The IL-4/STAT6/GATA3 axis regulates the differentiation of naïve $CD4^+$ T-cells to Th2 cells. Excessive IFN-γ also stimulates Th2 cell differentiation through JAK/STAT1 pathway to transactivate class II trans activator (CIITA). MHC class II genes are transactivated by recruiting CIITA and CREB to their promoters. The MHC class II loaded within the peptide is then expressed on the cell surface to T-cell. The MHC class II engages with T-cell receptor (TCR) and activates PI3K/mTORC2/Akt pathways. The engagement promotes STAT6-induced GATA3 transcription, thus producing Th2 effector cells. The Th2 cells express CD40L bind to $CD40^+$ on B cells to promote mass production of TSH receptor autoantibodies (TRAb). TRAb binds to epitopes in extracellular domain of TSHR, activates Gαs/AC/PKA/CREB, Gαq/PLC/PI3K/Akt, and Gαq/DAG/NF-κB pathways, which are pivotal for thyrocyte proliferation, function and survival. Upon SARS-CoV-2 binding to TLR4, MYD88 recruits and phosphorylates IRAKs. The phosphorylated IRAK then interacts with tumour necrosis factor receptor-associated factor 6 (TRAF6) to activate TAK1 and TAB. At the same time, TIR-domain-containing adaptor-inducing interferon-β (TRIF) serves as the adaptor of TLR3 and part of TLR4. TRIF interacts with receptor-interacting protein 1 (RIP1), causing its polyubiquination with TAB. Subsequently, IκB and MAPK are activated and translocate NF-κB and AP1 to the nucleus. The translocation upregulates inflammatory cytokines that worsens AITDs. Moreover, IL-6, IL-23, and TGF-β are the inducer of Th17 cell differentiation by stimulating STAT3 signalling pathways and RAR-related orphan receptor-γt (RORγt) transcription. IL-17 produced by Th17 cells binds to its receptor and recruits NF-κB activator 1 (ACT1) to initiate NF-κB signalling pathway. Activation of NF-κB by IL-17 results in enhanced Bcl-2 expression for thyrocyte survival. Thus, various signalling pathways synergistically regulate thyrocytes proliferation and survival by stimulating TRAb and cytokine productions, along with anti-apoptotic gene expression, contribute to the progression of Graves' disease (GD). (**b**) Both IL-12 and IFN-γ activate STAT1 and STAT4 to stabilize T-bet expression. These pathways differentiate Th0 cells into Th1 cells, and produce Th1-specific cytokines like IL-1β, IFNs, and TNF-α. IL-1β itself promotes ROS production through NADPH oxidase pathway to damage thyroid cells. The combination of IL-1β and TNF-α sensitize thyrocytes to TRAIL-induced apoptosis by recruiting Fas-associated death domain (FADD) and MAPK signalling. The MAPK-activated caspase 8 and FADD-activated caspase 9 cleaves procaspase 3 to its active form by direct proteolytic processing, and a series of downstream events that lead to thyrocyte apoptosis. Meanwhile, combination of IL-1β and IFN-γ sensitize thyrocytes to Fas-induced apoptosis. IFN-γ binds to type II IFN receptor and stimulates JAK/STAT1 pathway. The activated STAT1 induces caspase 8 expression and thus initiating thyroid cell death. IFN-α binds to type I IFN receptor and triggers a signaling cascade predominantly driven by JAK/STAT. IFN-α increases oligoadenylate synthetase 1 (OAS1) expression which is an innate sensor of viral infection, CXCL10 for mononuclear cell recruitment, Tg and TPO surface expression. The excessive surface Tg and TPO act as autoantigens, and bind to CD16 of NK cells to enhance antibody-dependent cytotoxicity (ADCC). Perforin and granzymes are then released from NK cells into thyroid cells to cause cell injury. IFN-α also increases MHC class I expression presented on the cell surface to $CD8^+$ cytotoxic T-cell. Combining the effects of cytokines, perforin, granzymes, and cytotoxic T cells on the thyroid cells, these propose COVID-19-related cytokine storm causes thyrocytes apoptosis and hypothyroidism, leading to Hashimoto thyroiditis (HT).

Th2-specific cytokines, including IL-4, IL-5, IL-6 and IL-13 are trans-activated by GATA3.[149] At the same time, STAT4 and IL-12 receptors required by Th1 are down-regulated due to the overexpression of IL-6 (Figure 4).

The predomination of Th2 cytokines stimulates humoral immunity rather than cellular immunity, boosting the synthesis of B lymphocyte autoantibodies. The elevated immunoglobulin G (IgG) levels caused by the Th2 cytokines

potentially downregulate Fas expression while upregulating anti-apoptotic molecules like Bcl-2.[103] As a result, the overexpressed Bcl-2 in the thyroid cells induces GD, making them resistant to Fas/FasL-mediated apoptosis. On the other hand, this resistance is unlikely to be observed in thyroid-infiltrating lymphocytes, where the pro-apoptotic proteins are expressed.[150] Thus, it indicates that the regulation of the thyroid microenvironment in GD is almost opposite to that of HT, where the infiltrating lymphocytes in GD are sensitive to apoptosis. Still, the thyroid cells escape cell death due to overexpression of anti-apoptotic molecules.

During SARS-CoV-2 infection, the NF-κB is activated by TLR on macrophages, dendritic cells and other innate immune cells, which operate as the first-line defence combined with anatomical barriers. The TLRs develop homodimers and recruit adaptor molecule MyD88, followed by the recruitment of IRAK to the receptor complex by MyD88's death domain.[151] Auto-phosphorylation of IRAK dissociates the complex and paves the way for TRAF6 recruitment. On top of that, the transforming-growth-factor-β-activated kinase 1 (TAK1) linked with adaptor TAB molecules stimulation inactivates IKK and phosphorylate IκB and initiates NF-κB nuclear translocation.[152] This canonical pathway leads to the augmented production of cytokines such as IL-6, IL-8, and TNF-α, directly related to AITD development. As previously mentioned, viral infections trigger an autoimmune response linked to MHC antigen expression in the non-immune cell. According to Hanafusa, Chiovato et al,[153] the IFN-γ produced in the target organ promotes human leukocyte antigen (HLA) class II expression in the epithelial cells for the first time. Subsequently, this allows the autoantigens to be presented and auto-reactive T cells to be activated. They revealed that such infection would aggravate first-time-MHC class II molecule expression on the thyroid follicular cells, and these cells could behave as APC to play a role in AITD induction. The increased T cells and cytokines would then perpetuate such thyroid disorders.

Upon recognising the presented peptide by the T cell receptor on the thyroid cell (particularly $CD40^+$), send the co-stimulatory signals required for T cell activation [84]. $CD40^+$ is a TNF receptor (TNF-R), a major immune-modulating susceptibility gene for GD. It is known to be expressed on APCs and thyroid cells and is essential for adaptive immunity.[154] Furthermore, it interacts with $CD154^+$ expressed on the T cells to give a co-stimulatory signal that induces autoreactive B cell proliferation, immunoglobulin class switching, and germinal centre development. Of note, the activation of $CD40^+$ in B cells suppresses Fas from inducing apoptosis. Zazzeroni, Papa et al[155] suggested that $CD40^+$-mediated cytoprotection implies the activation of protective gene gadd45β via NF-κB/Rel transcription factors. Additionally, $CD40^+$ in mature B lymphocytes stimulates pro-survival signalling by antagonising IgM-induced apoptosis in the immature B cells. As pro-inflammatory situations overtly drive B cell proliferation, pro-apoptotic cytokines activate the constitutive NF-κB signalling supporting thyrocytes proliferation and survival.

The overexpressed IL-6 during a cytokine storm induces a similar anti-apoptotic activity as $CD40^+$, signalling in COVID-19. Th17 cells, a $CD4^+$ T cell subset distinct from Th1 and Th2 cells, primarily generate IL-17, a potent inflammatory cytokine.[156] The STAT3 mediates IL-6 signals to the Th17 cells, allowing them to differentiate and function as effectors. Subsequently, the Th0 lymphocyte differentiates into Th17, intensifying IL-17 synthesis in the cellular environment, an essential factor of autoimmune diseases.[81] The synergistic interplay of IL-6 and IL-17 has been linked to viral persistence and worsening clinical outcomes during viral infection. Hou, Kang, Kim[69] proposed that the additive effect of these interleukins induces the anti-apoptotic molecule Bcl-2, which prevents SARS-CoV-2-infected cells from being destroyed by virus-specific $CD8^+$ T cells, allowing the virus to survive. Besides, it is indicated that IL-17 protects thyrocytes apoptosis by interfering with the Fas/FasL pathway, resulting in GD. Furthermore, the differentiation of Th17 into cells that perform various functions after prolonged exposure to various cytokines may indicate their substantial plasticity. For instance, after being exposed to IL-23 constantly, they develop into specialised pathogenic cells known as non-classic Th1, capable of producing IFN-γ.[157] This, without a doubt, significantly influences the pathophysiology of molecular damage during AITD (Figure 4).

Lui, Lee et al[158] suggested that three COVID-19 patients admitted to a non-intensive care unit presented detectable levels of TSH receptor autoantibodies (TRAb), at the same time, reduced serum TSH levels with normal fT3 and fT4, implying GD. The autoantibodies are produced due to loss of tolerance to TSHR, thus mimicking the action of TSH and causing hyperthyroidism [107]. This can be explained by the overexpression of the $CD40^+$ signalling, which is demonstrated to increase TSHR antibodies. It is pivotal in adaptive immunity, especially in differentiating B cells into antibody-producing plasma cells.[159] These autoantibodies, in turn, promote the proliferation and survival of thyroid

follicular cells via the phosphatidylinositol 3,4,5 triphosphate kinase/protein kinase B (PI3K/Akt) pathway.[160] It is worth mentioning that TSHR is a G-protein coupled receptor (GPCR) which stimulates the cAMP synthesis and PI3K/Akt signalling cascade after autoantibody binding. Although TSH and stimulatory autoantibodies trigger the same TSHR signalling pathway, the TRAb remains activated due to distinct pharmacodynamics and higher stability.[161]

Consequently, protein kinase A and CREB are activated, leading to inflammatory mediator synthesis and thyroid cell growth. Simultaneously, PIP3 is induced when G protein downstream signalling triggers the canonical pathway that phosphorylates Akt by 3-phosphoinositide-dependent protein kinase 1 (PDK1) to increase cell survival.[162] Taken together, the TRAb-TSHR signalling pathway, which activates G proteins and various cascades, is critical for thyrocyte proliferation and progression of GD.

Thyrotoxicosis

In a recent report, Muller, Cannavaro et al[163] claimed that 13 out of 85 (13.5%) patients exhibit varying degrees of thyrotoxicosis symptoms in COVID-19. It is characterised by decreased TSH and elevated T3 and T4 serum levels linked to excessive IL-6 production during COVID-19. The connection between thyrotoxicosis and the raised IL-6 levels in the individuals implies that the inflamed thyroid gland is a consequence of a COVID-19-associated cytokine storm, resembling thyroid diseases that arise during immunotherapy treatment.[164] The increased concentration of IL-6 disrupts deiodinases and thyroid hormone transport proteins and impairs pituitary cell TSH secretion, leading to abnormal thyroid functional parameters.[48] The THYRCOV study further supports this notion by concluding that patients with thyrotoxicosis exhibit abnormally higher levels of IL-6.[20]

Subacute thyroiditis (SAT) is a self-limiting thyroid disorder that results from a viral or post-viral inflammatory process.[15] It is characterised by neck discomfort, which is the hallmark of the clinical syndrome, plus a triphasic phase of thyrotoxicosis, hypothyroidism, and restoration to normal thyroid function.[165,166] Few studies have reported the incidence of SAT during or after the SARS-CoV-2 infection, thus raising the concern that physicians should consider COVID-19 an underlying cause in patients with SAT.[22,167] As mentioned, the thyroid gland and the whole HPT axis might be emerging and critical targets of SARS-CoV-2 damage. The prevalence of ACE2 and TMPRSS2 receptors in the thyroid explains the pathology of COVID-19-induced SAT. According to Caron,[48] thyrotoxicosis may be caused by thyrocyte lysis, which produces thyroid hormones, combined with a decline in deiodinase activity in COVID-19. The inflammatory deterioration of the thyroid gland renders colloid leakage from the injured follicles into the interstitial tissue and then into the circulatory system in the early stage. This follicular cell destruction is thought to release lysozymes, which decompose the colloid and release a range of iodinated compounds such as iodoproteins, proteases, and amino acids.[168] As a result, this leads to a rise in T3 and T4 levels, which simulates hyperthyroidism in this phase.

Moreover, the patients with SAT present decreased levels of thyroxine-binding globulin (TBG), a critical thyroid hormone transport protein that binds and transports thyroid hormones to the respective tissues. It is well-known for keeping serum thyroid hormone at a constant level. When TBG levels drop, fT4 levels rise, and TSH is adversely inhibited. Therefore, TBG is responsible for preventing thyroid hormone fluctuations.[169] IL-6 has a significant inverse relationship with TBG levels, suggesting that the rise in serum IL-6 decreases serum TBG levels. However, it is yet unclear how IL-6 affects TBG gene expression.

Therapeutic Opportunities and Challenges

With the rise of IL-6, the interaction of gp130 with cytokine-specific α-chain activates the immune cells and JAK/STAT and MAPK signalling cassettes, which subsequently actuates pro-inflammatory and ROS responses.[125] ROS formation plays a significant role in deiodinase malfunction; hence, inhibiting oxidative stress could be a probable strategy to restore thyroid function. An endogenous GSH deficit has been hypothesised to be a critical contributor to this redox homeostasis imbalance, leading to severe manifestations in COVID-19 patients. Antioxidant and anti-inflammatory activities of N-acetyl-cysteine (NAC) have been utilised in clinical trials to treat individuals with COVID-19-associated thyroid dysregulations in conjunction with standard therapies.[170] Wajner, Goemann, Bueno, Larsen, Maia[88] investigation on the impact of IL-6 on endogenous cofactor-mediated deiodinase function showed that T3 production by D1 and D2 is reduced by IL-6, despite the rise in deiodinase expression. In their study, the administration of NAC

prevented IL-6's inhibitory activity by restoring intracellular GSH concentration, highlighting that pro-oxidants are involved in IL-6-mediated effects. To regenerate active enzymes, all three deiodinases utilise a reducing agent, a thiol or thiol-dependent molecule, to release iodine from the selenocysteine residue.[171] The NAC reinstated deiodinase function by re-establishing intracellular cysteine levels and the enzyme thiol cofactor, restoring redox balance. Since D3 has been linked to ESS in clinical studies, the role of NAC in correcting ROS-induced D3 overexpression cannot be neglected.[172]

Total antioxidant capacity (TAC) is the ability to neutralise ROS, depending upon the extent of exogenous and endogenous antioxidants in the body fluids.[173] A late study showed that NAC-treated patients exhibited lower carbonyl concentrations with improved TAC parameters.[174] Moreover, NAC significantly suppresses NF-κB-driven oxidative stress and downregulates pro-inflammatory gene expressions.[175] During infections, cytokine production can be attenuated by inhibiting ROS-dependent activation of NF-κB by TLR3/hemagglutinin. The NAC can protect proteins from oxidative damage while restoring the antioxidant potential. Bhattacharya, Mondal et al[176] illustrated that moderate-to-severe COVID patients who administered NAC 1g IV with standard treatment exhibited better chances of survival, improved discharge rate and reduced need to transfer patients to the intensive critical unit.

The contribution of TNF-α to hyperinflammation of COVID-19 has been subject to study. While anti-TNF agents have yet to receive approval for COVID-19 treatment, research suggests their potential efficacy in severe cases.[177–179] Notably, the Inflammatory Bowel Disease Registry (SECURE-IBD) has reported the advantageous effects of TNF-α blockers in treating COVID-19-affected patients with inflammatory bowel disease (IBD). Analysis of 2307 IBD patients undergoing anti-TNF-α monotherapy before and during COVID-19, alongside 2088 patients receiving sulfasalazine/mesalazine treatment, revealed that 8% in the anti-TNF-α group were hospitalised and <1% died, as opposed to 20% hospitalised and 3% deceased in the other group.[178,180] Furthermore, the Global Rheumatology Alliance (GRA) registry affirmed the favourable impact of TNF-α blockers on COVID-19 treatment in rheumatoid arthritis (RA) patients. Among 1388 RA patients administered TNF-α inhibitors, 103 (7.4%) necessitated ventilation, with 36 (2.6%) fatalities. Conversely, other regimens such as rituximab and JAK inhibitors posed heightened risks of severe illness compared to TNF-α inhibitors. No significant associations were identified with abatacept or interleukin 6 inhibitors.[181] Data suggests that TNF-α blockers are associated with reduced rates of COVID-19-related hospitalisation.[182,183] Nevertheless, further investigations are warranted to elucidate the optimal timing of intervention and the potential implications on vaccine efficacy in severe COVID-19 cases.

Inactivation of NF-κB is a druggable targeted strategy to combat COVID-19-associated thyroid diseases. A synthetic glucocorticoid, dexamethasone, is an effective treatment in blocking the release of pro-inflammatory cytokines.[184] According to Bessler, Mendel et al,[185] the expression of IFN-γ, IL-1β, TGF-β and TNF-α are suppressed by dexamethasone, thus reducing cytokine-related thyroid complications. Additionally, as an immune modulator, it lowers the IL-6 synthesis and reduces the cytokine feedback of NF-κB.[66] The dexamethasone upregulates inhibitory IκBα which restricts NF-κB nuclear translocation.[186] On top of that, dexamethasone prevents NF-κB from activating by stoichiometrically binding to the glucocorticoid receptor (GR) in the nucleus.[187] The GR suppresses the transactivation of targeted genes by binding to transcription factors, NF-κB p65, or interacting with alternative protein IKK. Since the phosphorylation of IKKβ is essential for NF-κB activation, preventing such a process can provide therapeutic benefits against systemic inflammation.[188]

The dexamethasone at 6 mg/day for ten days in the Randomised Evaluation of COVID-19 Therapy study (RECOVERY) showed decreased mortality in one-third of ventilated patients. However, it failed to show significant benefits in mild-to-moderate COVID-19 and in patients who do not require oxygen support.[189] This strengthens the hypothesis that dexamethasone's positive effects on severe COVID-19 patients may be partially attributed to its ability to prevent NF-κB activation. Moreover, dexamethasone directly influences the HPT axis by affecting TRH in the hypothalamus.[190] A study by Alkemade, Unmehopa, Wiersinga, Swaab, Fliers[191] discussed the usage of glucocorticoids to reduce TRH mRNA levels in the hypothalamus, which is the leading cause of decreased pituitary TSH secretion. Formerly, human serum TSH levels were documented to be influenced by glucocorticoids. Wilber, Utiger[192] demonstrated that glucocorticoids in higher dosages lower TSH levels in both hypothyroid and healthy individuals. On the contrary,[193] suggested that glucocorticoid reduces TSH release from thyrotropes in a protein kinase C-dependent way via the protein annexin 1 and does not cause central hypothyroidism that requires thyroid hormone replacement.

Furthermore, the TRH suppression in the hypothalamus shows how glucocorticoids affect TSH secretion. The presence of GR in the TRH neurons of the hypothalamic paraventricular nucleus (PVN) and the glucocorticoid response element in the TRH gene promoter.[190] The ERK1/2 signalling is crucial for stimulating TRH mRNA levels in the hypothalamus.[194] According to Zhao, Su et al,[195] MAPK phosphatase-1 (MKP-1) negatively regulates MAPK through phosphate removal from tyrosine and threonine in ERK. Some researchers revealed that dexamethasone could stimulate its anti-inflammatory effect by increasing MKP-1 expression and reducing proteasomal degradation of MKP-1.[196] Subsequently, the CREB phosphorylation, an essential pathway for TRH gene transcription, is suppressed by administering dexamethasone.[197] Therefore, it is indicated that dexamethasone inhibits the TRH-TSH-T4 axis and simultaneously exhibits an anti-inflammatory effect in patients with COVID-19-related thyroid dysregulations.

As IL-6 is the significant JAK/STAT activator, targeting it seems to be a plausible strategy for treating COVID-19-associated thyroid disorders.[198] The STAT3-mediated IL-6 and IL-23 signalling are critical for maintaining Th17 cell differentiation and activating STAT3 via JAK2; hence, it is postulated that employing JAK2 inhibitors can suppress the pro-inflammatory function of Th17 cells.[75] Baricitinib, an ATP competitive kinase inhibitor, targets JAK1 and JAK2 by inhibiting the kinase activity and precluding STAT3 activation.[199] Moreover, inflammatory signalling of IL-2, IL-12, IL-23, and IFN-γ are also reported to be obturated by baricitinib.[200] Apart from reducing the inflammatory response, baricitinib also disrupts viral host cell entry and assembly by acting on ACE2 receptor regulators, including AP2-associated protein kinase-1 (AAK1) and cyclin G-associated kinase (GAK), which govern clathrin-dependent endocytosis.[201]

However, the idea of treating COVID-19-associated cytokine storm with baricitinib seems to be controversial and must be addressed accordingly. It is established that when a pathogen like SARS-CoV-2 invades, an inflammatory response will be incepted by the host cells as a defensive action. Given that the JAK/STAT signalling is responsible for incepting antiviral response (IFNs), employing JAK/STAT inhibitors seems illogical. According to recent reports, over 80% of COVID-19 asymptomatic cases do not require hospital admission and successfully clear the viral titter due to IFNs-driven endogenous antiviral potential; hence, it is not advised to administer baricitinib[202] in this population. In patients with cytokine release syndrome and ascending viral load, JAK/STAT pathway inhibition could potentially address systemic inflammation and disrupt viral entry and assembly intracellularly. It is worth mentioning that baricitinib exhibits low plasma protein binding and CYP450 interaction, making it a suitable candidate for combination therapy for critical care patients.[203] Remdesivir was previously repurposed during the outbreak to manage the Ebola virus, and yet again, it has been recently approved by the FDA for the management of COVID-19.[204,205] It is a monophosphoramidate prodrug that targets viral RNA and functions as a broad-spectrum antiviral. Remarkably, owing to a CoV-specific proofreading exoribonuclease (ExON) expressed in nsp14; various antivirals appear ineffective against SARS-CoV-2.[206] The remdesivir's unique ability to bypass viral proofreading, integration into viral RNA, and the subsequent suppression of RNA-dependent RNA polymerases (RdRps) allows it to limit viral replication.[207] Moreover, its maximum serum concentration (Cmax) can suppress 90% of SARS-CoV-2 replication, a significant parameter for effectively managing COVID-19.[208]

As with sepsis, the cytokine storm associated with COVID-19 is triggered by an infection. The efficacy of therapies targeting a single cytokine is limiting, as multiple cytokine signalling pathways are assumed to be involved in this process. Thus, combination therapies may be a better strategy for the following reasons. 1) Target different modes of action and manage multiple symptoms, for instance, an antiviral combination with an immune modulator to suppress the hyper-immune activity and simultaneously reduce viral load. 2) synergistic action between medications that target the same or different stages of the viral lifecycle or signalling pathways, allowing weak inhibitors to be more effective. 3) Enhance antiviral activity whilst lowering the risk of drug resistance. On the contrary, multiple combination therapies demerit safety concerns, including drug interactions, adverse drug reactions and multiple organ damage. For instance, combining baricitinib with remdesivir significantly suppresses virus load, infectivity, and hyper-inflammatory response. Kalil, Patterson et al[209] administered a loading dose of 200 mg remdesivir IV on day 1 and 100 mg as a maintenance dose from day 2–10 or until they were discharged from the hospital. At the same time, 4 mg of oral baricitinib was administered to the COVID-19 patients daily for 14 days. The group of patients that received combination therapy exhibited a shorter mean time of recovery. Despite the concerns of secondary infections and thrombosis, supplementation of baricitinib did not increase the incidence of drug-drug interaction, adverse drug reactions and thromboembolic events.[210]

The COVID-19 pandemic has led to an urgent need to identify prognostic biomarkers and effective therapeutic approaches for severe-critical manifestations. Immune checkpoint molecules such as PD-1 and PD-L1 are crucial in regulating the immune response.[211,212] According to Sabbatino, Conti et al[213] serum PD-L1 levels have been found to have prognostic significance in COVID-19 patients, and its dysregulation is associated with COVID-19 pathogenesis. These findings suggest a potential role of the PD-1/PD-L1 axis in COVID-19 and support the need for clinical studies using PD-1/PD-L1 inhibitors.

Notably, the study from two Italian medical centres compared the clinical outcomes of COVID-19 in patients undergoing biological therapy targeting type 2 inflammation with those not receiving such therapies. The study concluded that monoclonal antibodies including omalizumab, mepolizumab, benralizumab, and dupilumab, targeting type 2 inflammation appeared safe, showing no worsening of symptoms, prolonged infection, or increased hospitalisations. However, an increase in common cold-like symptoms and dyspnoea during COVID-19 was reported. The findings suggest that anti-Th2 biological therapy should not be discontinued during SARS-CoV-2 infection. However, further controlled studies and analyses are needed to draw comprehensive conclusions about the safety and potential benefits of anti-type 2 mAbs in specific clinical contexts.[214]

Although modest dose and short-term (< 3 weeks) use of dexamethasone are considered safe, the risk of side effects increases with the dose and length of therapy noticeable.[215] It exacerbates lymphopenia by further declining B- and T-cells in COVID-19 patients.[216] Moreover, it is suggested that early corticosteroid (CS) usage may lead to greater viral loads and bolster virus replication.[217] It is judicious to recall dexamethasone CYP3A4 inducing potential, ensuing interaction with the CYP3A4 substrates and decreasing plasma levels and efficacy of remdesivir in combination therapies.[215] The secondary infections are potential sequelae of dexamethasone treatment as it exacerbates the risk of bacterial, invasive fungal and pre-existing infections like tuberculosis.[218,219] Additionally, dexamethasone-induced strongyloidiasis and hyper-infection in low- and middle-income areas cannot be neglected.[220]

Recent studies have reported remdesivir adverse drug reactions ranging from minor flu-like symptoms to life-threatening end-stage hepatic failure in COVID-19 patients.[221] According to Gupte, Hegde et al[222] majority of the adverse events were reported nausea and elevated ALTs. Hepatic dysfunction and elevated transaminases were attributed to remdesivir hepatic biotransformation and hepatocyte permeability. Hepatocytes are inflicted by SARS-CoV-2 due to the prevalence of ACE2, which is later translated into elevated levels of ALT and bilirubin.[223] Hence, it is difficult to diagnose whether transaminase abnormalities are caused by remdesivir or cytopathic injuries.[224] Moreover, remdesivir's high affinity for human mRNA polymerase is responsible for mitochondrial malfunction, exhibited in sinus bradycardia and QT prolongation in treated COVID-19 patients.[225]

A potent JAK inhibitor, baricitinib, has the potential to reactivate latent infections of herpes simplex, tuberculosis, hepatitis B, EBV, and herpes-zoster virus in COVID-19 patients.[226,227] Deep vein thromboembolic events are frequently reported in rheumatoid arthritis patients as doses similarly administered for COVID-19 management.[228] This is concerning as pulmonary embolism, and venous and arterial thrombotic events are commonly reported in COVID-19 patients.[229] Kalil, Patterson, Mehta, Tomashek, Wolfe, Ghazaryan, Marconi, Ruiz-Palacios, Hsieh, Kline[209] and the team terminated earlier due to grade three to four adverse drug reactions reported in 207 out of 507 (40.7%) participants. In this trial, a combination of baricitinib and remdesivir was administered, resulting in potentially life-threatening adverse effects, including hyperglycaemia, anaemia, lymphocytopenia, and acute kidney injury.

Concluding Remarks

As a result of the global spread of COVID-19, it is reasonable to assume that endocrine abnormalities will prevail over time. ACE2 and TMPRSS2 allow the SARS-CoV-2 to bind, gain entry, and impose cytopathic injuries on the host cells. Viral entry activates PRRs, NF-κB, JAK/STAT and MAPK pathways and significantly increases the production of cytokines, chemokines and interferons. IL-1β, IL-6, IFN-γ, and TNF-α are identified as key orchestrators of cytokine release syndrome. Where the cytolytic effect directly damages the host cells, indirect detrimental effects are inflected by the hosts' hyper-immune response. The latter is characterised by SARS-CoV-2-induced cytokine storm, which leads to systemic inflammation and thyroid cell damage. The potential hormonal changes are due to the cytokine storm and due to which damage assessment during infection and after recovery from COVID-19 is highly warranted. The findings suggested that most patients are euthyroid and SAT and appear atypically without neck discomfort, but the development

of AITD is significantly higher in COVID-19. New therapeutic regimens have been developed to cater specifically to COVID-19-associated thyroid dysregulations. Still, data from larger, randomised, and controlled trials are warranted to optimise the balance between the advantages and possible risks of these therapies. Additionally, it is crucial to determine the patient subgroups where this ratio is most likely to promote a safe and effective treatment outcome.

It is rational to shift the focus from monotherapy to drug combinations, as there is no gold standard treatment, and several repurposed drugs have failed to demonstrate meaningful value in recent clinical trials. Further randomised controlled studies might improve overall therapy effectiveness by emphasising the safety and efficacy of the combined therapies against COVID-19-related thyroid diseases. Furthermore, interventions targeting various stages of disease processes, including viral replication, cytokine-induced damage and thromboembolic events, should be the vision and mission of future studies. Combination therapies delivered at the right time can effectively address various signalling pathways and attenuate disease progression. In contrast, some drug combination therapies have shown promising effects in small groups or secluded clinical settings. The disease's intricacy demands us to look into combining independent treatments to improve their potential in a much larger population.

Abbreviation

AAK, AP2-associated protein kinase; ADCC, antibody-dependent cytotoxicity; AITD, autoimmune thyroid disorder: Akt, protein kinase B; ALR, absent in melanoma-2-like receptor; ARDS, acute respiratory distress syndrome; ACE, angiotensin-converting enzyme-2; ALT, alanine transaminase; APC, antigen-presenting cells; AST, aspartate amino-transferase; AT, angiotensin; CARD, caspase recruitment domain; CCL, C-C motif chemokine ligand; CLR, C-type lectin receptor; Cmax, maximum serum concentration; CoV, coronavirus; COVID-19, coronavirus Disease 2019; CREB, cAMP response element-binding protein; CRP, C-reactive protein; CRS, cytokine release syndrome; CTD, C-terminal Domain; DAMP, damage-associated molecular pattern; eNOS, endothelial nitric oxide synthase; ERGIC, endoplasmic reticulum-golgi intermediate compartment; ERK, extracellular signal-regulated kinase; ESS, euthyroid sick syndrome; GAG, glycosaminoglycan; GAK, G-associated kinase; GD, graves' disease; GPCR, G-protein coupled receptor; GR, glucocorticoid receptor; GSH, glutathione; HepG2, human hepatoma cell line; HLA, human leukocyte antigen; HPT, hypothalamic-pituitary-thyroid; HT, hashimoto thyroiditis; ICAM, intracellular adhesion molecule, IFN, interferon; Ig, immunoglobulin; IκK, inhibitors of NF-κB Kinase; IL, interleukin; IL-6 Amp, interleukin-6 amplifier; iNOS, inducible nitric oxide synthase; ISG, interferon-stimulated gene; JAK, janus kinase; JNK, C-jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MERS-CoV, middle east respiratory syndrome coronavirus; MHC, major histocompatibility complex; MKP, MAPK phosphatase; MYD88, myeloid differentiation primary response 88; NAC, N-acetyl-cysteine; NADPH, nicotine adenine dinucleotide phosphate; NF-κB, Nuclear Factor Kappa-light-chain-enhancer of activated B cells; NIS, sodium iodide symporter; NK, natural killer cell; NLR, nucleotide oligomerization domain-like receptor; NLRP3, NLR pyrin domain containing 3; NSP, non-structural protein; NTD, N-terminal domain; PAMP, pathogen-associated molecular pattern; PDK, phosphoinositide-dependent protein kinase; PG, prostaglandin; PI3K, phosphatidylinositol 3,4,5 triphosphate kinase; PRR, pattern-recognition receptor; PVN, paraventricular nucleus; RAS, renin-angiotensin system; RdRp, RNA-dependent RNA polymerase; RNS, reactive nitrogen species; ROS, reactive oxygen species; RBD, receptor-binding domain; RER, rough endoplasmic reticulum; RLR, retinoic acid-inducible gene-1-like Receptor; RORγt, RAR-related orphan receptor-γ; rT3, reverse triiodothyronine; SARS, severe acute respiratory syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SAT, subacute thyroiditis; STAT, signal transducer and activator of transcription; TAC, total antioxidant capacity; TAK, transforming-growth-factor-β-activated kinase; TBG, thyroxine binding globulin; TCR, T-cell receptor; Tg, thyroglobulin; Th, T-helper; TLR, toll-like receptor; TMPRSS2, transmembrane protease serine protease 2; TNF, tumor necrosis factor; TPO, thyroid peroxidase; TRAb, TSH receptor autoantibodies; TRAF, TNF receptor-associated factor; TRE, thyroid hormone response element; Treg, regulatory T-cell; TSH, thyroid-stimulating hormone; TYK, tyrosine kinase; T3, triiodothyronine; T4, thyroxine; ULN, upper limit of normal; VCAM, vascular cell adhesion molecules; WHO, World Health Organization.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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