Review article

# The cytokine storms of COVID-19, H1N1 influenza, CRS and MAS compared. Can one sized treatment fit all?

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## ABSTRACT

An analysis of published data appertaining to the cytokine storms of COVID-19, H1N1 influenza, cytokine release syndrome (CRS), and macrophage activation syndrome (MAS) reveals many common immunological and biochemical abnormalities. These include evidence of a hyperactive coagulation system with elevated D-dimer and ferritin levels, disseminated intravascular coagulopathy (DIC) and microthrombi coupled with an activated and highly permeable vascular endothelium. Common immune abnormalities include progressive hyper-cytokinemia with elevated levels of TNF-α, interleukin (IL)-6, and IL-1β, proinflammatory chemokines, activated macrophages and increased levels of nuclear factor kappa beta (NFκB). Inflammasome activation and release of damage associated molecular patterns (DAMPs) is common to COVID-19, H1N1, and MAS but does not appear to be a feature of CRS. Elevated levels of IL-18 are detected in patients with COVID-19 and MAS but have not been reported in patients with H1N1 influenza and CRS. Elevated interferon-γ is common to H1N1, MAS, and CRS but levels of this molecule appear to be depressed in patients with COVID-19. CD4+ T, CD8+ and NK lymphocytes are involved in the pathophysiology of CRS, MAS, and possibly H1N1 but are reduced in number and dysfunctional in COVID-19. Additional elements underpinning the pathophysiology of cytokine storms include Inflammasome activity and DAMPs. Treatment with anakinra may theoretically offer an avenue to positively manipulate the range of biochemical and immune abnormalities reported in COVID-19 and thought to underpin the pathophysiology of cytokine storms beyond those manipulated via the use of, canakinumab, Jak inhibitors or tocilizumab. Thus, despite the relative success of tocilizumab in reducing mortality in COVID-19 patients already on dexamethasone and promising results with Baricitinib, the combination of anakinra in combination with dexamethasone offers the theoretical prospect of further improvements in patient survival. However, there is currently an absence of trial of evidence in favour or contravening this proposition. Accordingly, a large well powered blinded prospective randomised controlled trial (RCT) to test this hypothesis is recommended.

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## 1. Introduction

COVID-19 is a biphasic illness where viral driven fever predominates for between 7 and 10 days on average followed by a host mediated immune-inflammatory response of variable intensity [1,2]. In aggregate, the patterns and levels of inflammation and immune dysregulation observed in the periphery and lungs of COVID-19 patients are characteristic of "cytokine storm", and this phenomenon is deemed to be the main cause of mortality in patients suffering from this illness [3–8].

Cytokine storms are also considered to be the cause of high levels of mortality and morbidity in cytokine release syndrome (CRS) [9], macrophage activation syndrome (MAS) [10] and in H1N1 influenza virus-mediated pneumonia [11]. This raises the question of whether the processes which generate cytokine storms are the same in all these conditions or whether they differ. If they are similar, or even identical, then that would suggest that agents such as tocilizumab and anakinra, which have shown success in the treatment of CRS [12] and MAS [13], respectively, could be repurposed for the treatment of COVID-19. However, if these processes are significantly different, such treatments may be ineffective or even harmful as far as COVID-19 patients are concerned. Hence, this paper aims to compare the mechanisms involved in the generation of cytokine storms in each of the conditions above, with a view to proposing answers to these questions.

## 2. The cytokine storm of COVID-19

### 2.1. Immune abnormalities reported in patients with COVID-19

There is evidence of severe immune dysregulation, inflammation and hypercytokinemia in the periphery and lungs of patients with severe COVID-19. This is characterised by increased levels of tumour necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-18, IL-10, monocyte chemoattractant protein-1 (MCP-1) and interferon (IFN)-γ-induced protein (IP-10 or CXCL10) [3,6,14–17]. Importantly, this pattern of immune dysregulation is progressive and levels of proinflammatory cytokines and chemokines increase dramatically with illness severity and may be some ten-fold higher in ventilated individuals compared to hospitalised patients with milder disease [18]. In contrast, the weight of evidence suggests that interferon (IFN)-γ levels are reduced in patients with COVID-19 who have not progressed to acute respiratory distress syndrome (ARDS) although in the latter scenario secondary elevation of this molecule may be a significant source of irreversible tissue destruction [19–21].

Other reported abnormalities commonly associated with excessive systemic inflammation seen in COVID-19 patients include lymphopenia and lymphocyte exhaustion, as evidenced by drastically depleted CD4^{+} T cells, CD8^{+} T cells, B cells, and natural killer cell (NK) numbers [6,15,22–24]. This is combined with elevated expression of lymphocyte exhaustion markers including programmed cell death protein 1 (PD-1), natural killer cell receptor NKG2A, and T cell immunoglobulin mucin 3 (TIM-3) [22,25–27]. Finally an accepted marker of the intensity of systemic inflammation namely the plasma neutrophil: lymphocyte ratio
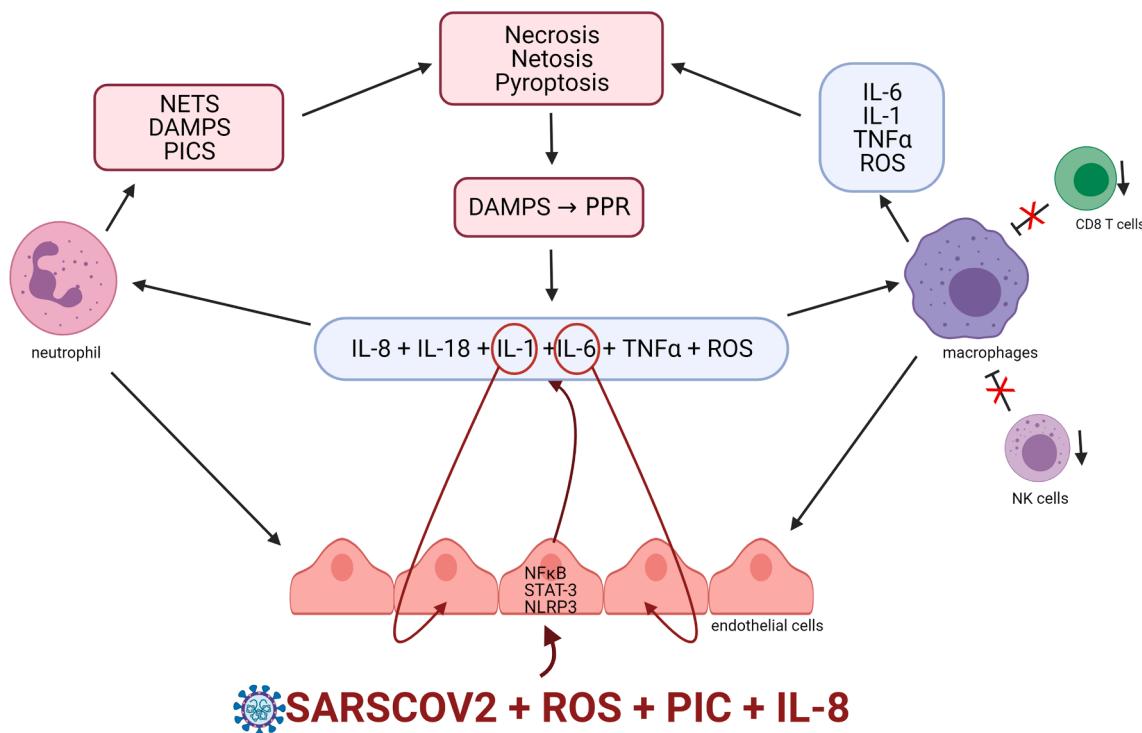


**Fig. 1.** The potential origin of the COVID-19 cytokine storm A proposed early event in the development of the COVID-19 cytokine storm is the activation of endothelial cells by SARSCOV2 and or the presence of high levels of proinflammatory cytokines chemokines and ROS species. Such activation is associated with increased STAT-3, NFκB and activation of the NLRP3 inflammazome. The net result is the release of proinflammatory cytokines IL-1, TNF alpha, IL-6, IL-8 and reactive oxygen species (ROS) and the subsequent recruitment of macrophages and neutrophils which become an additional source of IL-1, IL-6, TNF alpha, ROS and several damage associated molecular patterns (DAMPS). IL-1 and IL-6 may engage in autoinflammatory signalling via targeting their receptors on endothelial cells leading to a self-amplifying cascade of inflammation and oxidative stress. Increasing levels of PICs and ROS result in loss of NK and CD8 T cell numbers and function increasing macrophage survival further amplifying PIC and ROS production and compromising macrophage efferocytosis. The resulting increase in survival of NET producing neutrophils further adds to pathological levels of PICs and ROS ultimately resulting in the pyroptosis and necrosis of immune cells and widespread tissue damage The resulting release of DAMPs may trigger further activation of immune and endothelial cells which further sustains and amplifies the inflammatory cascade.

is predictive of both disease severity [28]and mortality [29]. A summary of the COVID-19 cytokine storm is presented on Fig. 1.

## 2.2. Biochemical abnormalities reported in patients with COVID-19

Another accepted index of severe inflammation seen in COVID-19 patients is hyperactivation of the coagulant cascade and a relatively exhausted anticoagulant and fibrinolytic system with increased levels of D-dimer; evidence of microthrombi in large and small blood vessels; and in many cases, disseminated intravascular coagulation (DIC) [30–34]. In addition, the excessive levels of inflammation seen in severe COVID-19 makes the presence of hyperferritinemia predictable [35,36].

## 2.3. Elements involved in the pathophysiology of the COVID-19 cytokine storm

The weight of evidence also suggests significant levels of inflammasome activity in the early and latter stages of the disease [37–40]. Authors have also reported extensive necrosis and pyroptosis of lymphocytes, leucocytes organ-specific cells, lymph nodes and the spleen, and vascular endothelial cells, using a range of histological techniques which is consistent with the inflammasome activation discussed above [41,42,15]. Increased IL-1 is also prognostic marker of disease severity and death and a major source of tissue damage in patients severely affected with this disease [43–46]. Unsurprisingly, several research teams have also reported escalating levels of IL-18 [47–49], which are approximately 4 times higher in patients with severe disease compared to those mildly affected [48]. In the light of these findings, it is interesting to note that SARSCOV2 infection of epithelial and endothelial cells and resultant endoplasmic reticulum (ER) stress is an acknowledged cause of NLP3 inflammasome activation and pyroptosis suggesting that direct viral infection of these cells is a source of inflammasome activation at least in the early stages of the disease [50–56].

Furthermore, while inflammasome activation would appear to be a significant source of inflammatory damage, the weight of evidence suggests that infiltrating TNF-α, IL-1 and IL-6-secreting monocytes and macrophages are also major drivers of tissue damage in the periphery and the lung [42,57,58]as reviewed by [41]. Additional evidence of macrophage involvement in the pathophysiology has been supplied by the results of a recent study revealing the presence of high serum levels of soluble haemoglobin Scavenger Receptor sCD163 and sCD164 in hospitalised patients [59]. In addition, several authors have reported increased levels neutrophils secreting histones, HMBG1, mitochondrial DNA (mtDNA),[50,56]review [6], which act as damage associated molecular patterns (DAMPS) which are a known source of extensive inflammation and tissue damage [60,61]. There is also accumulating evidence of increased activity of nuclear factor kappa beta (NFκB) in patients with severe COVID-19 [62–64].

Severe COVID-19 is also associated with the presence of systemic endotheliopathy characterised by a severely damaged permeable vascular endothelial barrier and activated endothelial cells in patients with severe disease [65–67]. This may be relevant from the perspective of COVID-19 pathophysiology as there is extensive evidence establishing a causative association between endothelial cell activation, inflammation, and damage with the development of self-amplifying inflammation, and coagulation [68,69]. Moreover, there is accumulating evidence establishing endothelial activation and damage with the genesis and exacerbation of the cytokine storms associated with severe cytokine release syndrome [70–72]and severe H1N1 influenza [73–76]. In addition, endothelial activation by IL-6 [77]could explain, at least in part, the a correlation between levels of this cytokine present in the circulation with illness severity and mortality [18,78,4,79].

Finally, the importance of hypercoagulation in the pathogenesis of severe COVID-19 should not be underestimated as findings from the original outbreak in Wuhan suggest that over 70% of people who died following SARSCOV2 infection satisfied the criteria of DIC compared to

only 1% of individuals that survived [80]. This is perhaps unsurprising given the context of data suggesting that the pathology associated with a range of self- amplifying inflammatory syndromes are underpinned by a complex interplay between a hyperactivated immune response and a hyperactivated coagulation cascade often described as immunothrombosis.

## 3. The cytokine storm of H1N1 ("Pandemic strain") influenza

### 3.1. Immune abnormalities associated with severe H1N1 influenza

Patients suffering from H1N1-induced pneumonia and consequent ARDS have excessively elevated levels of serum interferons, cytokines, and chemokines characteristic of a cytokine storm [81,82,74,11]. The extent and pattern of immune dysregulation seen in these individuals varies with the illness severity; however, elevated IFN-γ, IL-6, IL-1α, IL-1β, TNF-α, IL-15, IL-12p70, IL-17, IL-10, MCP-1, MIP-1β, IL-8, MIG, IP-10, MIP-1α, GM-CSF, and RANTES are the most commonly reported findings [83–87,75].

In addition, several authors have reported a positive association between levels of IL-6 and disease severity [83,88–91]. The same appears to be true of a high neutrophil to lymphocyte ratio [92]. Unsurprisingly, the cytokine storm of H1N1 is associated with the development of severe multiorgan tissue damage and dysfunction [81,82,74,11].

### 3.2. Biochemical abnormalities in patients with severe H1N1 influenza

Patients with severe H1N1 influenza-induced pneumonia also present with hypercoagulation, as evidenced by vascular leak activated platelets and endothelial cells, coupled with the presence of microemboli and, in many instances, DIC. Expectedly, there is extensive evidence of elevated D-dimer levels in these patients, often accompanied by significant upregulated production of lactate dehydrogenase (LDH) [93–95]. Importantly, the extent of elevation is predictive of disease severity and a poor outcome [93–95]. The overactivation of the coagulation cascade seen in such patients is associated with increased risk of deep venous thrombosis and acute cardiac injury [96]. Common manifestations include acute myocardial infarction [97,98], acute coronary syndrome [99,100]and several other cardiovascular diseases [99]. In addition, accumulating evidence suggests that an overactivated coagulation cascade and compromised fibrinolysis make an independent contribution to the development of the hyperinflammatory state and the cytokine storm seen in severely or critically ill patients [101–103] (reviewed in [104].

### 3.3. Elements involved in the pathophysiology of the H1N1 influenza cytokine storm

Abundant evidence suggests that an indispensable and early event in the generation of a hypercoagulable state in patients with severe H1N1 pneumonia is the activation of endothelial cells [105,102,106,103]. Some strains of influenza infect and activate endothelial cells leading to upregulation of platelet tissue factor (TF) and downregulation of thrombomodulin via Toll-Like receptor (TLR)-3 or TLR-4 activation [107–109]. However, unlike the case for SARSCOV2 where direct infection of endothelial cells has been reported [110], there is no evidence that H1N1 directly infects endothelial cells or targets membrane TLR-4 receptors [111,112]and the endothelial cell activation appears to result from the release of TNF-α, HMBG1, oxidized phospholipids and S100 proteins by already activated and damaged epithelial cells [107,113,112,76,109].

The source of HMBG1 and S100 proteins is not fully understood. However, there is evidence to suggest that H1N1 activates the NLRP3 inflammasome [114], which results in the secretion of HMBG1 from a wide range of immune cells [115], and damaged or stressed cells are a

well-documented source of S100 proteins as well a range of other DAMPs as reviewed by [116].

Furthermore, accumulating evidence suggests that endothelial cells orchestrate the H1N1 cytokine storm via the upregulation of sphingosine-1-phosphate (S1P) receptor 1 expression [73–76]. This conclusion stems from evidence produced by several research teams investigating the use of the S1P receptor agonists fingolimod or CYM5442 in animal models of the H1N1 cytokine storm which were invariably associated with the termination of the hyperinflammatory state accompanied by significant and large reductions in mortality [75,76,117,118]. Importantly, there is evidence to suggest that the absence of endothelial S1P receptor may aggravate immune-mediated pulmonary injury following H1N1 infection [119] (Reviewed [120].

Unlike the situation with COVID-19 there is considerable evidence regarding the influence of individual cytokines in the pathogenesis and pathophysiology of the H1N1 cytokine storm and hence we will consider this area in the hope that these findings might be extrapolated to inform the potential role of such cytokines in the pathogenesis and pathophysiology of COVID-19.

### 3.4. The potential role of individual cytokines in the genesis of the H1N1 cytokine storm

TNF-α is considered to be the prototypical proinflammatory cytokine at the "centre of the influenza cytokine storm", escalating the severity of disease in humans with highly pathogenic and pathological influenza infections [121–123]. This is foreseeable given the acknowledged role of this cytokine as the orchestrator and master regulator of the innate immune response [124–127]. TNF-α exercises autocrine roles via increasing NFκB activity and paracrine effects on neighbouring cells and tissue, as well as inflammation at the level of organs [128,127]. TNF-α also plays a major role in activating endothelial cells [129–131]and is the cytokine responsible for upregulating the production of IL-1 and IL-6 following pathogen invasion [74,11].

TNF-α blockade results in significant reductions in pulmonary levels of proinflammatory cytokines and chemokines in animal models of severe influenza [132]. More recently, a significant reduction in mortality in mice infected with H1N1 following the administration of etanercept was reported [133]. However, an early TNF-α response following a viral infection is transitory and may quickly fall below levels of detection, hence any opportunity to inhibit TNF-α is likely to be short lived [134–136].

The role of IL-1 in the genesis and/or exacerbation of an H1N1 cytokine storm is uncertain with most evidence suggesting that the early upregulation of this cytokine has antiviral and overall cytoprotective effects despite its role in inducing pulmonary inflammation [137,138,11]. There may be several mechanisms underpinning the net beneficial effects of IL-1 upregulation, which might include upregulated IL-1R receptor activity that is responsible for the recruitment of CD8+ T cells [139]. It is also noteworthy that genetic deletion of IL-1R is associated with increased mortality in H1N1 infected rodents [74]. However, there is accumulating evidence that IL-1 may make a significant contribution to the development and persistence of "secondary" cytokine storms, which may arise as a result of the activity of lymphocytes and leukocytes and inflammasome activation [114,140]. The sources of elevated levels of IL-1 seen in these patients is debated but one possible mechanism is the activation of the NLRP3 inflammazome which has been observed in mouse models and may play a vital role in the initial innate and latter humoral responses following H1N1 infection [114,140].

#### 3.4.1. IL-6

Similar to IL-1, the role of IL-6 in the genesis and/or exacerbation of the cytokine storm of H1N1 influenza is a matter of debate and currently the weight of evidence suggests that the early upregulation of this cytokine exerts protective rather than cytotoxic effects [141,142]. The

protective effects appear to stem from the role of this cytokine in regulating the influx of neutrophils into the lung and the differentiation and antibody production of B cells [143,141](reviewed [144]. This is somewhat puzzling in the face of data establishing a positive correlation between levels of IL-6 and disease severity, as discussed above [83,88–91]. However, IL-6 is upregulated during the development of chronic inflammation as a result of upregulated IL-1 and TNF-α, which upregulate the transcription of this cytokine indirectly via the upregulation of NFκB or directly via binding to sites in the IL-6 gene promoter region (reviewed in: [145]. In addition, IL-6 is upregulated as part of the antiviral responses and the pleiotropic roles of this cytokine in this arena are detailed in an excellent review by [146]. The protective effects and inflammatory effects of IL-6 are mediated by classical IL-6 and IL-6 *trans*-signalling mechanisms, respectively, via mechanisms involving the phosphorylation of STAT-3 and Janus kinase (JAK) [147]described in Fig. 2. Hence, elevated IL-6 levels may be a marker rather than a cause of disease severity and or may be upregulated in response to influenza virus infection.

## 4. The cytokine storm of cytokine release syndrome (CRS)

### 4.1. Immunological abnormalities associated with CRS

CRS is a systemic hyperinflammatory syndrome experienced by some patients following chimeric antigen receptor (CAR) T-cell and bi-specific T-cell engagers (BiTEs) therapy for soluble tumours [148]. IL-6, IL-10, IFN-γ, MCP-1 and GM-CSF appear to be elevated in all CRS patients, irrespective of the severity of the condition [149–153]. Other cytokines, including TNF-α, IL-1, IL-2, IL-2–receptor-α and IL-8 have also been reported in patients with more severe symptoms [154,155]. Other universal features of CRS include extensive CD4+ T cell and macrophage activation [156,157].

### 4.2. Biochemical abnormalities seen in CRS patients

Patients with severe CRS present with hypotension, fever, haemodynamic instability, increased vascular permeability, low levels of fibrinogen, increased levels of D-dimers, and increased angiopoietin-2 and von Willebrand factor as well as chronic activation of the coagulation cascade [71,155]. Other commonly reported biochemical abnormalities include grossly elevated levels of ferritin and C-reactive protein (CRP) [158–160].

### 4.3. Factors involved in the pathogenesis of CRS

While CRS has traditionally been viewed as a T cell-mediated syndrome, more recent research has proposed that the levels of inflammation and tissue damage seen in the condition are largely mediated by TNF-α, IL-6, IL-1, and nitric oxide (NO) secreted by activated macrophages and monocytes [156,157]. These findings are supported by the work of other authors who reported that the levels of these molecules produced by macrophages and monocytes in patients with this condition are far higher than the levels produced by T cells [158,71,161] (reviewed [162]). In addition, the high levels of IL-8, IL-10, IL-12, TNF-α, IL-6 IFN-α, MCP-1 and MIP-1α seen in CRS patients is a characteristic profile of activated macrophages and monocytes [149–153].

Multiple lines of evidence suggest that endothelial activation and/or dysfunction plays a crucial role in the development, maintenance and exacerbation of the syndrome [70–72]. Other biomarkers of endothelial cell activation, such as angiopoietin-2 and von Willebrand factor, predict CRS severity, before CAR T-cell infusion and during CRS [71]. For example, as previously mentioned, grossly elevated levels of von Willebrand Factor and angiopoietin-2 have been reported in patients with severe CRS, which may explain the vascular instability, capillary leakage and hypercoagulability seen in the condition [71,72]. Moreover, patients with pre-existing endothelial inflammation and/or activation

## IL-6 classic signalling

## IL-6 trans-signalling

**Activation of JAK, STAT3 and ERK signalling pathways**
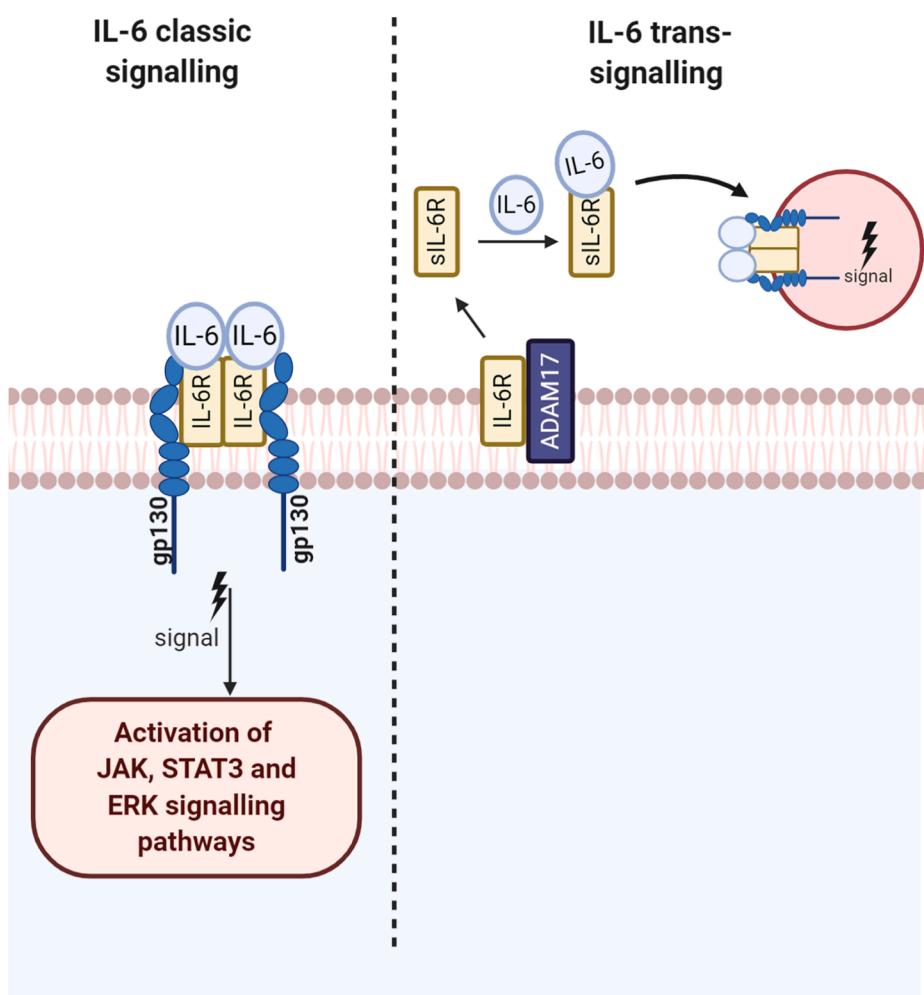
**Fig. 2.** IL-6 signalling Trans IL-6 signalling is initiated via binding with the soluble receptors and IL-6R/sIL-6R and subsequent engagement of the complex with the trans membrane gp130 receptor possessed by a endothelial cells lymphocytes and leucocytes reviewed this engagement results in the activation of STAT-3 which is in turn phosphorylated by JAK kinase resulting in the nuclear translocation of NFKB SOCS proteins are the main inhibitors of IL-6 -STAT-3 signalling in the immune response and plays a major role in preventing a prolonged or over exuberant immune response. In classical signalling both GP130 the IL-6 receptor are membrane bound and the consequences of signal activation are broadly anti-inflammatory in nature.

are at a higher risk of developing CRS and developing more severe symptoms than patients whose endothelium is in a quiescent state [163–167,157].

### 4.4. Role of individual cytokines IL-6

Extremely high levels of IL-6 are seen in CRS patients with severe symptoms compared to those with a milder illness profile and healthy controls [158,161,9,168]. In addition, much research suggest that this cytokine plays a key role in the pathophysiology of the condition [169,170,157]. This notion is supported by the results of numerous studies reporting the rapid resolution of the condition by the use of the IL-6 receptor antagonist tocilizumab either alone or in combination with the anti-IL-6 chimeric monoclonal antibody siltuximab [12,163,171,172]. Indeed, IL-6 appears to play a major role in the development of many of the characteristic features of CRS such as vascular leakage and activation of the coagulation and complement cascade, which in severe cases may induce DIC [173,170]. Interestingly, while macrophages and monocytes are significant sources of IL-6 levels in CRS, blood-vessel endothelial cells also appear to make a major contribution to the elevated levels of IL-6 typical of this syndrome [72].

However, the primacy of IL-6 as the central cytokine underpinning the pathophysiology of CRS is under challenge, especially in the early stages of development. For example, there is evidence to suggest that IFN-γ and TNF-α may play a role in the initiation of the CRS cytokine storm and the upregulation of IL-6 is a downstream occurrence [174,155]. Other authors have cited the importance of IL-1 and the importance of IL-1 blockade in the resolution of the condition

[156,9,154].

#### 4.4.1. IFN-γ, IL-1 and TNF-α

Overall, most evidence suggests that high concentrations of IFN-γ and TNF-α released by the hyperactivation of CAR T-cells and non-CAR T-cells may trigger macrophage activation, leading to secretion of host cytokines such as IL-6, TNF-α, IL-1 and IL-10 [174,175,155]. IL-6, TNF-α and IL-1 in turn activate endothelial cells leading to the production of IL-6 and TNF-α [176]. IL-6 and TNF-α may engage in autocrine signalling with STAT-3 and NFκB, respectively, resulting in self-amplifying and self-sustaining inflammation as explained in Fig. 1 [176–178], ultimately resulting in a cytokine storm, as reviewed by [179,180]. The mechanisms involved in the genesis of the cytokine release syndrome are described and summarised in Fig. 3.

### 5. The cytokine storm of Macrophage activation syndrome

#### 5.1. Immune abnormalities associated with MAS

The term Macrophage Activation Syndrome (MAS) describes an often fatal complication of rheumatic diseases reviewed in [181].

MAS is currently regarded as a form of acquired or secondary hemophagocytic lymphohistiocytosis (sHLH) that is most commonly seen in children with systemic juvenile idiopathic arthritis (SJIA) and, albeit to a lesser degree, in individuals suffering from adult onset Still disease (AOSD), and more rarely in adults with systemic lupus erythematosus (SLE) [182]. Treatment options are limited, and many specialist centres utilise etoposide as a first line treatment for adult and juvenile
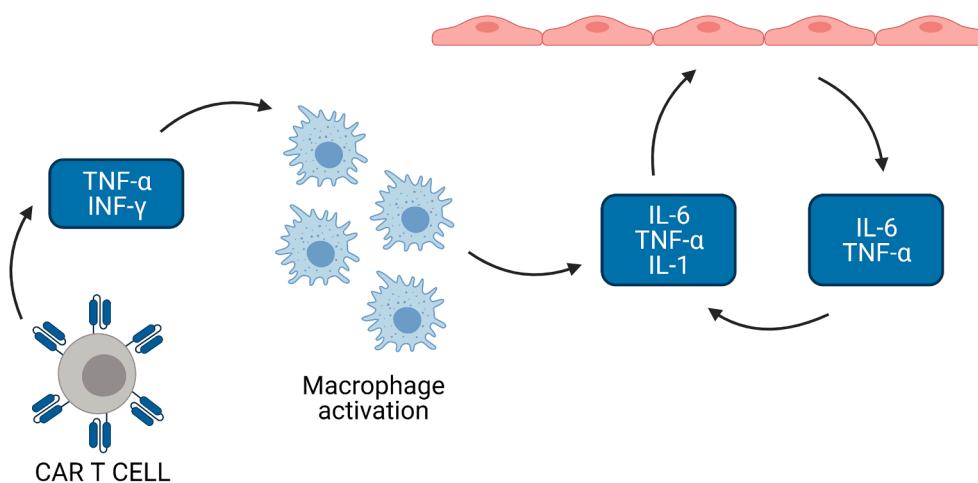
**Fig. 3.** Mechanisms underpinning CRS Massive production of TNF alpha and INF gamma by activated T cells activates monocytes and macrophages which in turn produce large amounts of TNF alpha IL-1 and IL-6. These cytokines activate endothelial cells which then increase the production of IL-1 TNF alpha and IL-6 resulting in the production of an autoinflammatory cascade and escalating activation of the coagulation cascade.

patients. Readers interested in a consideration of the evidence supporting the use of this drug are invited to consult the work of [183,184]. This condition is characterised by massive and unregulated expansion of IFN-γ-secreting CD8+ T cells and CD163+ expressing hemophagocytic macrophages [185], and increased NK activity [186]. The most commonly reported peripheral cytokine and chemokine abnormalities include elevated levels of IFN-γ, IL-1β, IL-6, IL-18, TNF-α, sIL-2Rα, CXCL9, CXCL10 and CXCL11 [187–191](reviewed [192]. Many patients suffering from this condition also possess activated but dysfunctional NK cells with evidence of impaired cytolytic capacity [193–195] (reviewed [196]). Other commonly observed abnormalities include high levels of soluble sCD163 [197,198], sTNFR and sIL-1Ra [199] and sIL-2R-α chain (sCD25) [200]. Increased levels of sCD163 would appear to be of particular significance as this molecule, a specific scavenger receptor for haemoglobin-haptoglobin complexes, is associated with disease severity [197,198,201]. In addition, the appearance of sCD163 in the serum of SJIA patients is predictive of the development of MAS [202].

*5.2. Biochemical abnormalities associated with MAS*

MAS patients commonly present with a decreased erythrocyte sedimentation rate (ESR) together with increased levels of D-dimers and fibrinogen [203]. Unsurprisingly, the latter may result in the development of severe coagulopathy and DIC, causing multi-organ failure and death in approximately 20% of patients with severe symptoms [181,204]. MAS is also characterised by macrophage-mediated hemophagocytosis in the majority of patients, leading to a decrease in the number of platelets, red blood cells, and neutrophils, which may result in thrombocytopaenia, anaemia and leukopenia [200,205]. Other biochemical abnormalities with diagnostic and pathophysiological significance include grossly elevated levels of CRP, the hepatic transaminases AST and ALT, and LDH, bilirubin, triglycerides and ferritin, together with the presence of hypoalbuminemia and hyponatraemia [206] reviewed [181].

*5.3. Factors involved in the pathophysiology of MAS*

MAS is associated with heterozygous defects in genes such as perforin 1 (PRF1) and UNC homolog D (UNC13D) involved in enabling and regulating CD8 and NK cytolytic activity [207–209]. Many patients suffering from this condition also possesses heterozygous gain of function mutations in NLR-family CARD domain-containing protein 4 (NLRC4) inflammasome [210,211]. Other mutations in genes associated with the development of MAS may be broadly categorised as those

involved in antiviral defences, the regulation of inflammasome activity, other immune response pathways and overall regulation of metabolism [212].

This is unsurprising given that bi-allelic mutations in syntaxin binding protein 2 (STXBP2), syntaxin11 (STX11), PRF1, UNC13D and other genes regulating and enabling the clearance of peripheral blood mononuclear cells (PBMCs) by CD8+ T lymphocytes and NK cells are the cause of familial hemophagocytic lymphohistiocytosis (FHL) [213,214]. In this illness, the impaired capacity to lyse antigen presenting cells (APCs) and T cells compromises the clearance of pathogen-infected cells and prolonged antigen stimulation of T cells leads to chronic macrophage activation and massive release of proinflammatory chemokines and cytokines [215,216,189,191,217].

However, MAS is not a purely genetic syndrome and is commonly triggered by viral infections, most notably influenza and herpesviruses such as Epstein-Barr virus (EBV) [218]– (reviewed [219]). Interestingly, a high rate of heterozygous mutations in genes associated with the development of FHL genes has been detected in patients who died as a result of H1N1 influenza infections, suggesting that impaired cytolytic killing may be involved in influencing mortality or recovery following infection with this virus [181,220]. MAS is also typically characterised by increased expression of TLR-2, TLR-4 and IL-1R on PBMCs, which suggests the presence of persistent antigens and high levels of IL-1α and/or IL-1β [221,222].

These findings have prompted several authors to propose a threshold model whereby high levels of systemic inflammation and genetic defects in CD8+ and NK cytolytic function predispose to the development of MAS, which is then triggered by an infection or a disease flare, resulting in increased CD8+ T cell activation and subsequent chronic macrophage activation [200,223]. The current consensus regarding the mechanisms involved following an acute exacerbation of disease and viral infection are discussed in more detail below.

Increased inflammation during a disease leads to upregulation of CD8+ T cell and NK activity and the resultant increase in secretion of TNF-α and IFN-γ in turn results in increased activation and proliferation of macrophages [200]. Reduced clearance of these macrophages due mainly to genetic defects in the cytolytic function of CD8+ lymphocytes and NK cells allows chronic macrophage activation [224]. Finally, autocrine engagement between the latter and the former allows the development of self-amplifying inflammation, resulting in a cytokine storm.

In the case of a viral infection, the activation and proliferation of TNF-α- and IFN-γ-secreting CD8+ T and NK cells result in massive activation and proliferation of macrophages [225]. In this scenario,

there is accumulating evidence that impaired cytolytic activity of CD8+ T and NK cells leads to impaired clearance of infected APCs, resulting in a prolonged immunological synapse and persistent antigenic stimulation [196,226]. This ongoing stimulation enhances proliferation of T cells and production of proinflammatory cytokines, resulting in further increases in macrophage activation together with the development of haematophagocytosis [196,226]. The failure to clear these macrophages leads to an autoinflammatory route, whereby increased macrophage activation leads to increased CD8+ T and NK cell proliferation and cytokine production, further increasing macrophage activity and proliferation, ultimately culminating in an often lethal cytokine storm [196,226,188]. The mechanisms thought to be involved in the aetiology of MAS are depicted and described in Fig. 4.

### 5.4. Role of individual cytokines Ifn-γ

High levels of IFN-γ are found in the serum and tissue of children and adults with MAS [187,227,188]. Moreover, these levels may predict increased mortality [228]. There is no evidence of increased serum IFN-γ in patients with SJIA, either during active disease or during remission, suggesting that IFN-γ may be the dominant cytokine driving MAS [229,230]. Furthermore, several research teams have failed to detect the presence of any increase in the expression of IFN-γ-induced genes in the PBMCs of SJIA patients not displaying any signs or symptoms of MAS [221,231,222]. In addition, increased levels of neopterin, a surrogate marker of IFN-γ-driven macrophage activation [232], is commonly found in children with MAS [233,234], and levels of this cytokine have the capacity to distinguish MAS from active SJIA [235]. Moreover, MAS episodes are frequently triggered by viral infections as discussed above,

which are known activators of IFN-γ-induced pathways [236]. In addition, several lines of evidence suggest that elevated IFN-γ is central to the pathogenesis of FLH. For example, IFN-γ expression is highly elevated in these patients, out of proportion to other proinflammatory cytokines, such as TNF-α and IL-6, and rapidly returns to normal upon effective treatment [237,238]. Further support for the view that MAS is an IFN-γ-mediated condition is supplied by evidence from several RCTs showing significant benefits from the use of emapalumab (an anti-interferon-gamma antibody medication used for the treatment of hemophagocytic lymphohistiocytosis) as a treatment for MAS [239,240]. Finally, IFN-γ potentiates the release of IL-1 from macrophages and monocytes, implying the possibility that the elevated levels of IL-1 seen in MAS patients, as discussed below, may be a consequence of increased IFN-γ production [241] (reviewed [242]).

### 5.4.1. IL-1

The bulk of the extant data suggests that serum IL-1 levels are significantly increased in MAS [221,243,244,202,235]. However, this cytokine is also upregulated in patients with SJIA and Still disease and the increased levels seen in MAS patients are relatively modest when compared to levels seen in patients with these conditions [244,245]. Hence despite convincing data suggesting that IL-1 plays a central role in the pathophysiology of SJIA and AOSD [245], it has been suggested that this cytokine may not be a major player in in the pathogenesis of MAS [244]. This contention is supported by several lines of evidence. For example, the haematological abnormalities seen in MAS are not typical of other IL-1-mediated diseases such as SJIA and AOSD [246]. In addition, IL-1-mediated illnesses tend to be characterised by neutrophilia and high platelet counts while neutropenia and thrombocytopaenia are
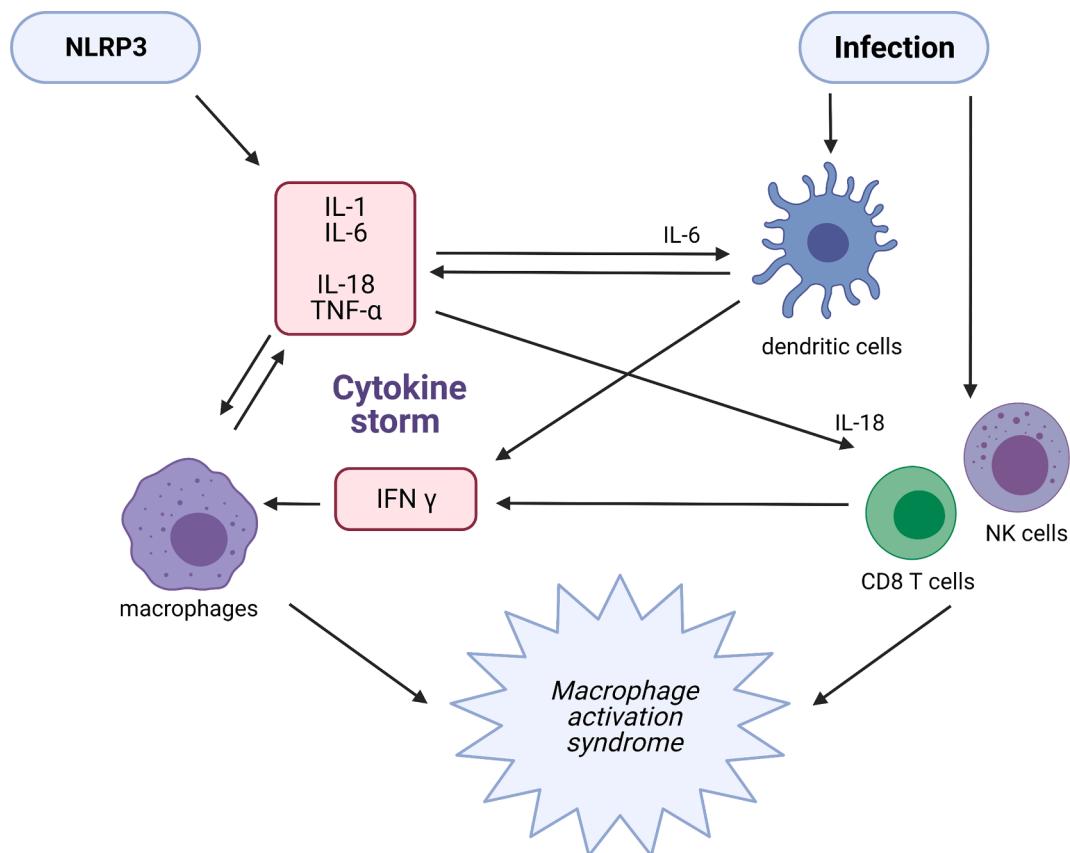


**Fig. 4.** Mechanisms underpinning the development of MAS Increased production of IL-1, IL-18 and secondary IL-6 and TNF alpha inflammation in the context of a viral infection or inflammazome activation upregulates CD8+ T cell and NK activity and proliferation of macrophages. Impaired clearance of the latter in the context of defects in the cytolytic function of CD8+ lymphocytes and NK cells predisposes to chronic macrophage activation resulting in prolonged and excessive production of TNF alpha and IL-1. The latter inducing further increases in the activity of CD8 T cells and NK cells and the development of self-amplifying inflammation, resulting in a cytokine storm.

the common findings in MAS [247,244]. Finally, patients with FHL do not present with increased serum levels of IL-1 [248].

However, the success of anakinra in the treatment of MAS either alone, or more commonly with high dose corticosteroids and IVIG [249–251], makes it difficult to conclude that IL-1 does not play a significant role in the development and/or maintenance of the condition, although the precise role is difficult to ascertain. However, there are potential routes that appear to be worthy of consideration.

First, there is evidence to suggest that IL-1α and IL-1β enhance survival, proliferation, differentiation and migration of antigen-primed CD4+ and CD8+ T cells [252,253]. Second, IL-1 plays a major role in the polarisation of activated macrophages towards an M1 phenotype [254]. Hence, by promoting CD8+ T cell survival and macrophage cytokine production, IL-1 could make a significant contribution towards the exacerbation of pathology. Finally, the direct cytotoxic properties of IL-1 should not be underestimated, as protracted elevations of this cytokine are associated with severe tissue damage [255]. It should, however, be emphasised that these propositions are speculative and the role of IL-1 in the pathogenesis and pathophysiology of MAS, if any, is unknown.

### 5.4.2. IL-18

Extremely high Levels of free IL-18 occur in patients with MAS compared to patients with SJIA and AOSD [256,257,235,190,258]. Moreover, levels of this cytokine strongly correlate with several measures of disease activity, including CRP, ferritin, lactate dehydrogenase, CXCL9 and S100 [257,235,190,258]. In addition, levels of IL-18 in SJIA patients are predictive of developing MAS and are higher in patients with a history of MAS [259,235,258]. Furthermore, the increase in IL-18 seen in MAS patients is accompanied by a relative decrease in the levels of IL-18 binding protein [257,235,190], which is a phenomenon not seen in other inflammatory diseases such as sepsis, rheumatoid arthritis (RA) and SLE [257,260,261]. This may be of pathophysiological significance, as a balance between levels of IL-18 binding protein and IL-18 is needed to restrain the inflammatory effect of the latter under physiological conditions [262]. Unsurprisingly, an imbalance between IL-18 and its binding protein is associated with increased severity of symptoms in several inflammatory diseases [257,260,261]. Moreover, there is *in vivo* evidence to suggest that elevated levels of this cytokine also results in the activation and proliferation of IFN-γ-producing CD8+ T cells [263,264,265]. Overall, the evidence suggests that IL-18 enhances the proliferation, survival and renewal of CD8+ cells [266–269]. Hence, it is tempting to speculate that increased levels of IL-18 may be one potential source of the massive CD8+ T cell expansion seen in MAS, which in many instances is not triggered by a viral infection, but seems to coincide with disease exacerbation and increased inflammation [200,245].

The source of IL-18 in MAS patients continues to be a matter of debate and there is some evidence to suggest that epithelial cells are one source of this cytokine and that increased activity of the NLP3 inflammasome may be involved [270]. Cases of MAS following SJIA are strongly suggestive of NLRC4 activity [271], although macrophages, monocytes and dendritic cells likely also make a contribution [272]. In the case of AOSD, there is considerable evidence to suggest that the source of this cytokine is upregulated by NLRP3 activity. For example, increased NLRP3 activity is a major driver of macrophage activation [273] and correlates with disease activity [274].

NLRP3 activation in macrophages, monocytes and neutrophils plays a major role in the immune response to RNA viruses, hence, IL-18 may dramatically increase following influenza or EBV infection [275–277]. In addition, inflammasome activity may be enhanced in an environment of increasing inflammation and oxidative stress characteristic of disease flares in SJIA and AOSD, leading to elevated levels of IL-18 [278,277]. Therefore, increased IL-18 would be expected to occur either following a virus infection or a disease flare-up if largely produced by inflammasome activity. Thus, the involvement of inflammasomes would explain

how disease flares and viral infections may be involved in the precipitation of MAS in the context of genetic vulnerability towards impaired macrophage or other PBMC clearance. Hence, it is tempting to speculate that increased levels of IL-18 may be one potential source of massive CD8+ T cell expansion and IFN-γ production seen in MAS, which in many instances is not triggered by a viral infection but seems to coincide with disease exacerbation and increased inflammation [200,245].

### 5.4.3. IL-6

Levels of IL-6 are elevated in patients with SJIA and the magnitude of elevation correlates with disease activity [279,280]. In addition, IL-6 levels are elevated in individuals with MAS, although the extent of such elevation is extremely modest in comparison with other inflammatory syndromes, most notably sepsis [215,191]. There continues to be debate regarding the potential sources of elevated IL-6 seen in the condition but evidence suggests that activated macrophages may make a major contribution [281]. IL-1 and IL-18 are potent inducers of IL-6 [282,283].

The role of IL-6 in the pathophysiology of MAS appears to be equally uncertain. Although high levels of tocilizumab may be highly effective in the treatment of SJIA [284], these treated patients remain at high risk of developing MAS [285], suggesting that IL-6 does not play a dominant role in the pathophysiology of the condition. However, it should be noted that elevated IL-6 is an acknowledged cause of impaired NK cytolytic performance [193–195] and increased levels of this cytokine prolongs virus-specific CD8+ T cell survival [146]. These data suggest that high IL-6 levels may enhance the defects in NK cell and CD8+ T cell function implicated in the pathogenesis of MAS.

### 5.4.4. TNF-α

Serum levels of TNF-α are increased in patients with SJIA, although of the same order as seen in other illnesses involving systemic inflammation, such as Kawasaki disease [235]. In addition, results from trials involving the TNF-blocking agent etanercept have been inconsistent, with positive [286,287], negative [285] and harmful results [288–291] reported. Furthermore, levels of TNF-α are only slightly elevated in MAS compared to those reported in children with active SJIA [228,235]. This is somewhat difficult to comprehend in the context of massive CD8+ T cell expansion characteristic of MAS, which would be expected to result in extremely high levels of the cytokines. However, there is evidence to suggest that TNF-α expression by CD8+ T cell activated macrophages is muted in the context of high levels of IL-10, which is seen in many MAS patients [292]. Hence it is possible that the relatively higher levels of the latter cytokine may compensate for the increased TNF-α produced by increasing CD8+ T cell activity in MAS so that overall TNF-α levels may only be moderately increased (reviewed [292]).

The similarities and differences in the immune and biochemical abnormalities seen in the cytokine's storms of H1N1 COVID-19 CRS and MAS cytokine storms are presented in Table 1. We will now proceed to a consideration of therapeutic targets based on the abnormalities identified beginning with NFκB for reasons which will become apparent upon perusal of the section below.

## 6. Potential therapeutic targets

### 6.1. NFκB

As previously discussed, NFκB activation plays an indispensable orchestrating and nurturing role in the initiation and amplification role in the development and progression of severe H1N1 influenza [73–76] and cytokine release syndrome [70–72] cytokine storms. This would also seem to be the case in the cytokine storms experienced by patients with severe COVID-19 [62–64] and less certainly MAS [293–295]. In addition, endothelial activation and damage mediated and maintained by the elevation of NFκB [296–300] Chronically increased NFκB activity is also associated with impaired T cell function, increased Th17

**Table 1**

Comparison and contrast of immunological and biochemical abnormalities reported in COVID-19, H1N1 influenza, CRS and MAS.

| Abnormality | COVID-19 | H1N1 | CRS | MAS |
|---|---|---|---|---|
| IL-6 | +++ | ++ | +++ | NO |
| IL-1 | +++ | ++ | ++ | ++ |
| High neutrophil to Lymphocyte ratio | ++ | ++ | NO evidence | NO evidence |
| Interferon gamma | + | + | +++ | +++ |
| TNF alpha | + | + | +++ | + |
| High D-Dimer levels | ++ | ++ | ++ | ++ |
| Elevated Ferritin | ++ | ++ | +++ | ++ |
| Hypercoagulative state | +++ | ++ | +++ | ++ |
| Activated macrophages | +++ | + | +++ | ++++ |
| Endotheliopathy | +++ | +++ | +++ | NO evidence |
| Elevated IL-18 | +++ | + | NO evidence | ++++ |
| NLRP3 inflammazome activation | +++ | ++ | NO evidence | +++ |
| DIC | ++ | ++ | NO evidence | ++ |
| DAMP production | ++ | ++ | NO evidence | NO evidence |
| CD4 T cell apoptosis and or dysfunction | +++ | NO evidence | +++ | +++ |
| CD8 T cell dysfunction and or apoptosis | +++ | NO evidence | NO evidence | +++ |
| Increased TH17/T reg ratio | +++ | NO evidence | NO evidence | NO evidence |
| Impaired NK cell function and or levels | +++ | NO Evidence | NO evidence | +++ |
| Immunothrombosis | ++ | ++ | ++ | ++ |
| Increased Neutrophil activity | +++ | NO evidence | NO evidence | NO evidence |

differentiation and reduced numbers and immunosuppressant capacity of regulatory T cells [301–303]. In addition, prolonged hyperactivity of NFκB and subsequent reactive oxygen species (ROS) production also leads to T cell apoptosis [304,305]. Furthermore, increased NFκB is also an essential element in neutrophil activation [306,307] and DAMP formation [308,309] and NLRP3 activity [310,311]. Finally, Increased NFκB upregulates levels of IL-6 and IL-1 which appear to be involved in the pathophysiology of COVID-19 cytokine storms and the cytokine storms of H1N1 and CRS at least to some degree. These are important findings as, once activated, IL-1 and IL-6 form autoinflammatory circuits which may speak to the origin of the cytokine storms in severe COVID-19 as we discussed below leading to self-perpetuating increases in their levels.

### 6.2. IL-6 signalling and autoinflammation

This signalling pathway is initiated when IL-6 binds to the cytokine's membrane bound receptor (mIL-6R) on endothelial cells resulting in homodimerization of gp130 leading to the phosphorylation of Janus Kinase (JAK) family members leading to the activation of the transcription factor STAT-3 [312]. This in turn results in the upregulation of the endothelial membrane receptor S1PR1, and increased activity of the enzymes sphingosine phosphate kinase 1 and 2 (SIPK1 and S1PK 2) [313]. Increased activity of SIPK1 and S1PK2, in turn, increases levels of S1P which then provokes further activation of S1PR1 via a mechanism often described as "inside out " signalling, resulting in further increases in the activation of JNK, and STAT-3 [314]. S1P also activates NFκB via an intracellular signalling pathways downstream [315,313,316–318]. The resultant upregulation of IL-6 induced via the transcriptional activity of NFκB forms the foundation of self-amplifying endothelial and systemic inflammation and tissue damage characteristic of CRS, H1N1 influenza MAS and severe COVID-19 [315,313,311,316–318] as discussed above.

Finally, it should be noted that another self-amplifying loop of IL-6 production may be seen in endothelial epithelial and other non-immune cells described as the IL-6 amplifier [180,319,320]. In this case the mechanism appears to rely on IL-17 produced by T lymphocytes following stimulation by IL-6 secreting antigen presentation cells which simultaneously activate STAT-3 and NFκB [180,319,320]. Readers interested in an in depth consideration of this mechanism are invited to consult an excellent treatment of the subject by [319]. The importance of this mechanism in the development of cytokine storms is currently unknown but there is evidence that the IL-6 amplifier plays a role in the pathophysiology of at least some autoimmune diseases [180].

### 6.3. IL-1 signalling and autoinflammation

IL-1α or IL-1β binding to IL-1R1 leads to the formation of a hetero-trimeric (TIR) complex. These recruits and phosphorylates MyD88 IRAK and TRAF-6 leading to the degradation of IκB and release of NFκB IκB and release of NFκB [321,322]. IL-1 engagement with ILR1R results in the upregulation of NFκB which, in turn, increases IL-1 transcription creating an autocrine autoinflammatory loop in a similar manner to the case for IL-6 [45,323,324] reviewed [325,326].

### 6.4. IL-6 versus IL-1

High levels of inflammasome activity in the early and latter stages of the disease is a plausible source of elevated IL-1 seen in severely and mildly affected patients with COVID-19 source of IL-1 [37,38,39,40]. There would seem to be little doubt that the extent IL-1 mediated tissue damage plays a role in determining the severity of the disease [43–46]. It is also noteworthy that high levels of IL-18 are seen in many patients with COVID-19 [47–49] also speaking to a role of NLRP3 activation in the pathophysiology of this illness. In addition, there is a wealth of data implicating NLRP3 mediated release of IL-1 from activated macrophages in self amplifying inflammation and tissue damage in a range of auto-inflammatory conditions [327,255,328].

IL-6 transcription is a downstream target of IL-1 [329–332,145]. For example, IL-1 promotes the transcription of IL-6 and the subsequent release of this cytokine from macrophages [333]. Furthermore, IL-1 activates endothelial cells and their resultant production of IL-6 [334–336]. This at least raises the possibility that increased levels of IL-6 seen in COVID-19 patients are secondary to elevated levels of IL-1. It is also noteworthy that IL-18 may transactivate the expression of IL-6 once again suggesting that NLRP3 activation and the production of IL-1 and IL-18 may precede elevations of IL-6 [337].

## 7. Therapeutic options

### 7.1. Tocilizumab

Tocilizumab is a recombinant IgG1 class humanised monoclonal antibody targeting the soluble and membrane bound IL-6 receptors. The product has a history of considerable success in reducing mortality and morbidity in systemic juvenile idiopathic arthritis [338] and CRS provoked by CART [339]. However, tocilizumab does not prevent the transition between SJIA and MAS and may even mask the clinical signs of the syndrome. The data regarding efficacy of tocilizumab mono-therapy in preventing mortality or reducing illness severity in COVID-19 patients is also equivocal and thus far prospective blinded RCTs have failed to detect a beneficial effect on patient survival despite a recent large prospective RCT reporting a significant reduction in the composite endpoint of mechanical ventilation and death [340]. In addition, a very recent open label RCT conducted by the REMAP-CAP investigators reported a positive effect on mortality in critically ill ventilated patients when the results were subject to a Bayesian analysis (2021) although a large blinded RCT concluded that Tocilizumab conferred no benefit on patient survival [341]. However there is robust data confirming

improved mortality when Tocilizumab is given to patients already on dexamethasone compared to those on dexamethasone alone [342]. Readers interested in an analysis aimed at explaining the apparently contradictory results in these studies are referred to an elegant review by [343]. Readers interested in a review of the studies and conclusions provided by *meta*-analyses of trial results thus far are invited to consult the work of [344]. Finally, it is noteworthy that prolonged tocilizumab therapy appears to exert no favourable effects on levels of IL-1, IL-18 or activity of NFκB [345,258].

IL-6 plays a number of essential roles in anti- viral defences including T cells responses including CD8 function and differentiation, specific IgG responses macrophage activation and migration [346,146]. In this context the presence of data suggesting that monoclonal antibodies targeting IL-6 is associated with reduced B and helper T cell responses, CD8 levels and function and memory T cell production would appear to caution against the use of tocilizumab in the early stages of the disease [347,143,348,349].

### 7.2. JAK inhibitors

There are several excellent reviews examining the mechanisms involving JAK-STAT activation and the role of this pathway as a major effector of cytokine mediated cellular signalling pathways [350]. Similarly, there are several excellent reviews of specific consequences stemming from the activation of various members of the JAK family of receptors and the mode of actions of various commercial Jak inhibitors. Readers interested in these areas are invited to consult the work of [351,352], respectively Several small trials have produced evidence suggesting that baricitinib might reduce morbidity in patients with severe COVID-19 [353–355]. This was also suggested in a larger prospective randomised clinical trial when the drug was combined with remdesivir [356]. However, significant benefits on mortality and morbidity have not been demonstrated in well powered RCTs either with baricitinib alone or in combination with Remdesivir. Indeed, the results of the recent phase 3 trial involving 1400 patients entitled "Study of Baricitinib (LY3009104) in Participants With COVID-19 (COV-BAR-RIER)" were negative with no significant effect on morbidity or mortality reported. This is also the case for Ruxolitinib where small randomised clinical trials have suggested potential benefit [357], but recent large prospective randomised clinical trial dubbed the RUXCO-VID study failed to meet any of its primary or secondary endpoints [358]. Finally, while there is evidence that JAK inhibitors reduce levels of IL-6, they appear to have no effect on levels of IL-1 [359–361] or IL-18 [362,363].

Moreover, JAK-STAT pathway activation by interferons is an essential player in antiviral defences cautioning against this use of these agents in patients with high viral loads and or relatively early in the course of COVID19 [364,365]. In addition, STAT-3 activation plays a major role in defences against a range of viruses [366]and may have an essential role in orchestrating anti-viral defences towards beta Coronaviruses such as SARS and SARSCOV2 as reviewed in [367]. There is also some concern with the use of JAK inhibitors in patients in a hypercoagulative state due to increasing risk of thrombosis as reviewed in [368].

### 7.3. Canakinumab

Canakinumab is a monoclonal antibody binding and neutralising human IL-1β [369]. The drug is administered subcutaneously resulting in peak plasma levels in approximately 7 days [370]. In addition, canakinumab has an elimination half-life of 26 days and a bioavailability of 70% [370]. This monoclonal antibody is Increasingly considered as a treatment option to prevent the recurrence of cardiovascular events [371]and has an excellent record of safety and efficacy in the treatment of SJIA and AOSD [372,373]. However, a clinical trial reported no benefit on MAS [285]. In addition, despite the promising results

suggesting that canakinumab might reduce the inflammatory status and improve oxygenation in COVID-19 patients [374]the negative results regarding any improvement in morbidity and mortality provided by the "Three Cs" study were extremely disappointing [375].

On a more positive note there appear to be no adverse effects on viral clearance and antibody production [376]and there appears to be little if any increased susceptibility to secondary infections following long term use [377]. In addition, there is evidence that the administration of this monoclonal antibody leads in the reduction of IL-6 levels [378,379] although as yet there is no evidence of any favourable benefit on levels of IL-18 [285,380,378,379].

### 7.4. Anakinra

Anakinra is a non-glycosylated form of human IL-1Ra, which acts as a dose related inhibitor of IL-1α and IL-1β binding to IL1-R [381,382]. This preparation is usually administered subcutaneously resulting in a peak plasma concentration in 3–7 h [382,383]. In addition, anakinra administered in this fashion has a bioavailability of 95% and an elimination half- life of 4–6 h [382,383]. This product has been used successfully in the treatment of Rheumatoid Arthritis (RA), SJIA and AOSD and has an excellent record of safety in the treatment of those conditions [384–386]. Moreover, this drug is increasingly being used as an effective first-line treatment for MAS and sHLH in children and adults [387,10,388]. Small prospective studies have reported significant benefits regarding patient inflammatory oxygenation status and reduced need for ventilation in patients hospitalised with severe COVID-19, but thus far there are no findings suggesting reduced mortality [389,390,382,391].

However, anakinra potentially offers additional benefits to the drugs considered above not least via directly inhibiting of NFKB translocation to the nucleus [392,324]and the activity of the NLRP3 inflammazome [393–395]. The latter is an important point as it offers the prospect of decreasing levels of IL-18 which is an independent driver of NFKB activation and directly induces the production of IFN-γ from T lymphocytes and NK cells [327,255,322]. In this context it is worth noting that anakinra therapy also results in decreased levels of IFN-γ, IL-17, IL-22, and Th17 and increased T regs [396]. There are also several reports of reduced IL-6 levels following anakinra therapy [397,380,334]lending further support to the proposition that IL-6 transcription may depend on elevated levels of IL-1 positive effects on endothelial functions in part by inhibiting the activation of tissue factor [331,398]. These are all highly pertinent findings as these abnormalities have all been identified in patients with COVID-19, suggesting that anakinra might be a "broad spectrum" approach to treatment.

This latter point is extremely important as, while excessive levels of proinflammtory cytokines are an important driver of pathology in cytokine storms, other factors are involved as discussed above. One such factor is the activation of the coagulation cascade which makes an independent and synergistic contribution to inflammation and tissue damage as well as well as being the origin of DIC microthrombi and endorgan failure. This pathological interplay between a hyperactivated immune system and hyperactivity of the coagulation cascade is increasingly described as immunothrombosis [399,400,311]. Readers interested in details of the mechanism driving this mutually self-amplifying cascade are referred to the work of [37]. Another source of cytokine storm initiation and amplification is the activation of Inflammasomes leading to the release of DAMPs such as ILA and HMGB1 which may perpetually activate pattern recognition receptors. The activation of inflammasomes may also result in cell death by necrosis and necroptosis releasing high levels of DAMPS resulting in spiralling levels of proinflammatory cytokine production, immune activation, coagulation, tissue damage and cell death [311].

However, NLRP3 activation and immunothrombosis is dependent on NFκB activation and hence the capacity of anakinra to inhibit both entities offer theoretical advantages over unidimensional cytokine

suppression and thus, at least hypothetically is a more rational choice in the treatment of COVID-19 than the other medicines discussed above. In the light of this we would suggest that a randomised clinical trial examining the effects of anakinra in combination with dexamethasone in an effort to improve reductions in mortality already achieved via the use of this drug alone and in combination with tocilizumab [401].

For the sake of completeness it should be noted that venous thromboembolism (VTE) is the most common complication in patients with severe COVID-19 [402] and may occur in almost 30% of patients in ITU [403]. In addition, up to 70% of non survivors display evidence of DIC as previously discussed [37]. Hence a brief discussion regarding the evidence for anticoagulant therapy appears to be warranted.

Unsurprisingly, there have been numerous studies of varying design investigating the use of anticoagulants in this patient group aimed at reducing mortality or at least improving clinical parameters such as oxygenation status [404]. However, the evidence for anticoagulant therapy is mixed. For example, a recent *meta*-analysis of retrospective observational cohort studies concluded that the use of high-dose anticoagulants in critically ill patients was associated with a significant reduction in 30 day mortality [405]. However, another recent *meta*-analysis concluded that there was no benefit to mortality but that that it was a significant increase in risk of bleeding [406]. The evidence from prospective RCTs is also mixed. A small phase 2 RCT has reported improved oxygen status in critically ill patients [407]. However a more recent prospective RCT examining the use of high dose enoxaparin at a dose of 1 mg per kilogram per day reported no significant improvement in mortality at 30 days [408].

## 8. Discussion

In this paper, key features of the cytokine storm associated with three conditions, namely H1N1 influenza, CRS, and MAS have been described. These are summarised in Table 1. Certain haematological and vascular abnormalities are common to all three, including hypercoagulation and increased D-dimer levels. In terms of immune abnormalities, increased levels of IFN-γ, IL-6, IL-1, and TNF-α also tend to be common to the three conditions. However, there are also marked differences between the three conditions in respect of biochemical abnormalities and the pathophysiology of the associated cytokine storm, as well as regarding immune abnormalities and haematological and vascular abnormalities. All cytokine storms and their proposed drivers are dependent on NFκB however and an approach targeting this transcription factor may have universal utility. From the perspective of COVID-19, anakinra has the theoretical potential to alleviate many of the immunological and biochemical abnormalities reported in patients suffering from this illness and thought to be involved in the genesis of cytokine storms potentially improving on decreases in mortality achieved by tocilizumab combined with dexamethasone. However, there is currently a lack of trial data in support of or contravening this hypothesis. Accordingly, large blinded RCTs to test this proposition are recommended.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

*Author's contributions*

All the contributing authors have participated in the preparation of the manuscript and approved the final version.

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