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Coronavirus receptors as immune modulators

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Abstract

The Coronaviridae family includes the seven known human coronaviruses that cause mild to moderate respiratory infections (HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1) as well as severe illness and death (MERS-CoV, SARS-CoV, SARS-CoV-2). Severe infections induce hyperinflammatory responses that are often intensified by host adaptive immune pathways to profoundly advance disease severity. Proinflammatory responses are triggered by coronavirus entry mediated by host cell-surface receptors. Interestingly, five of the seven strains utilize three cell-surface metallopeptidases (CD13, CD26, and ACE2) as receptors, while the others employ O-acetylated-sialic acid (a key feature of metallopeptidases) for entry. Why coronaviruses evolved to use peptidases as their receptors is unknown, but the peptidase activities of the receptors are dispensable suggesting the virus utilizes/benefits from other functions of these molecules. Indeed, these receptors participate in the immune modulatory pathways that contribute to the pathological hyperinflammatory response. This review will focus on the role of coronavirus receptors in modulating immune responses.

Introduction

The recent pandemic of SARS-CoV-2 infection, its pleiotropic and enigmatic presentation in patients of varying age and race and the recurring waves of infection by less severe, yet often lethal, coronavirus strains clearly illustrates the limitations of our knowledge regarding these viruses. How they so efficiently exploit the immune system and what determines severe, mild, or even asymptomatic disease outcomes among infected patients remain important outstanding questions and would benefit from comprehensive investigation. The coronaviruses comprise a large family of enveloped RNA viruses that derive from a common ancestor and, due to the characteristically high mutation rate of RNA viruses, their progeny are quite diverse (1, 2). The resulting coronaviruses are classified into 4 sub-groups, namely alpha, beta, gamma, and delta. Seven of the combined alpha (HCoV-229E and HCoV-NL63) and beta (HCoV-OC43, HCoV-HKU1, MERS-CoV, SARS-CoV and SARS-CoV-2) sub-group coronaviruses infect humans. Human coronaviruses produce respiratory infections ranging from mild to moderate to critical illness and death. MERS-CoV, SARS-CoV and SARS-CoV-2 are the most virulent and can cause severe lower respiratory tract disease, while the other four remain in the nasopharyngeal tract and are responsible for 15% of

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common colds (3). According to WHO, MERS has a high fatality rate of ~34.4% as of November 2019 with 858 fatalities across 27 countries but its low human-to-human transmission limits widespread outbreaks (R_0=0.45–0.98 in Saudi Arabia and R_0=2.5–8.09 in early stages in South Korea but dropping to R_0<1 in a later period or with intervention) (4). Similarly, SARS-CoV also has a high global fatality rate of ~9.5% with a low transmission rate (R_0=2–4, dropping to <1 with control measures). Contrary to these two viruses, SARS-CoV-2 has a lower global mortality rate of ~3.5–4% but a high reproductive number (R_0=2.4–5.7) (5–7) making it highly contagious and pervasive, resulting in devastating death tolls.

Coronavirus infections can eventually lead to an intense pathological inflammatory response that is accompanied by excessive activation of host innate immune mechanisms that further the damage. Viral entry is mediated by specific cell-surface receptors which are recognized by the C-terminal receptor-binding domains (RBD) of the distinctive coronavirus spike proteins (2, 8). The receptors for two of the viruses, HCoV-OC43 and HCoV-HKU1, have not been identified, but are known to employ the 9-O-acetylated-sialic acid modifications on glycoproteins as entry points (Table 1) (9, 10). By contrast, the remaining five coronaviruses utilize three cell-surface metallopeptidases as receptors: CD13/ANPEP/APN (aminopeptidase N), CD26/DPP4 (dipeptidyl peptidase 4), and ACE2 (angiotensin-converting enzyme 2) (11–16). Internalized viral RNA binds to cytosolic, extracellular, and endosomal pattern recognition receptors that activate standard downstream inflammatory signaling cascades (17). However, patients with severe coronavirus infections often have a massive overproduction of inflammatory cytokines, resulting in extensive neutrophil and macrophage infiltration and with dampened adaptive immunity (fewer $CD4^+$ and $CD8^+$ T cells), culminating in increased cell and tissue death and eventually, organ failure (18–29). Why coronaviruses have evolved to use peptidases as their receptors is unknown, but the possibility that this has occurred by chance is highly unlikely (30). Interestingly, viral entry is unaffected by abrogating the receptors' peptidase activities (11, 12, 14, 31), suggesting that these molecules contribute additional functions that may facilitate viral persistence. Indeed, independent of viral infection, these peptidases as well as 9-O-acetylated sialic acid have been implicated as multifunctional modulators of immune cells such as inflammatory cytokine production, inflammatory cell adhesion, phagocytosis, angiogenesis and immune receptor trafficking (32–41). Viral activation of these pathways could clearly amplify the immune response, resulting in hyperinflammation leading to pathology in the context of viral infection. In this review, we will focus on the potential role of the human coronavirus receptors CD13/APN, CD26/DPP4 and ACE2 in mediating immune responses observed in coronavirus infections.

Immune response in coronavirus infections

To better understand the role of coronavirus receptors in modulating immune responses, a brief overview of immune responses observed in coronavirus infections is necessary, specifically among the more severe MERS-CoV, SARS-CoV and SARS-CoV-2 coronaviruses. The common characteristic immunological features of these infections are: elevated levels of proinflammatory chemokines and cytokines, increased neutrophil accumulation leading to toxic neutrophil extracellular traps (NETs) and lymphopenia (fewer

CD4$^+$ T cells, CD8$^+$ T cells and B cells) (Figure 1) (18–28). Patients with severe SARS-CoV had extensive myeloid infiltrates, but lower levels of T cells (28) as did COVID-19 patients, (42) while patients who successfully recovered from COVID-19 had reestablished T cell and B cell numbers close to normal levels (18). COVID-19 patients also elicit a strong humoral response as IgM, IgA and IgG antibodies against SARS-CoV-2 spike protein become detectable by 14 days after the onset of symptoms and persist much longer (42). High titers of neutralizing IgG antibodies against SARS-CoV-2 were detected in 13/14 convalescent patients (43). Interestingly, a study comparing unexposed and SARS-CoV-2 infected patients revealed that ~40–60% of the unexposed individuals carried SARS-CoV-2-cross-reactive CD4$^+$ T cells, presumably produced against common cold coronaviruses that could underlie the natural immunity against SARS-CoV-2 seen in a sub-population of individuals (44). Taken together, these findings emphasize the importance of the adaptive immune response in fighting SARS-CoV-2 infection in addition to suppressing the hyperactivated innate immune response. This may hold true for SARS-CoV and MERS-CoV infections as well.

Mechanistically, induction of these immune responses begins with the binding and internalization of coronaviruses which leads to activation of the NF-kB and NLRP3 inflammasome and cleavage of pro-IL-1β to yield active proinflammatory IL-1β that can then induce expression of IL-6 (45, 46). Release of inflammatory mediators by the infected cells as well as the subsequently recruited innate immune cells, including neutrophils and inflammatory macrophages, promotes the proinflammatory response. Increased serum levels of proinflammatory cytokines, such as IL-6, is a common theme across coronavirus infections compared to healthy controls (26, 47, 48). The defensive antiviral IFN response against coronavirus infections is believed to be suppressed (lower levels of IFNβ), however an increase in the expression of interferon-stimulated genes has also been observed (47, 49). This suggests that the anti-viral interferon response could be dependent on the stage of the infection, while the proinflammatory status remains far more consistent (18–24). Plasma levels of IFN-α, IP-10, IL-6, and MCP-1 are highest in the acute phase (within 2 weeks of the onset of symptoms) of moderate and severe MERS-CoV cases and diminish in the convalescent phase (21). Similarly, moderately infected SARS-CoV patients have higher plasma levels of IFN-γ, IL-1β, IL-8, IL-6, MCP-1, and IP-10 for 19 consecutive days after onset of disease than healthy individuals (20). The initially high cytokine levels drop to normal levels in convalescent patients (19) and in patients treated with methylprednisolone (standard care of treatment) (20). Successful anti-viral therapy of COVID-19 patients also leads to reductions in the levels of proinflammatory cytokines and reestablishes CD4$^+$ and CD8$^+$ T cell numbers close to normal levels (18). Overall, increased levels of proinflammatory cytokines correlate with the viral load and track with the progression and regression of the disease, making them useful markers of pathology.

IL-6 – master regulator

As is evident from the various studies, the cytokine storm consists of pro-inflammatory cytokines such as IL-6, IL-8, MCP-1, IL-1β and TNF-α among others and is associated with the development of acute respiratory distress syndrome (50). However, in the fight against COVID-19, IL-6 has taken the center stage as it regulates a wide array of biological

responses which can amplify respiratory distress (51–57). IL-6 is a unique cytokine in that it can switch between anti-inflammatory (classical signaling) and pro-inflammatory (trans-signaling) responses depending on upon the cleavage state of its receptor. IL-6 binding to membrane bound IL-6Rα mediates anti-inflammatory responses, while binding its soluble receptor (sIL-6Rα) mediates pro-inflammatory responses and acts as a positive feedback signal to further generate IL-6 that is more potent than classical signaling (58). IL-6 knockout or neutralization with anti-IL-6 antibody leads to reduced inflammation and fibrosis (59). Therefore, targeting IL-6 presents a viable approach to mitigate the multitude of proinflammatory events resulting from coronavirus infection. Antibodies against IL-6 such as tocilizumab have shown promising results in severe COVID-19 patients and are in clinical trials for various inflammatory disorders (60–62).

Role of coronavirus receptors in modulating the inflammatory response.

The peptidase receptor molecules modulate IL-6 levels both as *bona fide* coronavirus-binding receptor molecules as well as participating as accessory molecules in immune modulatory pathways to amplify or attenuate the immune response observed in coronavirus infections. Although direct binding of the individual coronaviruses to their primary receptor molecules has been validated, there is ample evidence suggesting that these, as well as other host cell accessory proteins, also facilitate viral entry. Prior to virus binding to receptors, cleavage of coronavirus spike proteins by host cell proteases, designated ‘S protein priming’, is often required (63, 64). For example, cleavage of the SARS-CoV-2 spike protein by the membrane bound serine protease TMPRSS2 is essential to enable virus binding to its ACE2 receptor (13). It has also been postulated that the high infection rate of SARS-CoV-2 may be due to its enhanced ability to exploit host cell factors such as glycan modifications to facilitate attachment, (65, 66). Similarly, MERS-CoV replication is impaired in human monocyte-derived macrophages and dendritic cells regardless of CD26 expression, presumably due to a lack of accessory proteins involved in its internalization (67). Additionally, potential cross-reactivity with other receptors could provide additional modes of entry, as suggested by results from analyses predicting the SARS-CoV-2 spike protein bound CD26 with high affinity, albeit lower than that to ACE2 (68). Therefore, SARS-CoV-2 could potentially use CD26 as a receptor and its binding to either the CD26 or ACE2 receptor molecules could depend on differences in the affinity and/or on the relative abundance of CD26 and ACE2 on host cells. Although *in vitro* assays have shown that CD13 is not the receptor for SARS-CoV-2 (13), CD13 and CD26 expression is co-regulated with ACE2 in various monkey and human tissues (69), suggesting that CD13 and/or CD26 could be potential accessory molecules contributing to viral entry *in vivo*. Therefore, we propose that although individual coronaviruses may not use CD13, CD26 and ACE2 as their primary receptors, these molecules could conceivably influence coronavirus uptake and overall infectivity, as well as amplify the ensuing immune response (Figure 2). This thereby emphasizes the necessity of understanding the contribution of these receptors to disease progression and severity.

CD13/APN/ANPEP, inflammation and IL-6

Human CD13 is the prototypical member of the M1 family of zinc-binding metallopeptidases and is expressed on myeloid cells as well as in various tissues (70–72).

CD13 is a 150-kD type II single-pass transmembrane protein consisting of a short, highly conserved, 7–9 amino acid cytoplasmic tail, a hydrophobic transmembrane region and 7 extracellular domains which contain both its zinc-coordinating and active sites. As a peptidase, CD13/APN participates in the metabolism of regulatory peptides by several cell types, including small intestinal and renal tubular epithelial cells, macrophages, granulocytes, and brain pericytes. However, the majority of CD13-mediated functions occur independently of its enzymatic activity, ranging from angiogenesis, monocyte/endothelial adhesion in inflammation, integrin recycling, receptor endocytosis and maintenance of the stem cell niche (34–36, 73–77). Pertinent to this review, monoclonal antibodies (mAbs) that blocked infection of newborn pigs with the porcine Transmissible Gastroenteritis Virus (TGEV) identified porcine CD13 (pCD13) as the receptor for this fatal intestinal pathogen (31). Subsequently, human CD13 (hCD13) was identified as the receptor for the human coronavirus HCoV-229E (11). Importantly, CD13's enzymatic activity is not essential for receptor activity and neither HCoV-229E binding nor infection is affected by various peptidase inhibitors (11, 78, 79).

Evidence for the interconnection between CD13, inflammation and IL-6 in particular, is strong, and is observed in various normal and disease models (80–84). IL-6 and soluble IL-6R have been shown to induce CD13 expression and activity (81, 82), while anti-CD13 antibody inhibits IL-6 production (84), indicating a positive feedback loop between the expression of CD13 and IL-6. Indeed, antibody-mediated crosslinking of CD13 in mast cells leads to IL-6 production (83). Additionally, soluble CD13 is highly abundant in synovial fluid of rheumatoid arthritis (RA) patients where it increases expression of proinflammatory cytokines (84–91). With regard to HCoV-229E infection, treatment of primary human nasal and tracheal epithelial cells with GFB (glycopyrronium, formoterol, and budesonide), a cocktail of drugs used to treat chronic obstructive pulmonary disease caused by HCoV-229E infection, led to reduced CD13 expression, fewer acidic endosomes that are essential for the entry of HCoV-229E as well as decreased production of inflammatory cytokines (80). This suggests that in addition to preventing entry of HCoV-229E, this cocktail may also help mitigate proinflammatory signaling events observed in other coronavirus infections.

CD26/DPP4, inflammation and IL-6

CD26 is a type II cell membrane peptidase that is expressed in many tissues and hematopoietic cells (92). MERS-CoV utilizes CD26 as the receptor for viral entry and a neutralizing antibody (Mersmab1) against the receptor-binding domain of the MERS-CoV spike protein blocks viral entry (93). Independent of viral infection, CD26 activity promotes inflammation and inhibition of CD26 is beneficial in suppressing inflammation. CD26 is unique in the sense that its inhibition seems to have a dual effect on inflammation, discussed below.

Soluble CD26, generated by cleavage of membrane bound CD26, has been shown to upregulate the p-p65 NF-κB subunit, increase expression and secretion of IL-6, IL-8, and MCP-1 in human vascular smooth muscle cells, while CD26 inhibition and PAR2 silencing prevented this phenotype (94). Specific CD26 inhibition in different disease models has been shown to reduce expression of IL-6 and IL-1β and other proinflammatory cytokines,

suggesting that CD26 intensifies inflammation (95). Therefore, it appears that inhibiting CD26 would suppress various inflammatory responses. However, contradictory evidence implicates CD26 as an inhibitor of lymphocyte chemotaxis. Young, diabetic *Dpp4*$^{-/-}$ mice on high fat diet have increased MCP-1 protein. Additionally, CD26 inhibition in older diabetic mice resulted in cardiac impairment and dysregulated expression of inflammatory and fibrosis genes (96). Mechanistically, CD26 cleaves and inactivates the proinflammatory chemokine CXCL10 to a nonfunctional truncated form, leading to decreased lymphocyte chemotaxis and NK cell infiltration, demonstrated primarily in tumor models (97). This highlights the role of CD26 in mediating certain aspects of anti-inflammatory responses by suppressing NK and T cell infiltration. Therefore, while inhibiting CD26 seems logical considering its role in IL-6 production, it could lead to increased immune cell infiltration, that can potentially exacerbate tissue damage in the context of severe coronavirus infections. Clearly, a careful consideration of the dual role of CD26 in inflammation is needed in the context of coronavirus treatment.

ACE2, inflammation and IL-6

ACE2, the receptor for SARS-CoV and SARS-CoV-2 viruses is expressed in various tissues including small intestine, colon, breast, liver, testis, ovary, kidney, bladder, heart, thyroid, pancreas, lungs, adipose tissue, and adrenal gland (26, 98). This diverse expression profile may underlie the prevalence of widespread organ damage including kidney and cardiovascular tissue in severe SARS-CoV-2 infected patients (26, 99). ACE2 is a type I membrane metalloenzyme that cleaves angiotensin II (Ang II) to generate angiotensin 1–7 (Ang-(1–7) (13, 14). Full length Ang II binds to its receptor AT1 to trigger a strong pro-inflammatory response, including vasoconstriction, vascular permeability and proinflammatory signaling. By contrast, its cleavage product Ang-(1–7) produces antagonistic anti-inflammatory effects by acting as a competitive antagonist for AT1 (100) or by binding to and signaling through the Mas receptor (13, 14). AT1 receptor blockers, soluble ACE2, overexpressed ACE2, ACE2 inhibitors (MLN-4760) (101), *Ace2* deletion and exogenous Ang-(1–7) have all been shown to induce anti-inflammatory immune responses in various models of inflammatory disease (101–110). ACE2 expression is elevated in injured lung epithelial cells in chronic obstructive pulmonary disease (COPD) patients and smokers (111, 112). Therefore, these individuals are potentially more susceptible to SARS-CoV-2 infection, although at this time there is no conclusive evidence in humans to substantially prove this hypothesis. Interestingly, Type 1 diabetic patients exhibit increased circulating (serum) ACE2 activity compared to healthy controls (113) and soluble human ACE2 can prevent viral entry by binding to SARS-CoV, HCoV-NL63 and SARS-CoV-2 (16, 114), suggesting that Type 1 diabetic patients may be protected. Therefore, ACE2 acts as a crucial modulator of the anti-inflammatory immune response and activation of ACE2 or use of exogenous Ang-(1–7) could potentially counter the pro-inflammatory response seen in severe COVID-19 patients. This is an important consideration since treatment strategies aimed at blocking ACE2 may also target its beneficial anti-inflammatory effects.

Conclusions

The massive inflammation characterized by the cytokine storm that develops upon infection by MERS-CoV, SARS-CoV and SARS-CoV-2 clearly underlies the high morbidity and death toll that accompanies these viral infections. While mitigating infection by blocking the initial entry of coronaviruses into host cells is logically the gold standard to prevent new infection, once infected, addressing the question of why these particular viruses trigger such extreme responses may be an effective means of controlling the damage resulting from these infections. To this end, it is essential that we extensively explore the physiological capabilities of these immune modulatory peptidases that also function as viral receptors. A clear understanding of their potential contributions to the exaggerated immune activation in advanced infections may lead to strategies to alleviate morbidity and mortality of these and the inevitable pandemic coronavirus infections of the future.

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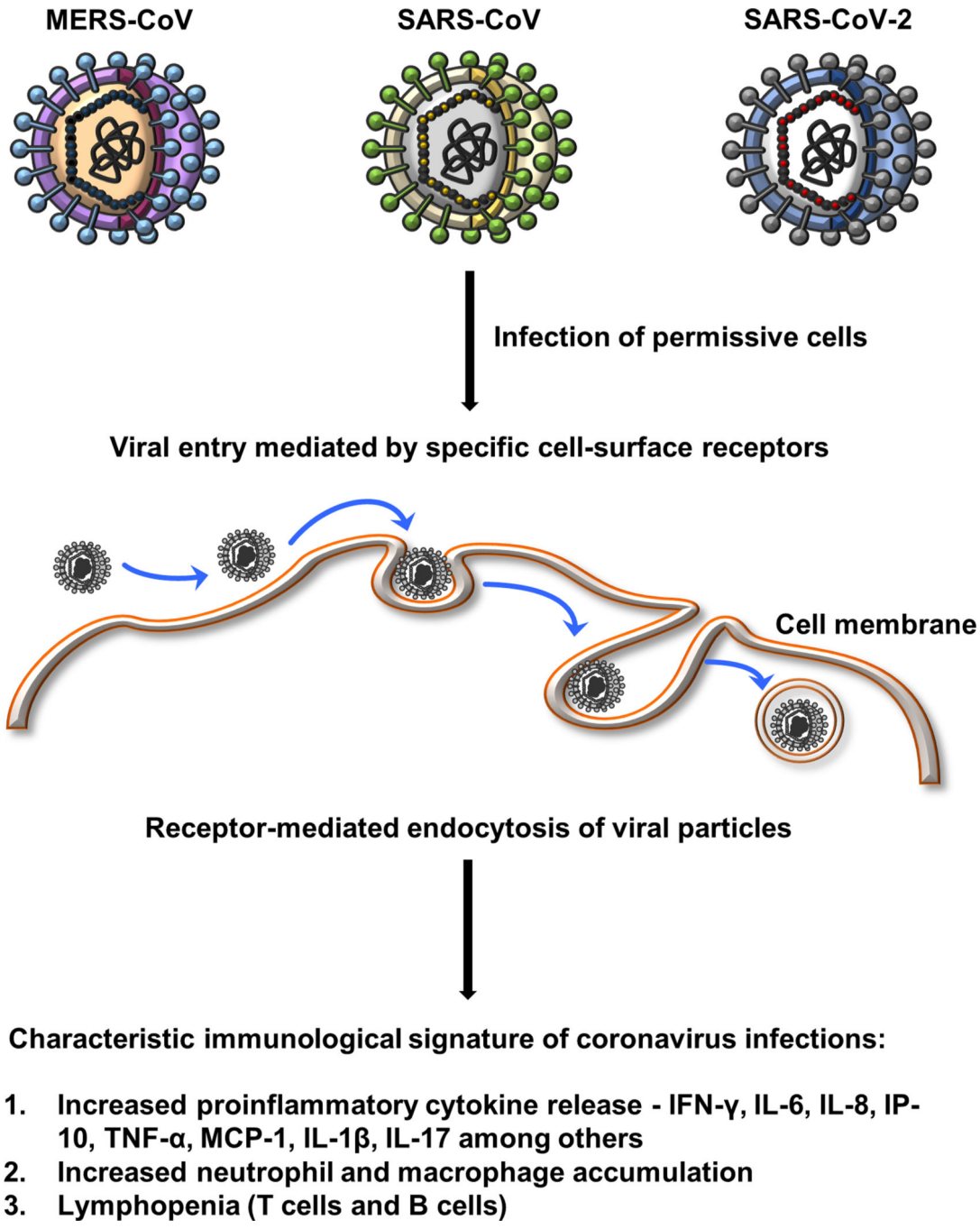

Figure 1: Common characteristic immunological features of coronavirus infections.

Induction of immune response begins with the binding and internalization of coronaviruses leading to elevated levels of proinflammatory chemokines and cytokines, specifically IFN-γ, IL-6, IL-8, IP-10, TNF-α, MCP-1, IL-1β and IL-17 among others. Increased chemokine and cytokine release causes neutrophil and macrophage accumulation as well as lymphopenia ($CD4^+$ T cells, $CD8^+$ T cells and B cells).

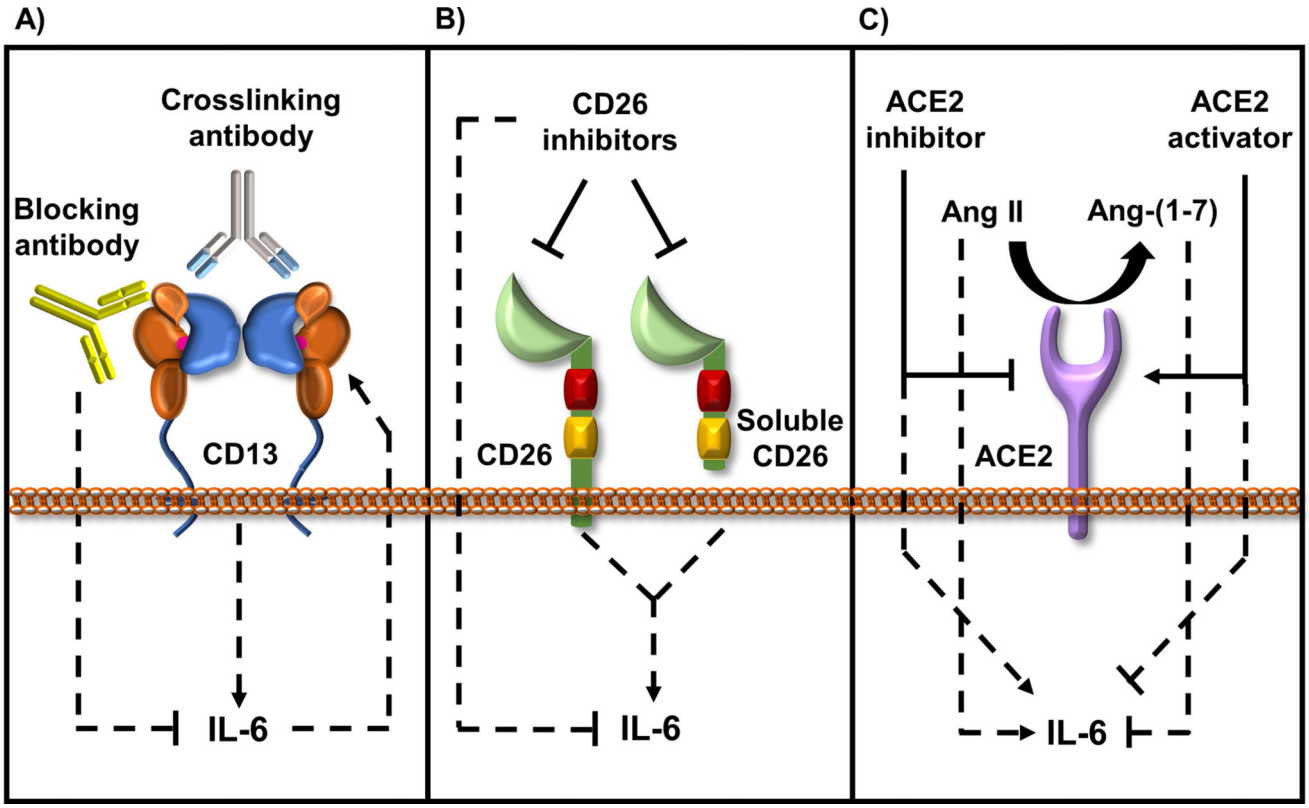

Figure 2: Role of coronavirus receptors in modulating IL-6 levels.

Evidence for the role of coronavirus receptors in modulating IL-6 levels is strong and is observed in various normal and disease models.

A) IL-6 production is enhanced by crosslinking CD13, while CD13 blocking antibodies inhibit IL-6 production. Also, IL-6 and soluble IL-6R induce CD13 expression and activity suggesting a possible positive feedback loop between CD13 and IL-6 expression.

B) Both the membrane bound and soluble CD26 induce IL-6 expression that can be inhibited using CD26 inhibitors such as anagliptin and alogliptin.

C) Ang II, the substrate for ACE2 triggers the production of IL-6, while the product of ACE2 enzymatic activity, Ang-(1–7) opposes Ang II signaling and inhibits IL-6 production. Consequently, loss of ACE2 or treatment with an ACE2 inhibitor (MLN-4760) induces IL-6 production and alternatively, activation of endogenous ACE2 with XNT–(1-[(2-dimethylamino) ethylamino]-4-(hydroxymethyl)-7-[(4-methylphenyl) sulfonyl oxy]-9H-xanthene-9-one} reduces IL-6 production.

Table 1:

Receptors used by the seven different human coronaviruses

Coronavirus	Receptor
Human coronavirus 229E (HCoV-229E) – alpha coronavirus	CD13
Human coronavirus NL63 (HCoV-NL63) – alpha coronavirus	ACE2 (only group I to use ACE2)
Human coronavirus OC43 (HCoV-OC43) – beta coronavirus	9-*O*-acetylated sialic acid (9-*O*-Ac-Sia) residues on glycoproteins
Human coronavirus HKU1 (HCoV-HKU1) – beta coronavirus	9-*O*-acetylated sialic acid (9-*O*-Ac-Sia) residues on glycoproteins
Middle East respiratory syndrome coronavirus (MERS-CoV) – beta coronavirus	CD26
Severe acute respiratory syndrome coronavirus (SARS-Cov) – beta coronavirus	ACE2
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – beta coronavirus	ACE2