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EDITORIAL

COVID-19 in the heart and the lungs: could we "Notch" the inflammatory storm?

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Abstract
From January 2020, coronavirus disease (COVID-19) originated in China has spread around the world. The disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The presence of myocarditis, cardiac arrest, and acute heart failure in COVID-19 patients suggests the existence of a relationship between SARS-CoV-2 infection and cardiac disease. The Notch signalling is a major regulator of cardiovascular function and it is also implicated in several biological processes mediating viral infections. In this report we discuss the possibility to target Notch signalling to prevent SARS-CoV-2 infection and interfere with the progression of COVID-19- associated heart and lungs disease.

Keywords Coronavirus disease · COVID-19 · Cardiovascular disease · Angiotensin-converting enzyme 2 · Furin · ADAM17 · Notch

On COVID-19 and the heart

From January 2020, coronavirus disease (COVID-19) has spread fast from China, mainly to Southwest Asia and Europe, especially to Italy, and it is now found everywhere around the world. The disease is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the seventh member of the coronavirus family which infects humans and to which Middle East Respiratory Syndrome Coronavirus (MERS)-CoV and SARS-CoV also belong [55]. The classical clinical picture of COVID-19 is that of a flu-like syndrome of mild severity in most cases, but in 15% of cases it is complicated by interstitial pneumonia and a variable degree of respiratory failure [40]. The underlying pathological changes, responsible for the respiratory failure, have been characterised in two patients who underwent lung lobotomies for lung adenocarcinoma and were retrospectively found to be COVID-19 positive [6, 48]. Among COVID-19-positive patients, there are those that consult the doctor for heart symptoms, such as palpitations or chest pain rather than respiratory problems [53]. Little is known about a possible relationship between COVID-19 and cardiovascular disease. An early report on 99 patients hospitalised from 1st to 20th January 2020 at Jinyntan Hospital, Wuhan, China, for SARS-CoV-2-related pneumonia, shows that pre-existing cardiovascular disease was present in 40% of them [7]. A second report from the same period of time on 138 patients hospitalised at Zhongnan Hospital of Wuhan University shows that 26% of the patients required cardiologic intensive care. Among these patients, 16.7% developed arrhythmias and 7.2% experienced an acute coronary syndrome in addition to other complications [51]. Furthermore, patients diagnosed with pneumonia due to SARS-CoV-2 infection showed an increase in high-sensitivity cardiac troponin I levels, suggesting myocardial injury [23]. Other published and anecdotal reports indicate the presence of myocarditis, cardiac arrest, and acute heart failure in SARS-CoV-2- infected patients. It is not clear whether these cardiac conditions are provoked by SARS-CoV-2 or are complications typical of any other pathology with higher cardio-metabolic demand, and thus unrelated to the viral infection. Epidemiological studies conducted during the flu epidemic in USA in 1990

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show that influenza and its related complications, such as secondary pneumonia, may cause myocardial infarction due to inflammation-induced destabilisation of coronary artery plaques [10]. This results from multiple mechanisms, such as tachycardia, hypoxia, increased wall stress, and thrombophilia or release of inflammatory cytokines [11]. So, a possible causal link cannot be excluded.

A similar link with myocardial infarction and acute heart failure was shown for the recent epidemics of SARS-CoV and MERS-nCoV [53]. In the absence of a specific treatment or a vaccine, which, according to experts, will not be ready before a year from now, there are only three possible remedies: (1) attempts to contain the spread of the infection with drastic and likely unpopular measures, such as quarantine or restriction of free movement in a specific area with the aim of getting the epidemic exhaust itself "naturally". This, hopefully, should be facilitated by the coming of the summer in the Northern hemisphere; (2) supportive treatment of respiratory and cardiologic complications of the infection, including admission to intensive care units (ICUS) and use of mechanical ventilation or extracorporeal membrane oxygenation (ECMO); (3) proposal of novel approaches, based on evidence from a variety of fields of expertise, which could help in finding a possible therapy. With our short report, we would like to contribute with our experience on Notch signalling to the third option.

Cardiovascular drugs in the context of COVID-19

CoVs are enveloped single-stranded positive-sense RNA viruses with genomes ranging between 26.2 and 31.7 kb RNA. The genome encodes four major structural proteins: the spike (S) protein, nucleocapsid (N) protein, membrane (M) protein, and the envelope (E) protein, all required to produce the viral particle [46]. Sequencing analyses on RNA of SARS-CoV-2 variants isolated from COVID-19 patients show 96% homology with a bat virus [54] suggesting that, as for the other coronaviruses, SARS-CoV-2 jumped from bats to humans, probably through an intermediate host, not yet identified, after the occurrence of a mutation that allowed the infection of human cells [3]. The S (spike) glycoprotein mediates the SARS-CoV-2 entry into cells following the binding to the angiotensin converting enzyme 2 (ACE2) [22]. ACE2 is highly expressed on cell surface of many tissues and organs including the lungs and the myocardium [53]. Of relevance, ACE2 is mainly located in the inner track of the respiratory system, thus explaining why SARS-CoV-2, differently from the flu virus which binds to the upper airways track, might cause serious respiratory insufficiency. This also explains why COVID-19 is not just a common influenza, like somebody believed [33]. Differently from ACE1, which catalyses the formation of Angiotensin (Ang) II, the active component of renin–angiotensin system involved in blood pressure regulation and cardiorenal function, ACE2 cleaves Ang II in Ang (1–7). Thus, ACE2 antagonises ACE1 activity. Ang II receptor blockers (ARBs), which are widely used to treat hypertension and heart failure, increase the levels of Ang II [44] and, indirectly, could activate ACE2 [1]. It has been proposed that patients receiving ARBs have higher susceptibility to COVID-19 [15] and, as a consequence, hypertensive or patients with heart failure should switch from ARBs to other drugs. This way of thinking, however, is not supported by any evidence [16]. Actually, there are caveats here: (1) ACE2 expression is reduced in hypertension models; (2) there is no evidence of increased ACE2 expression with ARBs in the lung; (3) hypertension and its treatment with ARBs did not affect previous coronavirus infections [16].

Based on the evidence discussed above, ACE2 could be targeted to prevent SARS-CoV-2 from entering the cells. To this aim, Lei et al. generated a recombinant protein by connecting the extracellular domain of human ACE2 to the Fc region of the human immunoglobulin IgG1 which neutralised SARS-CoV and SARS-CoV-2 in vitro [27]. Another approach to prevent viral infection could be the downregulation of ACE2 on cell membrane. Of relevance, ADAM17 (A Disintegrin And Metalloproteases 17), a metalloprotease significantly expressed also in the lungs and heart, is involved in the shedding of surface proteins, including ACE2 [26]. Ablation of ADAM17 expression reduces ACE2 shedding, whereas overexpression of ADAM17 significantly increases its shedding [26]. Furthermore, membrane translocation of ADAM17 leads to a reduction in myocardial ACE2 protein levels and activity which is associated with an increase in plasma ACE2 activity [32]. Based on these data, it is tempting to speculate that increasing ADAM17 levels and/or activity to enhance shedding and increase soluble/plasma ACE2 levels could represent a way of blocking SARS-CoV-2 entry into cells (Fig. 1a). Of relevance, treatment with the chemotherapeutic agent 5-fluorouracil strongly activates ADAM17 in an animal model of colorectal cancer [25]. Furthermore, in non-small cell lung cancer cell lines, estradiol increases the expression levels and activity of ADAM17 [41]. This last finding would suggest higher shedding of ACE2 in women and could, at least partially, explain the reduced incidence of COVID-19 in women compared to men [19].

Other than ACE2, the protease furin is also required to promote entrance of the virus into the cell [50]. Furin, a member of the subtilisin-like proprotein convertase family that processes protein of the secretory pathway, is a type 1 membrane-bound protease that is expressed in multiple organs, including the lungs. SARS-CoV-2, differently from SARS-CoV, presents a furin cleavage site between

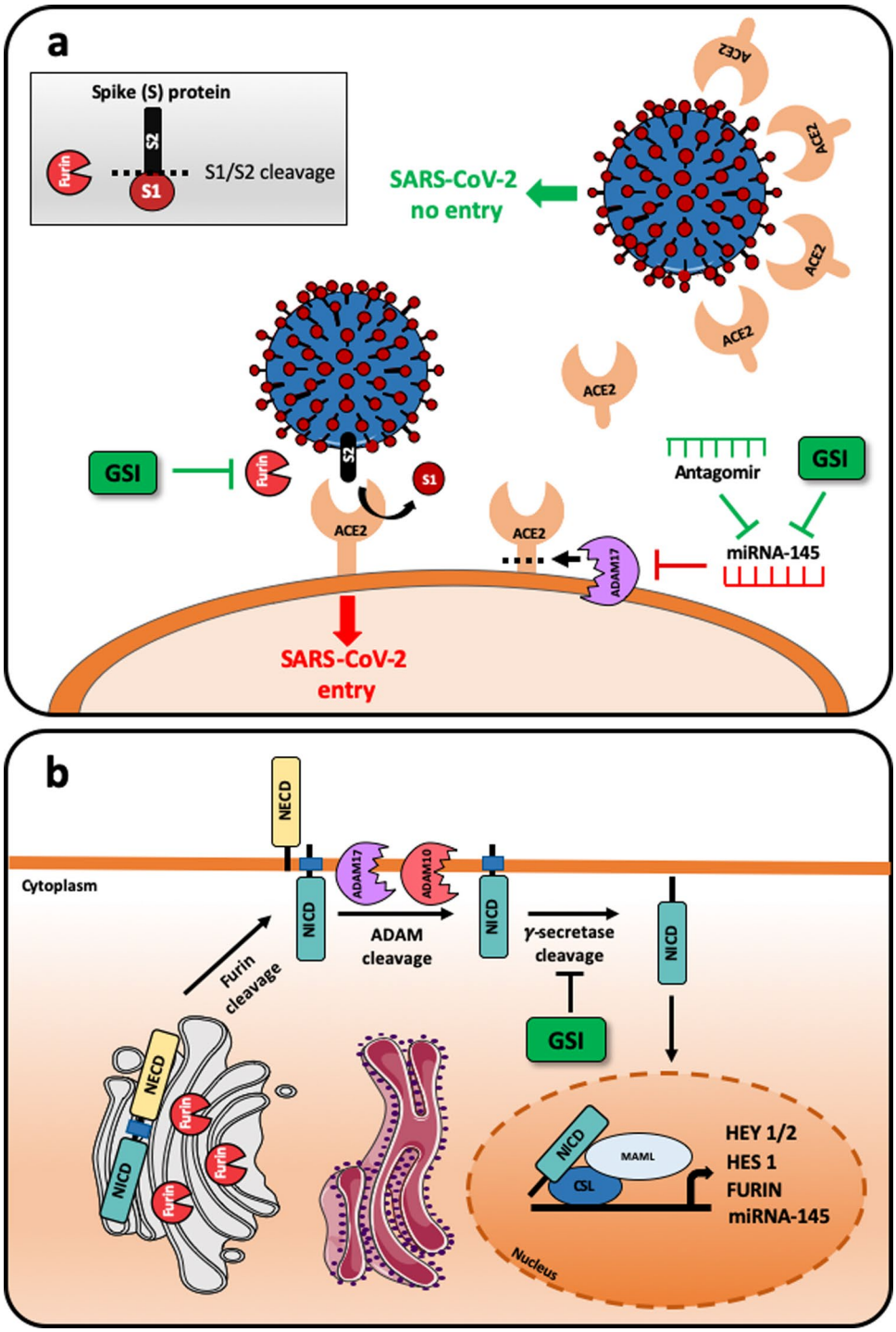

Fig. 1 **a** Severe acute respiratory syndrome- coronavirus-2 (SARS-CoV-2) entry into the cells is mediated by the binding of the viral spike (S) glycoprotein to the angiotensin converting enzyme 2 (ACE2) on the cells, followed by the proteolytic cut at the S_1/S_2 site of the S glycoprotein by the host protease furin. ACE2 levels on the plasma membrane are regulated by ADAM17, which promotes the shedding of the protein. The Notch signalling is a positive regulator of furin and a negative regulator of ADAM17 (through the transcription of miRNA-145), and thus γ-secretase inhibitor (GSI), which prevents Notch activation, may represent a strategy to interfere with the virus entry into the cells by reducing furin and increase ADAM17 shedding. An antagomir to miRNA-145 could represent an alternative approach for upregulation of ADAM17. **b** Notch precursor is cleaved by furin in the Golgi apparatus leading to a heterodimer on the plasma membrane consisting of Notch extracellular domain (NECD) and Notch transmembrane (TM), which contains the Notch intracellular domain (NICD). After the binding with the ligand, Notch is cleaved by ADAM (A Disintegrin And Metalloprotease) 10 or 17, and, after, by the γ-secretase complex. The resultant NICD translocates into the nucleus, where it interacts with the transcription factor CSL (CBF-1/RBP-Jk/Suppressor of hairless/Lag-1) and the transcriptional co-activator MAML (mastermind-like) to regulate the transcription of Notch target genes, such as HEY1 and 2, HES1, FURIN, and miRNA-145

the S1/S2 subunits of the S glycoprotein. Following the binding of the S glycoprotein to ACE2, furin-mediated proteolytic cut of the S protein is necessary for viral entry into the cell [50]. Inhibiting the expression of furin could then be a possible approach to prevent SARS-CoV-2 infection (Fig. 1a, b). Of relevance in this context, nanomolar concentrations of a peptide designed from the furin cleavage sequence of the avian influenza A H5N1 virus provide protection against infection by several furin-dependent pathogens [47].

Furin and ADAM17 are both intertwined with Notch, an evolutionarily conserved system of communication between adjacent cells, and thus targeting Notch could represent an alternative approach to inhibit furin and upregulate ADAM17 (Fig. 1b). Of interest, a recent study has investigated the physical association between SARS-CoV-2 and

human proteins, identifying 66 potential cellular proteins that could be targeted to prevent viral infection [13]. With this approach, it is impossible to identify host proteins crucial for viral infection, which do not interact directly with viral proteins, as is the case for furin and ADAM17. Thus, hypothesis-driven studies based on the knowledge of the molecular details of virus–cell interaction are still crucial for the identification of therapeutic targets to treat COVID-19.

Targeting Notch to prevent SARS-CoV-2 infection

The Notch signalling pathway plays a major role in controlling cell fate during the development and in postnatal life [2]. Growing evidence shows that the Notch signalling is involved in maintaining the homeostasis of the cardiovascular system and could represent a novel target to reduce atherosclerosis progression [18, 42] and remodelling following a myocardial infarction [17, 20, 34]. In humans, there are four receptors (Notch1–4) activated by binding with ligands (Jagged1,2 and Delta-like ligands (Dll)1,3,4) on the surface of adjacent cells [2]. Notch precursor is first cleaved by furin in the Golgi apparatus and then is found as a heterodimer on the cell membrane. Following ligand binding, Notch is first cleaved at the cell membrane by ADAM10 or ADAM17 thus enabling the final cleavage by the γ-secretase releasing the active Notch intracellular domain which migrates to the nucleus and regulates the transcription of target genes (Fig. 1b).

Furin is transcriptionally induced by Notch1 [38]. Inhibition of Notch signalling could, then, be useful to reduce furin levels and interfere with viral entry into the cell. Since Notch dysregulation is a feature of the majority of cancers, Notch inhibitors that target the γ-secretase are available and are being tested, with manageable gastrointestinal toxicity, in several clinical trials in cancer patients. Favorable response has been so far obtained in a limited number of patients indicating that it will be crucial to develop new strategies to identify "responders" to Notch inhibition-based cancer therapies [2].

Notch1-dependent enhancement of furin activity activates ADAM10 but not ADAM17 [38], suggesting that Notch1 does not control ADAM17. Nevertheless, a study on abdominal aorta showed that ADAM17 expression is downregulated by the γ-secretase inhibitor (GSI) DAPT [*N*-(*N*-[3,5-difluorophenacetyl]-L-alanyl)-*S*-phenylglycine *t*-butyl ester]) [8]. Since GSIs with different specificities toward each isoform of Notch exist [2], more of these compounds could be tested to investigate their effects on ADAM17 and, possibly, on ACE2 shedding. Of interest, miRNA-145, which downregulates ADAM17 [14], is a target of Jagged1/Notch1 signalling in vascular smooth muscle cells [4]. It would be of interest to investigate whether antagomir to miRNA-145 would increase ADAM17 activity (Fig. 1a).

Notch and the "cytokine storm"

Among the proposed mechanisms of myocardial and lung injury caused by SARS-CoV-2, there is a "cytokine storm" triggered by an imbalanced response by type 1 and type 2 T helper (Th) cells [53]. The Notch pathway plays a major role during the differentiation and the activity of innate and adaptive immune cells [30, 49]. Dll4/Notch signalling is an important inducer of M1 macrophage polarisation and experiments in vitro and in vivo have shown that inhibition of the Notch by GSI or by anti-Dll4 antibodies leads to a dampening of the inflammation [49]. In macrophages, Notch1 directly binds to interleukin (IL)-6 promoter in response to interferon (IFN)-γ and positively regulates IL-6 production [52]. It is important to underline that IL-6, in turn, increases the expression of the Notch ligand Dll1, thus amplifying the Notch signalling and establishing a positive feedback loop that promotes the further production of IL-6 [21]. In Th cells, Notch signalling triggered by Dll1,4 ligands promotes the production of inflammatory Th1/Th17 cytokines, whereas Jagged1 suppresses IL-6-induced Th17 activation [49] (Fig. 2). A multicentre randomised controlled trial to test a monoclonal antibody against the IL-6 receptor (tocilizumab, Roche) in patients with COVID-19 pneumonia and elevated IL-6 has been conducted in China with promising results (ChiCTR2000029765). Based on these results, a phase II clinical trial to test the efficacy of tocilizumab in 330 Italian patients with COVID-19 pneumonia has been approved by the Italian Medicines Agency (https://www.agenziafarmaco.gov.it/en) and a phase III clinical trial enrolling 330 patients globally has been announced in the US (https://www.roche.com/media/releases/med-cor-2020-03-19.htm). In addition, other strategies have been attempted to reduce the cytokine storm. CytoSorb is an extracorporeal cytokine adsorber and, according to the manufacturers, over 65 patients with severe COVID-19 have been treated with CytoSorb in China, Italy and Germany (https://cytosorb-therapy.com/en/covid-19). However, data on the effectiveness of this approach are not yet available.

IL-6 is a predictor of mortality in COVID-19 patients [43]. However, in severely affected patients, IL-6 is moderately increased (25.2 pg/mL) [36] compared to typical levels in cytokine release syndromes (more than 1600 pg/mL in sepsis) [29]. This may explain why no serious vasoplegic shocks were observed. Nevertheless, the cytokine storm in COVID19 patients is characterised not only by hyperinnate immune response but also by activation of Th cell-mediated immunity. In this scenario, the idea of combining Notch

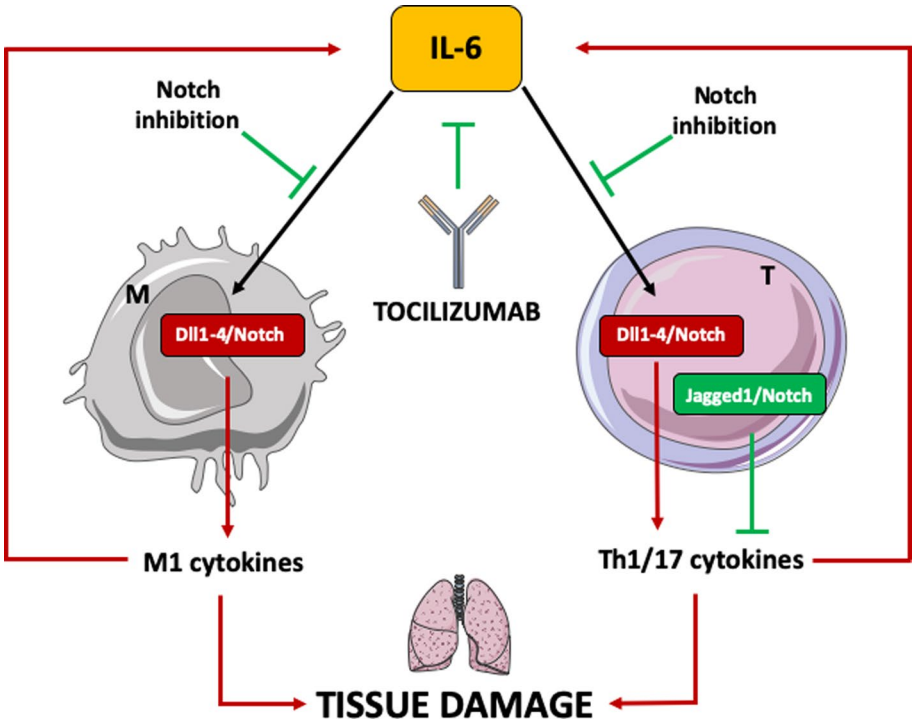

Fig. 2 Notch and IL-6 cooperate to activate the immune system and perpetuate the cytokine storm. In macrophages, Dll4/Notch signalling promotes the production of inflammatory cytokines, IL-6 among those. IL-6, in turn, increases the expression of the Notch ligands (Dll1,4), thus amplifying the Notch signalling and establishing a feedback loop that promotes the further production of IL-6. In T cells, Notch signalling triggered by Dll1/Dll4 ligands promote inflammatory Th1/Th17 cytokines; on the contrary, Jagged1 ligands dampen IL-6-induced Th17 activation. Tocilizumab is expected to block cytokine storm and prevent tissue damage. Notch inhibition by blocking Dll1,4 ligands may help to interrupt the positive feedback loop that fuels the cytokine storm. *M* Macrophages, *T* T cells

inhibitors with anti-IL-6 to dampen the cytokine storm is captivating (Fig. 2).

However, it must be also considered that Notch inhibition could interfere with the immune response during viral infection. Ito et al. [24] found that in mice infected with influenza A virus (H1N1), macrophages increase Notch ligand Dll1 expression. In these mice, inhibition of the Notch pathway using an anti-Dll1 antibody, or GSI by intranasal administration, resulted in increased mortality, defective viral clearance, and decreased IFN-γ production in lungs [24]. Notch signalling also modulates the immune response following respiratory syncytial virus (RSV) infection [28]. Of note, it has been reported that RSV infection causes an increase of Jagged1 in bronchial epithelial cells and, when co-cultured with CD4 + T cells, promotes Th2 differentiation. Conversely, the reduction of Jagged1 expression with siRNA abrogates this effect and promotes an increase in Th1 differentiation. On this basis, it has been suggested that Jagged1-mediated Th2 differentiation may cause RSV-induced airway hyperresponsiveness [37]. On the basis of these studies, it could be hypothesised that it may be preferable targeting specific components of the Notch signalling, such as Dll4 or Jagged1, rather than inhibiting Notch with a GSI. Of relevance, soluble Jagged1 has been shown to efficiently inhibit neointima formation after balloon injury by decreasing smooth muscle cell proliferation and migration through inhibition of Notch signalling [5].

Preclinical studies have shown that Notch inhibition can be useful not only for treatment of atherosclerosis but also for other inflammation-based conditions such as graft-versus-host disease [39], chronic obstructive pulmonary disease (COPD) [12] and arthritis [31]. It is important to point out that before Notch inhibition becomes a reality in the clinical managements of these patients, we should address issues that could arise upon chronic exposure to Notch inhibitors, likely required for many of these pathologies, such as (1) toxicity related to the multiple cellular targets of GSIs, due to the promiscuous activity of the γ-secretase, (2) alteration of the immune system activities and of the stem cell compartment, in which Notch plays a pivotal role, and (3) the potential oncogenicity of the treatment, given the tumour suppressor role of Notch in tissues like the skin, as observed in Alzheimer's patient treated with GSIs to inhibit the formation of amyloid A4 peptide [2, 35]. A possible approach to avoid systemic toxicity could be delivery of GSIs and Jagged1/Dll4 inhibitors directly to the lungs by the use of nanoparticles [45].

Based on these data, we should conclude that, even if it holds great promise, Notch inhibition to block the cytokine storm in COVID-19 patients is still not feasible and targeting the IL-6 receptor or depleting the cytokines by other means represent the only approaches available at this time.

Conclusions

The relationship between Notch and viruses is well documented. To replicate, some viruses, such as Human Papilloma Virus and Simian Virus 40, highjack the cell machinery, including the Notch signalling, and by doing so they can cause cancer [9]. Therefore, it has been proposed that the dysregulation of Notch signalling could provide diagnostic and therapeutic tools for virus-associated cancers [9]. By uncovering new aspects of this relationship, we might be able to target Notch also to fight heart and lung disease caused directly by SARS-CoV-2 infection and by the cytokine storm in response to the virus.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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