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Possible therapeutic options and management of COVID-19

Possíveis opções terapêuticas e gestão da COVID-19

Posibles opciones terapéuticas y manejo de la COVID-19

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Abstract

Currently, there is no effective therapy against Coronavirus disease 2019 (COVID-19). Thus, there is crucial requirement for effective therapy against COVID-19. To our knowledge, few investigations have been conducted on AT2 progenitor cells as target for the (SARS-CoV-2). Hence, alveolar type 2 progenitor cells may be a possible therapeutic agent against COVID19. This review focused on the pathogenesis and pathophysiology of COVID19 disease on AT2 cells and explored potential mechanisms to prevent infection and death of AT2 progenitor cells as possible therapy against COVID-19. We propose that inhibition of IL-1 receptor, IL 1, NFkB and JNK signalling pathway may serve as therapeutic target for COVID-19

Keywords: COVID-19; Alveolar type 2; Pathogenesis; Therapeutic.

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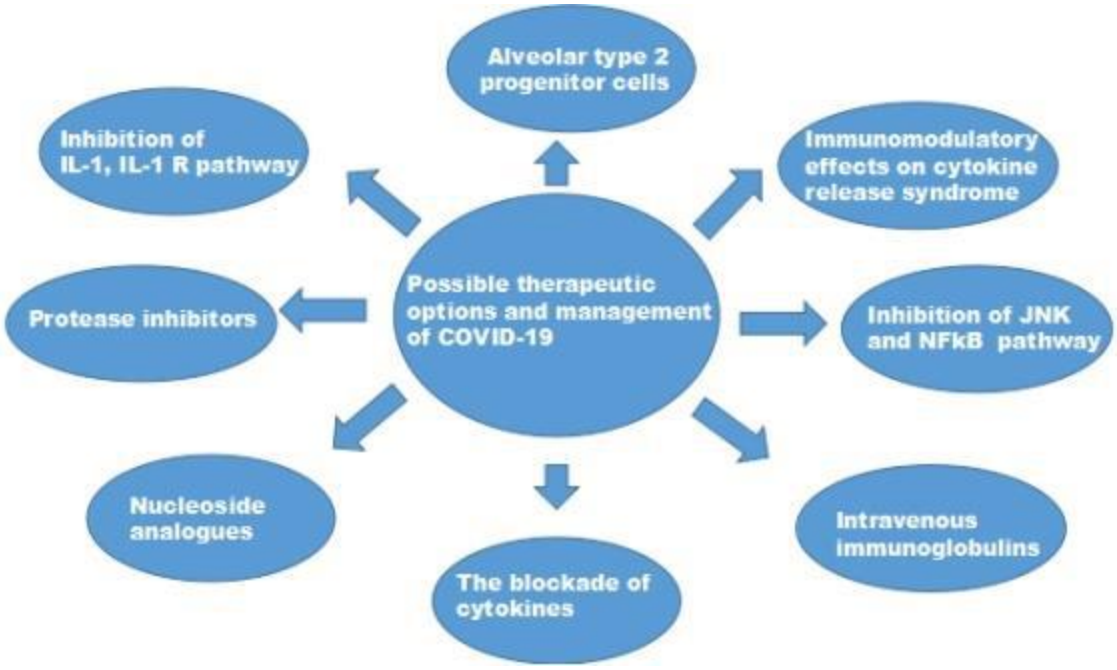
Running Title: AT2 cells may be a target for SARS-CoV2

Graphical Abstract



Source: Authors.

Resumo

Atualmente, não existe uma terapia eficaz contra a doença de Coronavírus 2019 (COVID-19). Assim, há um requisito crucial para uma terapia eficaz contra o COVID-19. Até onde sabemos, poucas investigações foram conduzidas em células progenitoras AT2 como alvo para o (SARS-CoV-2). Assim, as células progenitoras alveolares tipo 2 podem ser um possível agente terapêutico contra o COVID19. Esta revisão se concentrou na patogênese e fisiopatologia da doença COVID19 em células AT2 e explorou mecanismos potenciais para prevenir a infecção e morte de células progenitoras AT2 como possível terapia contra COVID-19. Propomos que a inibição da via de sinalização do receptor de IL-1, IL 1, NFkB e JNK pode servir como alvo terapêutico para COVID-19.

Palavras-chave: COVID-19; Alveolar tipo 2; Patogênese; Terapêutica.

Resumen

Actualmente, no existe una terapia efectiva contra la enfermedad por coronavirus 2019 (COVID-19). Por lo tanto, existe un requisito crucial para una terapia eficaz contra COVID-19. Hasta donde sabemos, se han realizado pocas investigaciones sobre las células progenitoras AT2 como objetivo para el (SARS-CoV-2). Por lo tanto, las células progenitoras alveolares tipo 2 pueden ser un posible agente terapéutico contra COVID19. Esta revisión se centró en la patogenia y la fisiopatología de la enfermedad COVID19 en las células AT2 y exploró los posibles mecanismos para prevenir la infección y la muerte de las células progenitoras AT2 como posible terapia contra la COVID-19. Proponemos que la inhibición de la vía de señalización del receptor IL-1, IL 1, NFkB y JNK puede servir como diana terapéutica para COVID-19.

Palabras clave: COVID-19; Alveolar tipo 2; Patogenia; Terapéutica.

1. Introduction

Coronavirus belong to *Nidovirales* order and *Coronaviridae* family. The RNA genome of coronavirus is about 26 to 32 kilobases, a single-strand, non-segmented, positive-sense (Agostini et al., 2018). It has been discovered in mammals such as dogs, bats, masked palm civets (Erles et al., 2003), cats, mice, etc. In 2018, acute diarrhoea syndrome in pigs due to the infection from an HKU2-related coronavirus which originated from bat (Zhou et al., 2018). Most of the coronavirus that are linked to humans are pathogenic with mild conditions (Su et al., 2016) except for MERS-CoV, SARS-COV and SARS-COV2 which shows severe clinical symptoms. Presently, seven different coronavirus strains have been discovered to affect humans. These include severe acute

respiratory syndrome coronavirus (SARS-CoV) (Peiris et al., 2003), SARS-CoV-2 (Hoffmann et al., 2020a; Wu et al., 2020; Zhou et al., 2020), Middle East respiratory syndrome coronavirus (MERS-CoV) (Raj et al., 2014; Wu et al., 2020; Zaki et al., 2012), HCoV-OC43 (OC43), HCoV-229E (229E), HCoV-HKU1 (HKU1), HCoV-NL63 (NL63) (Kin et al., 2015).

Epidemiologically the rate of death toll worldwide is alarming for COVID-19. As of 18th of July 2020 about 14,102,399 cases of coronavirus has been reported worldwide while on 24th November 2020 it has increased to 61,781,835 cases worldwide Total death toll of about 595,434 and people who have recovered are about 8,393,078 in July. In November 2020, total death toll of about 1,445,919 and people who have recovered are about 42,675,034. Investigations have shown the reproduction number (R_0) of SARS-CoV-2 is 1.4–6.47 (Tang et al., 2020Tang et al., 2020). Meanwhile the reproduction number (R_0) of SARS-CoV-1 and MERS-CoV is 0.3–1.3 and 2.2–3.7 respectively (D. Tang et al., 2020) which shows that SARS-CoV-2 infection is more infectious than previous human coronavirus strains. Currently as of 18th November 2021, 255,324,963 cases worldwide total death toll of about 5,127,696 and people who have vaccinated about 7,370,902,499.

Acute respiratory distress syndrome (ARDS) is the causes of mortality of COVID 19 patients which currently can only be managed using supportive intensive care (Ruan et al., 2020). They may undergo a cytokine storm (aka cytokine release syndrome, or CRS) and progress to secondary hemophagocytic lymphohistiocytosis (Seguin et al.,2016; Usmani & Woda, 2013) (uncontrolled immune activation of T cells and organ failure) (sHLH), which results to acute respiratory distress syndrome (ARDS). ARDS is responsible for approximately 50 % death (Seguin et al., 2016). Cytokine storms are seen in sepsis, secondary hemophagocytic lymphohistiocytosis and macrophage activation syndrome (MAS). Secondary hemophagocytic lymphohistiocytosis is mostly occurred as a result of elevated Granulocyte colony stimulating factor (GCSF), TNF-α-6, IL-7, IL-2, Interferon -γ inducible protein 10, macrophage inflammatory protein 1-α, which is activated by viral infection (Ramos-Casals et al., 2014). Hence, inadequate information of these syndromes could contribute to poor prognosis. It was discovered that Cytokine release syndrome (CRS) may play a pivotal role in mortality in patients infected with SARS-CoV and MERS-CoV (Channappanavar & Perlman, 2017). The biomarkers of coronavirus and severe MERS include increased serum cytokine, Serum C-reactive protein (CRP), interleukin-6 (IL-6) and other inflammatory cytokines (Fehr et al., 2017). CRS is found in COVID-19 patients, and increase in serum IL-6 associates with lung injury, acute respiratory distress syndrome, respiratory failure, and hostile clinical results (Fehr et al., 2017). Here in we hypothesis that alveolar type II cells may be a target of COVID 19 and inhibition of some signalling pathways such as IL-1, 1L-1R, JNK, NF-KB may serve as a therapeutic target for the COVID-19. Apoptosis, NETosis, ferroptosis, parthanatos, alkaliptosis, necroptosis, autophagy-dependent cell death, and oxeiptosis may be useful for the treatment of COVID-19.

2. Methodology

Web of Science (WOS), Scopus, Google Scholar were utilized to discover publications based on the following keywords: COVID-19, Alveolar type 2, Pathogenesis, therapeutic and coronavirus. Relevant and updated articles from 2000 to 2021 were used from google scholar, scopus and web of science. Herein, we used review articles, conference papers, research articles, case report and focuses more on those papers that were indexed by the Web of Science.

3. Pathogenesis of COVID-19

The pathogenesis of COVID-19 is still debatable however with the assistance of the previous coronavirus strains such as SARS-COV and MERS-COV assist to understand the novel coronavirus also known as SARS-COV2. It is very complex. The virus enters into the cell and the major receptor responsible for both SARS-COV and SARS-CoV2 is the angiotensin converting enzyme

2 (ACE2) (Wan, Shang, Graham, Baric, & Li, 2020). This period may be referred to as the asymptomatic stage. The individual inhale SARS-CoV2 probably attached to the epithelial cells in the upper respiratory region (tracheobronchial or nasal) and virus multiplication commences afterwards. Ciliated and the epithelial cells of the alveoli are the cells primarily affected (Qian et al., 2013; Sims et al., 2005; To & Lo, 2004).

After some days, the virus spreads and moves down the respiratory tract which results to the activation of innate immunity. The CXCL10 and other innate immunity biomarker (N. L.-S. Tang et al., 2005) are biomarkers for early diagnosis of SARS-CoV-2. Interferons are produced from the cells as a result of insults and infection (Hancock et al., 2018). CXCL10, IL29, IL8, IL1, TNF-alpha are cytokines that are very crucial in coronavirus, acute respiratory distress syndrome, acute lung injury, influenza, pulmonary fibrosis etc. Hence, these cytokines are suitable biomarker and therapeutic target in the management and treatment of respiratory diseases and most especially SARS COV2 (Qian et al., 2013). CXCL10 has also been described to be appropriate as biomarker in SARS (Rockx et al., 2009). Most of the cases approximately 80% of SARS-COV patients are mild and generally constrained to the upper and conducting airways. Therefore, such patients should be quarantined at home and administered the necessary supportive therapy.

In this stage, it progresses to acute respiratory distress syndrome, ground glass opacity and hypoxia. Regrettably, approximately 20% of the ill patients progress to this stage and will develop to a very critical illness culminating in mortality (J. Wu et al., 2020). Hence, coronavirus migrate to the alveolar type 2 (AT2) cells and infects the cell. Most of the time the infection occurs on the AT2 cells (Mossel et al., 2008). Coronavirus and Influenza favorably infects AT2 cells than ATI cells (Weinheimer et al., 2012). The subpleural and peripheral are the major unit of the alveolar where infections usually occur (J. Wu et al., 2020). Apoptosis occur in the cell as a result of the replication of the SARS-CoV in AT2 cells which leads to pulmonary toxins (Qian et al., 2013). Hence, most of the AT2 cells are lost which will results to regeneration of new AT2 cells (Kumar et al., 2011; Yee et al., 2017). Alveolar injury with numerous fibrins in the hyaline membrane and some multinucleated cells are the major pathological features of SARS-COV and COVID-19 virus (Cheung et al., 2004; Ding et al., 2003; Gu & Korteweg, 2007; Nicholls et al., 2003; Tse et al., 2004; Xu et al., 2020).

4. Management of COVID-19 patients

COVID-19 patients management is very imperative because of the death rate is alarming all over the world. Hence, researches are ongoing seriously all over the world to combat the virus which is really creating a lot of problems globally.

5. Immunomodulatory Effects on Cytokine Release Syndrome may be Useful for Management of COVID-19

The major means of managing COVID-19 presently is using supportive approach. The major causes of mortality are acute respiratory distress syndrome, age, cytokine release syndrome and other comorbidities are major risk factors (Du et al., 2020; Qin et al., 2020). Early diagnosis is very important in order to know how to treat the patient effectively and the immune system should be monitored. Some of the biomarker which includes lymphopenia, hypoalbuminemia, leukopenia, prolonged thrombin time, significantly elevated CRP and IL-6, hyperfibringenemia are crucial (Ferro et al., 2020; Y. Gao et al., 2020; Huang et al., 2020). However, the need for identification and discovery of different novel biomarker which are very sensitive and specific is vital.

Previous cases of cytokine storm syndrome have been reported and the major therapy utilized was immunosuppressive drugs which includes etoposide, steroids (Seguin et al., 2016). High dose (dexamethasone), chemotherapy with etoposide, calcineurin inhibitor cyclosporine A (Henter et al., 2007) and stem cell therapy may be very useful.

Corticosteroids: These are used mainly to reduce inflammation and used in HLH. Therefore, may be used to control inflammation in ARDS and COVID-19 (Chen et al., 2006; Yi et al., 2020). Utilization of corticosteroids at low-to-moderate dose in patients with coronavirus infection have been reported to be useful in the management of coronavirus (Shang et al., 2020). However, some investigations on the corticosteroids are still debatable in the treatment of coronavirus which need further investigations.

Inhibition of Janus kinases: This is an important signalling pathway which may be useful as therapeutic target for diseases aggravated as a result of cytokine release syndrome (Kubler, 2014). It may also be referred to as cytoplasmic tyrosine kinases. They are associated with cytokine signalling from membrane receptors to signal transducers and (STAT) activator. The majorly known members of the JAK family includes JAK1, JAK2, JAK3 and TYK2. The discovery of the cytokine biology is majorly by the JAK signalling pathway (Menet et al., 2013). It is associated with the interferon receptors and the interleukins (Cron & Chatham, 2020; Seo & Kweon, 2019). Type 1 interferon (T1IFN), is an abundant cytokine, which is very good candidate for a critical function. The significance of T1IFN in controlling of the internal environments and acute inflammation has been investigated in mouse models (Kole et al., 2013; Rauch et al., 2014). JAKs play a pivotal function in the regulation of the expression of T1IFN which has significant effects on the reduction of virus and clearance of pathogens (Zhou et al., 2020). During the first stage of COVID-19, the multiplication of virus and infection may be in the alveolar epithelium cells and the expression of the T1IFN may be reduced due to the infection. However, Janus kinase pathway is an interesting pathway which required further investigation to unravel its molecular mechanism when antioxidant, small molecules, inhibitors and nanoparticles are utilized to inhibit the pathway to prevent cytokine and hence prevent COVID19.

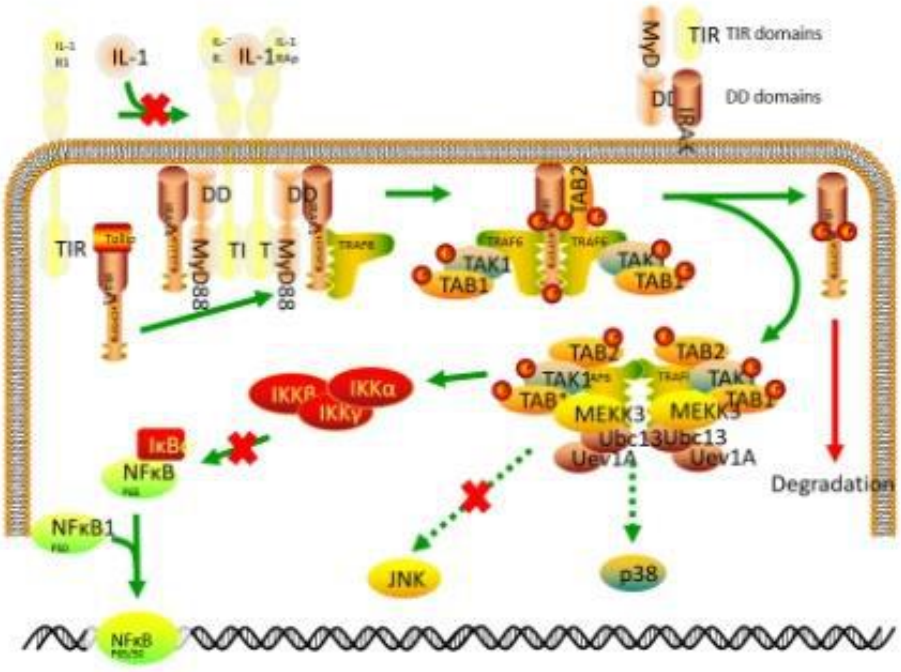
Intravenous immunoglobulins IVIG: This is a very useful therapy which is utilized majorly in inflammatory conditions to regulate systemic inflammation which may be effective utilizing different mechanism such as neutralization of antibodies, inhibition of Fcγ receptors, prevention of the T and B lymphocyte activation, etc (Hoffmann et al., 2020b). Immune complexes comprising of virus may trigger infection initiate Fcγ receptors and pro-inflammatory responses (Liu et al., 2019). However, the mechanisms responsible for the cytokine release syndrome and inflammation is still debatable. Antibody may have response roles in the outcome of COVID-19 patients have been described by previous researchers who investigated the effects of antibody on SARS-COV. They discovered that glycoproteins N and S -specific NAB reponses were higher in patient which recovered (J. S. M. Peiris et al., 2003; Zhang et al., 2006). Hence, Intravenous immunoglobulins may be useful in some patients for therapeutic purposes, prophylactic applications and can be applied as a tool for vaccine development (Marston, Paules, & Fauci, 2018). Additionally, inflammation and cytokine release syndrome may be reduced in such patient who has recovered from COVID-19 and established unique antibodies (Liu et al., 2019). The major monoclonal antibodies used for treatment of infectious diseases includes, anthrax, respiratory syncytial virus and *Clostridioides difficile*. USFDA United State Food and Drug Administration has approved several monoclonal antibodies (Marovich et al., 2020).

6. Inhibition of Cytokines and IL -1 Receptor Signalling Pathway

Inhibition of cytokine may be very useful to combat COVID-19 infections aggravated with cytokine release syndrome which is a possible therapy. This method has been proved to be effective in some patients. Tocilizumab (IL6 receptor inhibitor) has

been used in patients with cytokine release syndrome and it reduced the cytokine significantly (Maude et al., 2014). It has also been used successfully in COVID-19 patients (Michot et al., 2020; X. Zhang et al., 2020). Currently different researchers are investigating novel drugs for COVID-19 (Mehta et al., 2020). Anakinra, a recombinant IL -1 receptor which was established for the treatment of cytokine release syndrome has been used successfully (Hedrich et al., 2012; Nigrovic et al., 2011; Sönmez et al., 2018). It is also useful in infectious diseases (Sönmez et al., 2018). We hypothesised that as a result of inhibition of IL-1 R, IL-1, NFkB and JNK pathway may serve as therapeutic option for COVID-19 Figure 1.

Figure 1: Inhibition of IL-1 R, IL-1, NFkB and JNK pathway.



Source: Authors.

(Hydroxy-) Chloroquine

Chloroquine has been known for its antimalaria activities but recently, researchers discovered that it may also be very useful as an antiviral drug. Medically, hydroxychloroquine is known for its immunomodulatory activities while the sulphate and phosphate are used as antimalarials. Chloroquine has antiviral properties (Gao et al., 2020; Savarino et al., 2003; Vincent et al., 2013). Researchers have also investigated the effects of chloroquine on COVID19, which inhibits the virus successfully invitro (Wang et al., 2020). Hence, chloroquine has been introduced into the clinical environment to combat COVID-19. However, the use of chloroquine is still debatable and need further investigation (Gao et al., 2020). A French scientist has also investigated the effects of hydroxychloroquine and azithromycin which shows to be effective (Gautret et al., 2020; Molina et al., 2020). However, it is still debatable and need further investigations.

Cytokine release syndrome may be treated using hydroxychloroquine due to its immunomodulatory effects. Alkalization of endosomes lessens chemotaxis, proteolysis, signaling transductions, phagocytosis, and interferes with immunity (Zhou et al., 2020).

It is connected with the reaction of IL-6, IL 1 and can also affects some important signaling pathways that may be responsible for the cell activities. A very important step in triggering of innate and adaptive immunity is avoiding the acidification of lysosomes due to the ability of the hydroxychloroquine to damage cellular autophagy (Magagnoli et al., 2020). Antithrombotic activities may be present in hydroxychloroquine. Cytokine release syndrome and endothelial injury may trigger coagulation (Tang et al., 2020). However, the usage of chloroquine and its derivatives is still debatable and need further investigations (Chatre et al., 2018; Costedoat-Chalumeau et al., 2015).

7. Azithromycin

Researchers have discovered that there are synergists effects in the administration of Azithromycin and hydroxychloroquine invitro which may be therapy for COVID-19 (Costedoat-Chalumeau et al., 2015). Azithromycin is folded in the endosomes and has alkalinizing properties like hydroxychloroquine. Interestingly, azithromycin is also a weak base, and also fold in endosomes, with an alkalinizing effect at least equivalent to hydroxychloroquine. Azithromycin has antimicrobial properties and may also possess immunomodulatory activities mostly in respiratory patients. Azithromycin has some effects on signaling pathways such as STAT1 and NFκB. It also exhibits an anti-inflammatory property due to its polarization M2 macrophages (Gensel et al., 2017; Haydar et al., 2019). Due to its anti-inflammatory properties, it may be useful in other respiratory and critical care illness which may be triggered due to cytokine release syndrome and may be useful to combat and ameliorate the illness effectively (Kawamura et al., 2014; Walkey & Wiener, 2012). The administration of azithromycin and hydroxychloroquine need further investigation on its cardiac effects (Garcia-Cremades et al., 2020). ECG, pharmacokinetics, patient previous travel and contact history, fluid and electrolyte status and others are important factors in the management of COVID19 patients (Sapp et al., 2020).

8. Remdesivir and other nucleoside analogues

Remdesivir is a nucleoside analogue which is being explored as a therapy for COVID-19 and still need further investigations (Siegel et al., 2017). It was discovered to be useful for the treatment of some viruses such as Ebola, hemorrhagic fever and Marburg virus (Shereen et al., 2020). Nucleoside analogues includes ribavirin, favipiravir, geldesivir etc. Previously, researchers have investigated the effects of nucleoside analogues as a therapy for coronavirus. It was recently described that remdesivir (GS-5734) inhibits coronavirus invitro. RNA-dependent RNA polymerases (RdRps) is inhibited by remdesivir (Agostini et al., 2018; Gordon et al., 2020; Hillaker et al., 2020; Sheahan et al., 2020). When remdesivir is administered at specific doses and time, it may be effective (Sheahan et al., 2020). It has also been discovered that it may be useful when the administered during critical stage (Hillaker et al., 2020). Researchers have unveiled the potency of remdesivir as an inhibitor of COVID-19 invitro which may be also useful in vivo (Grein et al., 2020; Holshue et al., 2020).

9. Protease Inhibitors

There are various investigations on novel molecules or compounds which may serve as a protease inhibitor, which may be useful in the treatment of COVID19. Different computational biology tools have been utilized to unveils the inhibitory capability of novels compounds such as andrographolides, alkaloids and terpenoids on coronavirus (Enmozhi et al., 2020; Gyebi et al., 2020). Hence, different computational tools can be used to analyze the inhibitory effects of novel compounds such as calotropin and other natural products on the protease of SAR-CoV2 which may be useful as a therapy. ADME prediction is very crucial for the

determination of the pharmacodynamics properties of the novel's compounds (Adsorption, Distribution, Metabolism and Excretion) which may be useful as new drugs. The website which may be utilized for drawing the structure of the drug like molecule is SWISS-ADME meters such as (https://www.swissadme.ch) which can provides some essential parameters such as Medicinal Chemistry (PAINS, Synthetic accessibility, Leadlikeness, Brenk), lipophilicity (Log P0/w, iLOGP, SILICOS-IT, WLOGP, XLOGP3, MLOGP), water solubility- Log S (Ali, ESOL, SILICOS-IT). drug likeness rules (Ghose, Lipinski, Egan, Veber and Muegge) (Daina et al., 2017). Ligand preparation, molecular docking, toxicity prediction and target prediction are very important factors that need to be considered in the discovery of new druglike compounds or molecules (Daina et al., 2017).

10. Cell Death of AT2 Cells in Severe Acute Respiratory Distress Syndrome Coronavirus

Different forms of molecular mechanisms and signaling pathways are related to different types of cell death in viral infections (D. Tang et al., 2020). A form of cell death which depend on caspase 1 and occurs individualistically of other pro-apoptotic caspases which is widely investigated in epithelial cells, triggered majorly by inflammation is referred to as pyroptosis (Bergsbaken et al., 2009; Lamkanfi & Dixit, 2010; Zhu et al., 2018). Pro inflammatory factors such as (IL1, IL8), and HMGB1 (high mobility group box1), DAMP and coagulation factor III, may be released due to over activation of pyroptosis mainly through inflammatory caspase 1 (CASP1) and caspase 11 (CASP11) (CASP4 and CASP5 in humans). Gasdermin D can also activate pyroptosis (Ding et al., 2003; Kayagaki et al., 2015; Shi et al., 2015; Tang et al., 2019). Researchers have investigated the roles of compounds or molecules which can inhibit GSDMD such as disulfiram which has proved to be effective in viral infections (Hu et al., 2018). Hence, the use of pyroptosis associated with canonical and non-canonical to various immune cells and alveolar epithelia cells for COVID19 are interesting for further investigations (Lieberman et al., 2019).

Cell death is pathological, physiological and biochemical process which is of great concerned in human well-being and illnesses. There are different classifications of cell death which includes accidental cell death (ACD) or regulated cell death (RCD). The major types of RCD include apoptosis, pyroptosis, necroptosis, netotic, ferroptosis, entotic, lysosome-dependent, parthanatos, alkaliptosis, autophagy-dependent cell death, and oxeiptosis (Brinkmann et al., 2004; Franko et al., 2000; Overholtzer et al., 2007; Sun et al., 2012). Hence, these may be useful for the treatment of COVID19. Apoptosis, which has the following characteristic features: plasma membrane blebbing, shrinking of the cell, fragmentation of the nucleus, condensation of chromatin, fragmentation of the DNA and finally apoptotic body formation. Autophagy, the distinguishing features are cytoplasmic vacuolization leading to the formation of autophagosome, phagocytosis and degradation by the lysosome. Necrosis, show distinctive morphological changes which include organelle and plasma membrane rupture, culminating in the disposal of cell corpses. Entosis, this describes "cell-in-cell" invasion of a living cell into another living cell, cell engulf and kill another (D'Antiga, 2020; Lai et al., 2020b).

11. Apoptosis

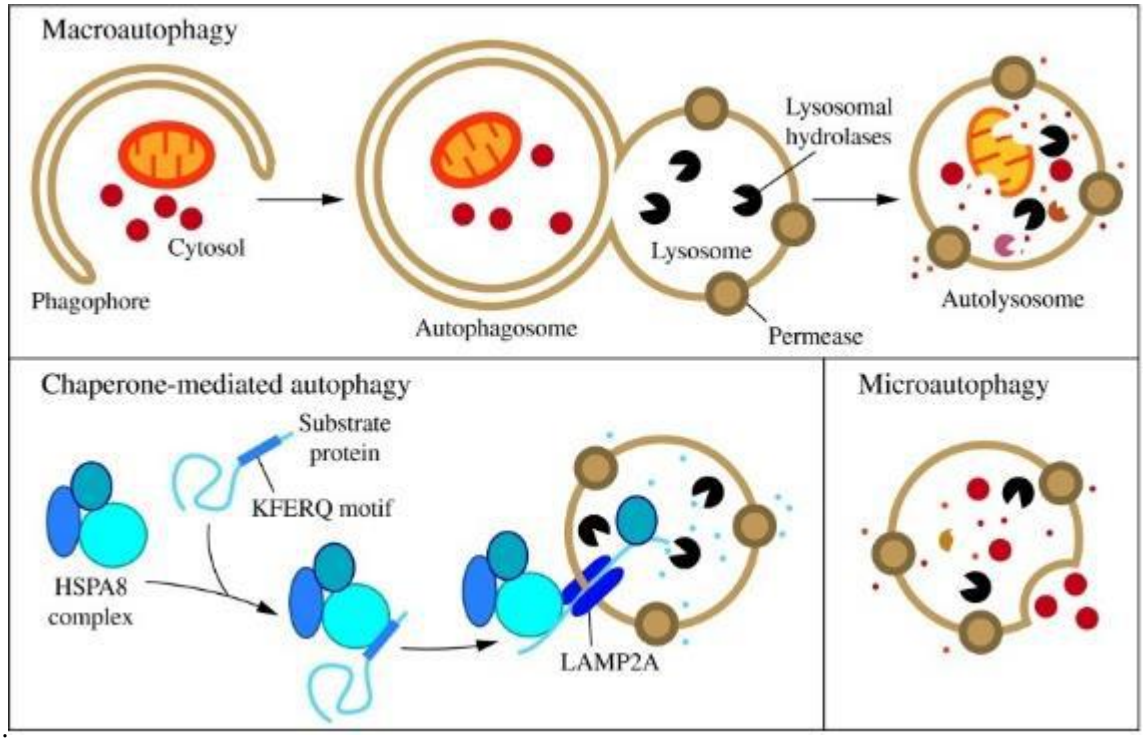
Apoptosis, otherwise referred to as programmed cell death, is a most rapid form of cell death. The key biochemical features of apoptosis are the caspases induced proteolytic cascade (D'Antiga, 2020). There are two major pathways involved; these are extrinsic pathway and intrinsic pathway. The extrinsic pathway is also known as the death receptor pathway, it is triggered by the binding of death ligands to their homologous receptors, example is the tumor necrosis factor-α (TNF-α) and Fas, which subsequently trigger cell death. This is followed by caspases activation and which give rise to apoptosis (D'Antiga, 2020). On the other hand, the intrinsic pathway is also called the mitochondrial pathway. The complex permeability transition pore, which are a group of proteins form a megapore, cell death modulators in the mitochondrion for instance, cytochrome C (Cyto C), intense temperature requirement

protein A2 (HtrA2)/Omi, and second mitochondria-derived activator of caspases/direct inhibitors of apoptosis-binding protein (Smac/Diablo) are therefore released into the cytosol. Cytorome C and apoptosis protease activating factor-1 (Apaf-1) combine to form "the apoptosome", this apoptosome is thereafter instrumental to the downstream cleavage and activation of caspases which finally leads to the dismantling of the cell (Schnabel & Hedrich, 2019).

12. Autophagy

Autophagy can be defined as a natural process of cellular degradation and recycling in which dysfunctional cell constituents are engulfed and removed mechanistically by the lysosome (W. Zhang et al., 2020). A significant amount of cellular content can be targeted for degradation in the lysosome by autophagosome. Autophagy is an important process in eukaryotic cells and it play a very significant role in the ontogenesis of multicellular organism (Cecconi & Levine, 2008). Autophagy primarily has three types: microautophagy, macroautophagy and chaperone-mediated autophagy. In macroautophagy, the sequestering vesicle (autophagosome) is formed newly, and isolates targeted cytoplasmic constituents. These will combine with lysosomes, and lead to the dismantling of their content, for subsequent recycling (Klionsky, 2005). The remaining two types employ completely dissimilar targeting approach and are likely not capable of bulk degradation of intracellular components. In literature, autophagy most times refers to macroautophagy. All the three types of autophagy mentioned have very important role in cellular metabolic process (Rabinowitz & White, 2010) resistance to pathogen and several other cellular processes including programmed cell death (Ouyang et al., 2012).

Figure 2: Types of autophagy in mammalian cells. Macroautophagy, Chaperone-mediated autophagy and Microautophagy. Macroautophagy use *new* formation of cytosolic double-membrane vesicles, autophagosomes, to sequester and transport cargo to the lysosome. Chaperone-mediated autophagy transports unfolded proteins directly across the lysosomal membrane. Microautophagy involves the direct uptake of cargo through invagination of the lysosomal membrane.



Source: Parzych et al. (2014).

13. Necrosis

Necrosis or necrotic cell death has characteristic features of cytoplasmic and organelle inflammation, which lead to the disruption of cell membrane integrity, and subsequently to the dismantling of the contents of the cell into the extracellular space (Duprez et al., 2009). An insult may initiate either apoptosis or necrosis, the main pathway initiated mostly depends on the type and severity of the insult, also the type of cell (Duprez et al., 2009). Apoptosis is pivotal for the remodelling of tissues during embryogenesis, though necrotic cell death can replace apoptosis in some cases to help get rid of undesirable cells. Necrotic cell death is also involved in the activation-induced cell death (AICD) of T lymphocytes, this is mostly directed by Fas and it constitutes a pivotal mechanism for the decline in the number of T-cells after immune response (Holler et al., 2000). Necrosis is most times always observed alongside apoptosis, which presupposes that it acts as a backup mechanism and not as a sole cell death pathway.

14. Entosis

Entosis can simply be defined as the takeover of a living cell by another similar living cell, the takeover involves adhesion molecules, actin cytoskeleton and expenditure of energy (Mlynarczuk-Bialy et al., 2020). The epithelial cells and cancer of the epithelial both have characteristic entosis, and it is initiated by cells detachment from the basement membrane. A characteristic cell-in-cell complex are formed due to entosis (Mackay & Muller, 2019). After being overwhelmed, entotic cells can be destroyed via regulated cell death in the entosome, through a specialized autophagy-related process, known as LC3-associated phagocytosis (Florey, Kim, Sandoval, Haynes, & Overholtzer, 2011). The mechanism by which the inner entotic cell enters into the host cell involve the activation of Rho proteins, adhesion bonds formation and actomyosin filaments (Zeng, Zeng, Dong, Liu, & Xing, 2020). After the host cell has been invaded, the invading cell is then surrounded by a double membrane of the entotic vacuole (Mlynarczuk-Bialy et al., 2020). The formation of the entotic vacuole distinguishes entosis from cell cannibalism, in which the phagocytosed cell is surrounded by a thin double-membrane space, and subsequent degradation of the inner membrane (Overholtzer et al., 2007). Both cells during entosis can die, the inner cell alone can die, the outer cell alone can die and both cells can survive (Hayashi et al., 2020).

15. The AT2 Infection by SARS-CoV-2 Activates Cellular Apoptosis

Coronavirus disease 2019 (COVID-19) infection begin in the proximal airways and sometime fatal symptoms have been shown to be orchestrated by infection of the alveolar type 2 (AT2) cells of the distal lung (Mulay et al., 2021). Evolving literatures suggest that the cells of the proximal airways and the alveolar type 2 (AT2) cells of the gas exchange region of the distal lung are targeted by SARS-CoV-2 (Hoffmann et al., 2020b). The infection of the AT2 cells directs acute respiratory distress syndrome (ARDS) noticed in the critical cases of COVID-19 infection (Heinen et al., 2021). An important pathway triggered in SARS-CoV2-infected alveolar cultures is the protein ubiquitination pathway (Heinen et al., 2021). Transcripts for genes with their products acting either as chaperons, co-chaperons or that sensitize cells to apoptosis were seen to be significantly up regulated (Heinen et al., 2021). A significant upregulation of cellular stress associated genes that interrelate with vital elements of apoptotic pathways was noticed with the upregulation of other genes related to apoptosis, such as CASP6 and BCL2 in cultures infected with SARS-CoV-2 (Heinen et al., 2021). It was reported that a fraction of the apoptotic cells was infected, implying that SARS-CoV-2 infection caused a direct and indirect cytopathic effect on the alveolar epithelial cell. The SARS-CoV-2-elicited apoptosis of surrounding uninfected epithelial cells demonstrate the potential for non-cell-autonomous effects of viral infection on alveolar epithelial wholeness. It was therefore

suggested that SARS-CoV-2 infection activates both cell-autonomous and non-cell-autonomous apoptosis which may support alveolar injury (Heinen et al., 2021). However, more investigations are required.

Two types of epithelial cells exist, that line the distal alveolar, these include alveolar epithelial type 1 (AT1) and alveolar epithelial type 2 (AT2). Squamous AT1 cells produce a specific surface for gas exchange, while cuboidal AT2 cells produce pulmonary surfactant that block alveolar disintegration during expiration (Heinen et al., 2021). Alveolar epithelium of the lungs comprises of a monolayer of alveolar type 1 (AT1) cells and AT2 cells, linked with a tight junction to control the flow of alveolar fluid and ions across the epithelial transporters. The surfactant produced by AT2 facilitates the alveolus expansion along with surface tension reduction. AT2 cells and resident alveolar macrophages are the first set of cells to be infected by SARS-CoV-2 in the lung and the entry of the virus into the host cell is dependent on a homotrimeric S glycoprotein, which has affinity for the cell surface receptor of 10–20 times more than that of SARS (Najafi-Ghalehlou et al., 2021). AT2 cells play important roles as facultative progenitors, contribute to epithelial maintenance and also fulfilling specialized functions, which include the production of surfactant (Barkauskas et al., 2013). AT2 cells infected by SARS-CoV-2 showed remarkable up regulation of heat shock proteins and chaperon-inducing cellular apoptosis (144).

16. Comorbidities

Due to previous outbreak of coronavirus, it has been discovered that comorbidities (metabolic disorder, diabetics, lung cancer, asthma, heart failure, tuberculosis, kidney diseases etc), old age, obesity, COPD, ARDS, old age are some of the major risk factors that may result to COVID-19 (Lai et al., 2020a). Precisely in USA, France China, Africa and Italy, immune modulation or suppression was not discovered as a key factor for poor prognosis. However, low immunity in patients could expose such a patient to COVID-19 infections and cause the multiplication of the disease. Hence, as COVID-19 is linked with lymphopenia, it indicates that COVID-19 patients may be exposed to other infections which may require other treatment strategies when diagnosed. Actually, immunomodulatory drugs may have some inhibitory effects on viral infections.

17. Conclusions

The use of computational tools in the discovery of novel drugs is very important and useful to discover new therapy for COVID19. Interleukin 1 Receptor, Interleukin 1, Nuclear factor kappa-light chain enhancer of B cells pathway and Janus kinase pathway are interesting pathway which required further investigation to unravel its molecular mechanism when antioxidant, small molecules and nanoparticles are utilized to inhibit the pathway to prevent COVID19. Hence, the utilization of Alveolar type 2 progenitor cells may be considered as a therapeutic target for the treatment of COVID-19 patients. The use of pyroptosis associated with canonical and non-canonical to various immune cells and alveolar epithelia cells may also serve as therapy for the treatment of COVID-19. Other forms of cell death such as NETosis, ferroptosis, parthanatos, alkaliptosis, necroptosis, autophagy-dependent cell death, and oxeiptosis may be useful for the treatment of COVID-19.

Hence it is of great significance to conduct further investigations on the cell death, AT2 cells, IL1, IL1-R, JNK and NFkB signalling pathways which may serve as a therapeutic target for COVID-19

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Competing interests

The authors declare that they have no competing interests.

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