Purinergic P2X7 Receptor as a Potential Targeted Therapy for COVID-19-associated Lung Cancer Progression

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Abstract

Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection is a serious threat to lung cancer patients. Hereby, we hypothesize that Coronavirus disease 2019 (COVID-19) may contribute to lung cancer progression by increasing extracellular adenosine triphosphate (ATP) levels and hyperactivating the purinergic P2X purinoceptor 7 receptor (P2X7R). Hyperactivation of P2X7R by increased extracellular ATP may stimulate multiple signaling pathways and factors such as NLRP3 inflammasome; as a result, interleukin (IL)-1β, and IL-18 pro-inflammatory cytokines are released, JNK, Rho kinase, HMGB1-RAGE, PI3K/AKT, hypoxia-inducible factor-1 alpha (HIF-1α), and ERK. NLRP3 activation may play a pivotal role in fatal cytokine storm in critically ill patients with COVID-19 and tumor progression in patients with lung cancer. Consequently, inhibiting these signaling pathways may deviate immune responses toward anti-tumoral responses, and suppress lung cancer progression and cytokine storms. Therefore, targeting P2X7R by means of oxidized ATP and anti-P2X7 monoclonal antibodies may provide promising therapeutic approaches to prevent lung cancer progression in COVID-19 patients; however, no clinical trials have yet been conducted, and their clinical efficacy remains to be elucidated.

Introduction

COVID-19, which emerged in Dec 2019, has caused a concerning epidemic worldwide by SARS-CoV-2 [1-5]. Glycoprotein S or spike protein is the main contributor to virus entry into the host cells and its infection through binding to angiotensin-converting enzyme 2 (ACE2) receptor [6]. This interaction leads to activation of the transmembrane protease/serine subfamily member 2 (TMPRSS2), a human protease primarily located in the airways and alveolar cell membranes, thereby facilitating the virus entry via supporting the protein S and ACE2 cleavage [1]. At the moment, several researchers/scientists are investigating all possible pathways affected by SARS-CoV-2 infection, particularly in susceptible individuals, such as cancer patients, to develop a rapid treatment and decrease their mortality [7-11]. It has been suggested that COVID-19 can lead to multiple cancer progression and chemo-resistance [1,8-13]. Recently we discussed the P2X7 receptor,

as a cation channel highly expressed in the central nervous system (CNS) and lungs that is activated at high concentrations of adenosine triphosphate (ATP) [1,14]. Long-term activation of the P2X7 receptor leads to cell death and increased ATP release into the extracellular environment [1]. On the other hand, a study by Kong et al. showed that COVID-19 patients with lung cancer are more susceptible to severe complications of COVID-19 than patients without cancer [15]. Due to the fact that lung cancer is one of the leading causes of cancer-related mortality [16,17], lung cancer patients must be considered a vulnerable group to COVID-19-related complications and death. Hereby, we hypothesize that hyperactivation of the P2X7 receptor (P2X7R) by COVID-19 not only may predispose lung cancer patients to experience a severe course of COVID-19 but also may contribute to cancer progression in these patients.

COVID-19 and P2X7 Receptor Hyperactivation and Downstream Signaling Pathways

Purinergic P2X7R is a gated ion channel with an ATP ligand. Multiple tissues (e.g., lung, CNS, etc.) and immune cells (e.g., tumor-associated macrophage (TAM), etc.) express P2X7R, which activated P2X7R has been demonstrated to be involved in physiological and pathological processes such as tumor cell growth, inducing apoptosis, or stimulating cell proliferation [1,18,19]. According to recent investigations, P2X7R is overexpressed in lung cancer and may strongly underlie lung cancer progression [18]. The bronchoalveolar lavage fluid (BALF) of patients with acute respiratory distress syndrome (ARDS) also contains elevated ATP levels. Elevated levels of extracellular ATP induced by SARS-CoV-2 infection may induce P2X7 receptor hyperactivity [1,20-24]. A central role of this receptor in inflammation is the stimulation of NACHT, LRR, and PYD domain-containing protein 3 (NLRP3) inflammasome, resulting in caspase-1 activation and IL-1β and IL-18 release. ROS production is triggered by the P2X7 receptor [25]. In severe inflammation, its increased activation may decrease lymphocyte function by impairing mitochondrial function, as has been seen in monocytes in sepsis [26]. In response to the activation of P2X7 receptors, MHC-I expression is down-regulated and IL-6 is released simultaneously [25]. It can also activate JNK and Rho kinase as well as the high mobility group box 1- receptor for advanced glycation end products (HMGB1-RAGE) pathway [27-29]. Researchers found that serum HMGB1 levels were related to the severity of pathogen-induced tissue damage as well as excessive cytokine storms [30,31]. In addition to ACE2, HMGB1 was recently shown to bind to the RNA of SARS-CoV-2, carrying it into the cytoplasm when attached to the RAGE-lysosomal pathway [32].

Lung Cancer and P2X7 Receptor Hyperactivation

As SARS-CoV-2 primarily affects lung tissue and leads to severe acute respiratory syndrome, individuals with respiratory disorders, such as lung cancer, may be more susceptible to COVID-19 and should be given extra attention [33,34]. In this line, previous studies indicated that P2X7R could cause carcinogenesis, progression, survival, and metastasis of lung cancer cells through its up-regulation and activation of numerous intracellular signaling pathways such as JNK, Rho, HMGB1, and Epithelial-Mesenchymal Transition (EMT) pathways in bronchoalveolar cells [35,36]. In normal cells, the P2X7 receptor has moderate activity because of its smooth affinity for low concentrations of ATP. Increased aerobic glycolysis in cancerous cells will result in hyper-activated mitochondria leading to Ca^{2+} release from the endoplasmic reticulum and subsequently, high levels of ATP. A high concentration of ATP can promote lung cancer cells' progression and survival through the activation of P2X7 receptor [35]. Also, the P2X7R activation itself can increase the cytosolic Ca^{2+} and ratio of Bcl-2/Bax ratio to promote cancer cell survival [36]. Moreover, it induces several intracellular growth-promoting pathways, such as NFATc1, JNK, Phosphoinositide 3-kinase (PI3K)/AKT, Hypoxia-inducible factor 1-alpha (HIF-1α), and ERK in cancerous cells [14,37]. Besides that, high levels of vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMP) mediated by activated P2X7R elevate the proliferation and metastasis rate and decrease the apoptosis of cancerous lung cells [15,38]. This observation can be proved by the study of Takai et al. who demonstrated that transforming growth factor-β1 (TGF-β1) activates the P2X7Rs through ATP release and subsequently, accelerates lung cancer cell metastasis via actin remodeling. Then, it was indicated that cell metastasis and actin remodeling are related to mitogen-activated protein kinases, such as JNK, and Rho kinase, respectively [39].

Conclusion

Hyperactivation of P2X7R is involved in either inducing apoptosis or stimulating cell proliferation in many tissues, especially lung cancer cells. SARS-CoV-2 may hyperactivate P2X7R by increasing extracellular ATP levels. It can activate multiple signaling pathways, including NLRP3 (inflammasome), JNK, Rho kinase, HMGB1-RAGE, PI3K/AKT, HIF-1α, and ERK [1,20,22-24,35]. In this regard, IL-1β and IL-18 pro-inflammatory cytokines are released after NLRP3 inflammasome activation. Therefore, NLRP3 activation may play a pivotal role in fatal cytokine storm in critically ill patients with COVID-19 and tumor progression in patients with lung cancer. Consequently, inhibition of this signaling pathway may deviate immune responses toward anti-tumoral responses and suppress cytokine storm. In light of this hypothesis that purinergic P2X7R may facilitate the progression of lung cancer, P2X7R antagonists and inhibitors (e.g. ATP Oxidized, JNJ47965567, AZ11645373, GW791343, Brilliant Blue G (BBG), KN-62 and KN-04, A740003 and A438079, CE-224535, anti-P2X7 monoclonal antibodies, and natural compounds such as Rhein, Emodin, Teniposide, and Baicalein) may inhibit cancer progression in
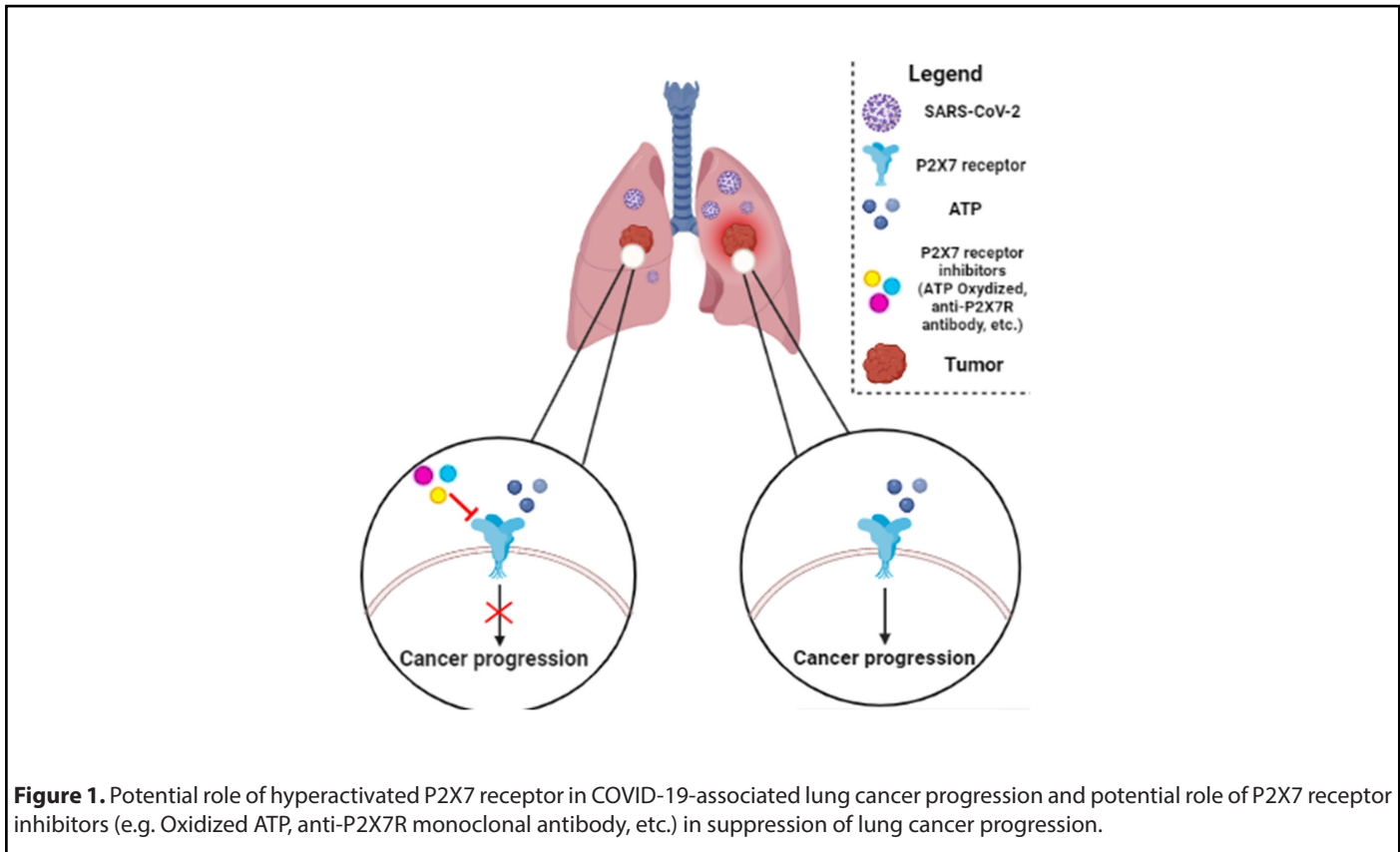
Figure 1. Potential role of hyperactivated P2X7 receptor in COVID-19-associated lung cancer progression and potential role of P2X7 receptor inhibitors (e.g. Oxidized ATP, anti-P2X7R monoclonal antibody, etc.) in suppression of lung cancer progression.

lung cancer patients who are afflicted with COVID-19 (**Figure 1**) [40]. This is because of several pre-clinical trials of them. For instance, oxidized ATP was utilized to target P2X7R in an *in vivo* mouse model of islet allograft dismissal and was shown to safeguard islet unites [40,41]. Also, A438079 has been shown to reduce inflammation in an *in vivo* mouse model of salivary gland exocrinopathy [42]. However, no clinical trials have yet been conducted and their clinical efficacy remains unknown.

Abbreviation

P2X7R: P2X7 Receptor; CNS: Central Nervous System; NLRP3: PYD domain-containing protein 3; EMT: Epithelial-Mesenchymal Transition; ATP: adenosine triphosphate; HIF-1α: Hypoxia-Inducible Factor 1-alpha

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Authors' Contributions

H.Z conceived the study and designed the headings. H.Z, A.A, M.N-A, A.N, and F.S wrote the manuscript text. H.Z created the figure. H.Z, F.S, and M.N-A, edited the manuscript for important intellectual content. M.N-A, H.Z, and A.N revised the manuscript. F.S and M.P supervised the study. All authors read and approved the final manuscript.

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Declarations

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Not applicable.

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Competing interests

The authors declare no conflicts of interest.

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