Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review Article

PAK1-blockers: Potential Therapeutics against COVID-19☆

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ABSTRACT

PAK1 (RAC/CDC42-activated kinase 1) is the major "pathogenic" kinase whose abnormal activation causes a wide variety of diseases/disorders including cancers, inflammation, malaria and pandemic viral infection including influenza, HIV and COVID-19. Since Louis Pasteur who developed a vaccine against rabies in 1885, in general a series of "specific" vaccines have been used for treatment of viral infection, mainly because the majority of pre-existing antibiotics are either anti-bacterial or anti-fungal, thereby being ineffective against viruses in general. However, it takes 12–18 months till the effective vaccine becomes available. Until then ventilator (O_2 supplier) would be the most common tool for saving the life of COVID-19 patients. Thus, as alternative potentially more direct "broad-spectrum" signalling mechanism–based COVID-19 therapeutics, several natural and synthetic PAK1-blockers such as propolis, melatonin, ciclesonide, hydroxy chloroquine (HQ), ivermection, and ketorolac, which are readily available in the market, are introduced here.

Contents

1. Introduction

Like Polio, HIV, Ebola and Flu viruses, the currently pandemic virus coined COVID-19 is among RNA virus family called "corona" [1,2]. Since RNA viruses need their RNA-dependent RNA polymerase (RdRP) for their replication, in theory, COVID-19 pandemic could be treated effectively by a series of RdRP inhibitors such as Remdesivir which is an ATP antagonist and originally developed in 2019 by Gilead Sciences in California for the treatment of Flu and Ebola viruses [1]. However, ATP antagonists in general could potentially inhibit many other ATP-dependent enzymes such as ATPases, protein kinases, and Chaperons, and therefore could cause a number of side effects, depending on their doses, as "conventional" anti-cancer

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chemos (DNA/RNA poisons). Thus, ideally, far more selective chemical drugs, which target a specific "host" enzyme essential for viral infection, but not for normal physiology of hosts, would be desirable for the COVID-19 treatment as well. Among such target enzymes is the major "pathogenic" kinase PAK1 in hosts that is essential for malaria and viral infection in general [3].

Mammalian family kinases called PAKs (RAC/CDC42-activated kinases) were cloned more than 25 years ago. Among them PAK1 is the major "pathogenic" kinase whose abnormal activation is responsible for a wide variety of diseases such as cancers, inflammation, viral infection, malaria, immuno-suppression, ageing, and so on [3]. Among PAK1-blockers, caffeic acid (CA) and its ester (caffeic acid phenethyl ester = CAPE) in a bee-product called "propolis" were the first natural ingredients that were shown to inhibit RAC, which activates directly PAK1 [4]. Interestingly in 2005, an old anti-malaria drug "Chloroquine" (CQ) was also shown to suppress SARS/ coronavirus infection in cell culture with IC_{50} around 1 μM [5], although the precise molecular mechanism underlying its anti-viral activity remains unknown till recently. The anti-coronaviral effect of CQ and Remdesivir (IC_{50} around 1 μM of each) was recently confirmed *in vitro* by a team at Chinese Academy of Sciences as well: https://www.nature.com/articles/s41422-020-0282-0/

In 2016, a Korean team found that the CQ up-regulates p21 (a CDK inhibitor) whose expression is suppressed by PAK1 [3,6]. More recently, a tumor-suppressing phosphatase called PTEN, that inactivates PAK1, was shown to suppresse the coronavirus-induced LLC2-dependent fibrosis (lung inflammation) [7]. Further-more, expression of LLC2 depends on the coronavirus receptor (called ACE2 = Angiotensin-converting enzyme 2) -induced CK2/RAS-PAK1-RAF-AP1 signaling pathway [[8], Fig. 1]. These observations altogether clearly indicate the PAK1-dependency of coronaviral pathogenesis, and strongly suggest, if not proven clinically as yet, that PAK1-blockers in general could be useful for the treatment of current "pandemic" COVID-19 infection outbroken from Wohan in China since the end of 2019, which infected over 2,000,000 people world-wide, and whose death toll has reached over 120,000 people (death rate around 6%) till now: https://corona.help/

In addition, PAK1 is normally responsible for the suppression of immune system in hosts [9]. Thus, like viral vaccine, these PAK1-blockers could boost the immune system for the production of antibody against this virus as well (see Fig. 2).

2. Natural PAK1-blockers

A specific vaccine (based on Louis Pasteur's approach against rabies virus in 1885) is an effective cure for each viral infection. However, it takes at least 12 months (and realistically 18 months) to prepare its vaccine (according to the WHO). Until then the majority of these coronavirus victims would perish. Thus, here as "alternative" or "unconventional" fast-track broad-spectrum therapeutics of coronaviral infection, several natural or synthetic PAK1-blockers readily available in the market are introduced.

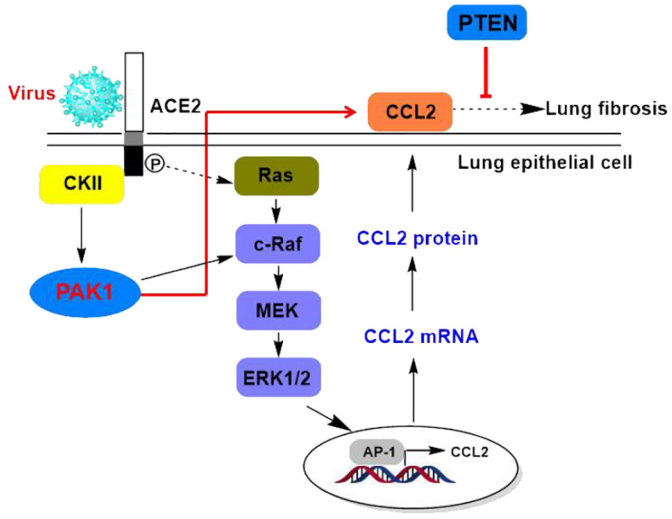

Fig. 1. PTEN, a PAK1-blocker, interferes with coronavirus –induced PAK1-dependent signalling pathway leading to lung fibrosis.

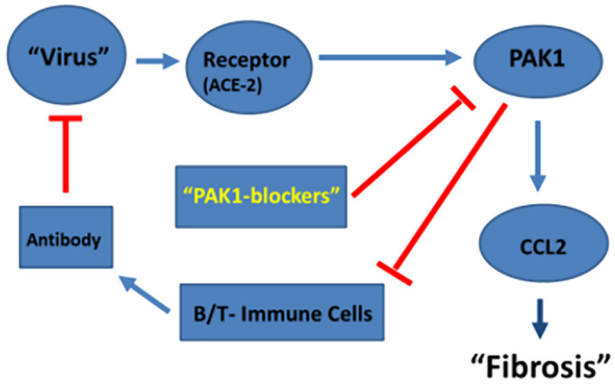

Fig. 2. "Double" blows of PAK1-blockers against viral infection

2.1. The bee product "propolis"

Among them the bee product called "propolis" is the most popular and ancient as well. It has been used as a traditional medicine for more than 4 thousand years since the ancient Egyptian era. The father of medicine in ancient Greece, Hippocrates, was the first to coin this bee product (an alcohol-extract of beehives) "propolis" ("pro" for protection, and "polis" for beehive or city). Originally honey-bees extract something from young buds of trees such as poplar and willow and blend the extract with their saliva to make the hexagonal beehive to protect their larva from various pathogens. Thus, propolis is a "herbal" medicine prepared by bees. It is both anti-bacterial and anti-viral. It is well known to be used as a mixture of antibiotics for preparing mummies of deceased royal families to be stored under pyramids.

In modern era, propolis was recognized as an anti-cancer medicine in late 1980s by a team at Columbia University in NYC [10]. The major anti-cancer ingredient in Egyptian or Israeli propolis turned out to be CAPE, an ester of caffeic acid [10] which was later known to down-regulate RAC, thereby inactivating PAK1 [4]. Interestingly, however, the anti-cancer ingredients in propolis vary from one product to another, depending on where bees harvest the extract. The major anti-cancer ingredient in Brazilian green propolis is artepillin C (ARC), whereas those in subtropical propolis from Okinawa or Taiwan are polyphenols called Nymphaeols which directly inhibit PAK1 [11]. What is common to all propolis is that they contain PAK1-blockers without any exception.

Since PAK1 is responsible not only for cancers, but also for infection with a wide variety of viruses such as influenza, HIV, pappiloma virus and SARS/coronal virus in generally, as well as immune-suppression [3,9], propolis would be useful for blocking coronavirus-induced fibrosis of lungs and stimulating the immune system as well.

However, the potency of propolis varies from one product to another, depending on both chemical nature of ingredients and their content. Among propolis in the market, so far the CAPE-based New Zealand propolis called "Bio 30" (alcohol-free liquid, 25%) is the most potent [3]. Its recommended daily dose is 1 ml (250 mg) /10 kg (body weight). Unfortunately, however, its stock is rather limited for COVID-19 patients, because it has been saved mainly for therapy of deadly pancreatic cancers and the life-long treatment of a rare genetic brain tumor called NF (neurofibromatosis types 1 and 2). Furthermore, the cell-permeability of both caffeic acid (CA) and ARC is rather poor, mainly due to their COOH moiety. Thus, a few years ago, via Click Chemistry (CC), we managed to boost their cell-permeability by making their 1,2,3-triazolyl esters (called 15A and 15C),

which are 100 and over 400 times more potent than ARC and CA, respectively [12].

2.2. Pineal hormone "melatonin"

Melatonin, a serotonin derivative from pineal glands was first recognized as an anti-melanogenic hormone by Aaron Lerner at Yale University in 1953 [13]. A few years ago, we found that melanogenesis in fact depends on PAK1 [14]. Melatonin shares a wide variety of other anti-PAK1 activities such as anti-cancer, immune stimulative, anti-infectious, anti-inflammatory, analgestic, sleepy etc. Thus, it is almost certain that melatonin, a popular sleeping pill for jet-lag treatment, could be very useful for the treatment of coronaviral infection as well. In fact, the world-leading expert in melatonin, Russel Reiter, recently high-lighted melatonin as an alternative or adjuvant COVID-19 therapeutic: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102583/

2.3. Glucocorticoid hormone "Ciclesonide"

Ciclesonide is used to treat inflammatory disesaes such as asthma and allergic rhinitis. It is marketed under the brand names Alvesco for asthma etc. It was patented in 1990 and approved for adults and children 12 and over by the FDA in 2006. Regarding the molecular mechanism underlying its anti-inflammatory effect, it is most likely that this hormone blocks PAK1, mainly for following reasons: (i) first of all, inflammation in general requires PAK1 [3], and in PAK1-null mutant of mice no inflammation takes place [15], (ii) ciclesonide (10 mg/kg/day) almost completely suppresses the PAK1-dependent growth of lung cancer (A541 cell line) xenografts in immune-deficient mice as well [16], and (iii) this hormone was recently shown to block both PAK1-dependent replication and pathogenesis (fibrosis = lung inflammation) blocks COVID-19 pathogenesis clinically [2]: https://writening.net/page?FC3QPm

2.4. Triptolide from thunder god vine and its water-solulble derivative

A herbal triterpene or steroid called "Triptolide "from thunder god vine, a Chinese traditional medicine, was also found to inactivate RAC, thereby blocking PAK1 [12]. Interestingly, more than a decade ago, triptolide was found to suppress virus production during dengue virus infection of human lungs by blocking PAK1 signaling pathway [17]. However, its water-solubility is rather poor. Thus, several years ago, a team at University of Minnesota led by Gunda George, a German organic chemist, phosphorylated OH group at position 14 of Triptolide to boost its water-solubility over 3000 times [18]. The resultant phosphatase-sensitive prodrug of triptolide called "Minnelide" is currently in clinical trials for cancers. Thus, both Triptolide and Minnelide would be potentially useful for treating coronaviral infection as well.

2.5. Ivermectin from soil bacterium (Streptomyces avermitilis)

Around 1975 Avermectin (a precursor of Ivermectin) was discovered from a soil bacterium by a team led by Satoshi Omura at Kitasato Institute in Tokyo, but it causes a side effect. Thus, to reduce its side effect, a Merck team led by William Campbell chemically reduced it to develop "Ivermectin" (dihydro-Avermectin), sharing the Nobel prize in 2015. It was eventually marketed by Merck into medical use in 1981. It has been used to treat many types of parasite infestations including head lice, scabies, river blindness (onchocerciasis), etc. Three decades after its discovery, it was shown by a Russian team to suppress the growth of cancers as well, and eventually we found that inactivation of PAK1 is the major molecular mechanism underlying its anti-cancer action [19]. Thus, it could potentially serve as an alternative (and inexpensive) therapeutic to eradicate the PAK1-dependent coronaviral infection as well. In fact, very recently Ivermectin was proven to block the COVID-19 infection in Vero cell culture with IC_{50} around 2.5 μM: https://www.sciencedirect.com/science/article/pii/S0166354220302011

Very interestingly, the IC_{50} against COVID-19 is basically same as IC_{50} against the PAK1-dependent growth of cancer cells [19], strongly suggesting, if not proven as yet, the PAK1-dependency of COVID-19 replication.

2.6. Artemisinin: anti-malaria from an old Chinese medical herb

In 2015 a Chinese scientist, Youyou Tu at Chinese Academy of Science, shared a Nobel prize in medicine for her discovery of anti-malaria compound called "Artemisinin" (AM). This compound was originally isolated by her "523" project team from the plant *Artemisia annua*, sweet wormwood, a herb employed in Chinese traditional medicine around 1972. Although the precise molecular mechanism underlying its anti-malaria and anti-viral action still remains rather unclear, the target is not the pathogens (*Plasmodium falciparum or virus*) themselves, but some thing in host cells, most likely PAK1 or its up-stream essential for both malaria and viral infection [20,21], based on the following observations: (i) the AM suppresses both RAS (up-stream of PAK1) and RAF (down-stream of both RAS and PAK1) in T-cells [3,22], and (ii) the dihydro derivative of AM suppresses the growth of pancreatic cancer cells by up-regulation of p21 (a CDK inhibitor) whose expression is suppressed by PAK1 [3,20].

2.7. Extract of Chinese (Sichuan) Pepper (Hua Jiao)

Chinese reddish peppercorns from Sichuan Province called "Hua Jiao" are among traditional spices used for the preparation of an old spicy Chinese cuisine called "Marbo-beancurd". In 2006, we found that 70% ethanol or hot (above 45 °C) water extract of Hua Jiao inhibits PAK1 with IC_{50} around 10 μg/ml, and thereby suppressing cyclin D1 expression in both NF1-deficient triple negative breast cancer (MDA-MB-231) and MPNST cell lines in which PAK1-is abnormally activated. Just like the propolis "Bio 30", this reddish extract (110 mg/kg, twice a week) strongly suppresses the growth of these cancer xenografts in mice [23]. Thus, it is most likely that daily drinking of an inexpensive "Hua Jiao" tea (extract) could potentially contribute to both prevention and cure of COVID-19 infection, although its major PAK1-blocking ingredient has not been chemically identified as yet. For detail of health benefits from this peppercorns (promoting immune system, suppressing inflammation etc), click the following website: https://www.organicfacts.net/sichuan-pepper.html

2.8. FK228 (Istodax): Blocking HDAC-PAK1 pathway

A ring peptide called FK228 was isolated from a soil bacterium by a team of Fujisawa Pharm around 1995. It strongly inhibits the growth of so-called RAS cancers such as pancreatic and colon cancers which carry oncogenic mutant of Ki-RAS [24]. A few years later it was found to inhibit directly HDAC (histone deacetylase) with IC_{50} around 1 nM [24]. Around 2005, we found that FK228 inactivates PAK1 in several cancer cells including Tamoxiphen-resistant breast cancers and NF1-deficient MPNST (malignant peripheral nerve sheath tumor) with IC_{50} below 1 nM in cell culture, and suppresses their growth with IC_{50} below 2.5 mg /kg (i.p., twice a week) in xenografts in mice [25]. Around 2009, it was approved by FDA for the treatment of a rare cancer called Cutaneous T-cell Lymphoma (CTCL) etc., and sold by Celgene under the brand name "Istodax". Thus, it is most likely useful for the therapy of COVID-19 infection as well.

3. Synthetic PAK1-blockers

3.1. Anti-malaria drugs: Chloroquine (CQ), and Hydroxychloroquine (HQ)

As previously described, CQ suppresses SARS/coronal viral infection in cell culture with IC_{50} around 1 μM [5], by upregulating p21 whose expression is suppressed by PAK1 [3,6]. However, due to CQ-resistance, CQ is no longer used for malaria treatment, Instead, its derivative called Hydroxychloroquine (7-chloro-4(4-(N-ethyl-N-B-hydroxyethylamino)-1-methylbutylamino)-quinoline diphosphate (HQ) has been more widely used for malaria treatment. Thus, shortly after one of us (HM) urged both

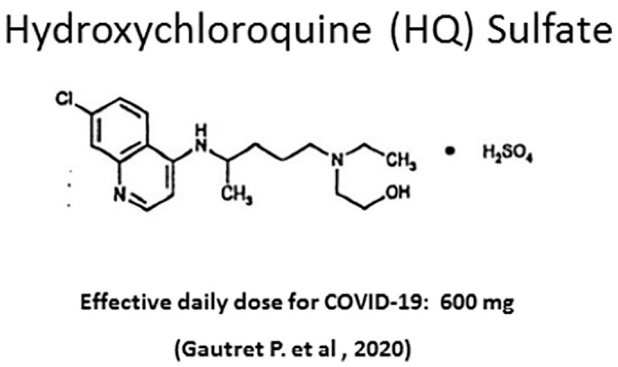

Fig. 3. Effective daily dose for COVID-19: 600mg.

the White House and NIH to use a series of PAK1 blockers including HQ for the treatment of coronaviral infection, FDA quickly approved to use HQ or CQ for clinical trials for COVID-19 patients in NY City, the hottest-bed of COVID-19 in US. According to a French team's clinical trial for 30–40 COVID-19 patients, the effective daily dose of HQ was found to be around 600 mg [[26], see Fig. 3]. Very interestingly, the combination of HQ and another old anti-malaria drug called Azithromycin (AZ) was far more effective than HQ alone clinically [26]. AZ is a macrolide discovered 1980 by Pliva and approved for medical use in 1988. In 2017, AZ was found by a Chinese team at Wuhan to block VEGF/PAK1-dependent angiogenesis with IC_{50} below 5 μM [27], strongly suggesting that AZ is also a PAK1-blocker.

3.2. Ketorolac: an old pain-killer

An old pain-killer called "Toradol" is a racemic (1:1) mixture of S- and R-forms of ketorolac. Since S-form directly inhibits COX-2 which is essential for synthesis of prostaglandin, it has been used as a pain-killer. However, a few years ago, R-form was found to down-regulate RAC, thereby inactivating PAK1 [28]. Thus, "Toradol" also could be used for the treatment of PAK1-dependent coronaviral infection. However, due to its COOH moiety, its cell-permeability is rather poor (with IC_{50} around 13 μM against A549 lung cancer cell line). Thus, via Click Chemistry (CC), we have boosted its cell-permeability over 500 times (with IC_{50} around 5–24 nM against B15F10 melanoma and A549 lung cancer cells, respectively) [29]. The resultant potent PAK1-blocker, called 1,2,3-triazolyl ester of Ketorolac (15 K), suppresses both growth and metastasis of chemo-resistant human pancreatic cancer xenogrfats in mice with IC_{50} below 0.1 mg/kg/day, and causes no side effect even at 5 mg/kg/day [30]. Thus, 15 K could be used not only for pancreatic cancer therapy, but also for therapy of infectious diseases caused by coronavirus (COVID-19) and many other deadly viruses in the future.

3.3. Vitamin D3 and its derivative (MART-10)

The most widely known pharmacological activity of Vitamin D3 is calcemic, i.e., stimulating the absorption of calcium into bone tissues. However, around late 1980s, a team in Melbourne found that Vitamin D3 can suppress the growth of cancers in mice fed with calcium-less diet [31]. However, clinically therapy of cancers with Vitamin D3 has never been successful. The main reason for its clinical failure is that Vitamin D3 is inactivated by an enzyme called CYP24 which hydroxylates at position 24 of Vitamin D3 in human body.

Thus, around a decade ago, a Japanese group led by Atsushi Kittaka at Teikyo University in Tokyo developed a derivative called "MART-10" which is very resistant to CYP24 and clearly less calcemic [32]. The "MART-10" is 1000 times more effective than Vitamin D3 in human breast and pancreatic cancers [32]. Interestingly, a few years ago, a German group at Tuebingen University found that Vitamin D3 down-regulates RAC, thereby inactivating PAK1 and leading to depolymerization of actin filaments [33]. Independently MART-10 was also found to induce the depolymerization of actin in cancer cells [34]. Furthermore, CYP24 expression turned out to depend on the oncogenic RAS-PAK1-NFκB/Ets signalling pathway [35]. Thus, it is most likely that either "MART-10" alone or a combination of Vitamin D3 and a CYP24-resistant PAK1-blocker such as propolis could be potentially useful for the treatment of coronaviral infection.

4. Concluding remarks

According to the case in China, more than 90% of COVID-19 patients recovered from its illness in 3 months with the death rate around 4%, under strict nation-wide curfew or lockdown. In other words, when its vaccine becomes available sometime in 2021, 12–18 months after its outbreak, it is most likely that the vaccine would be no longer useful in a practical sense. Thus, non-vaccine "fast-track" therapeutics would be definitely needed for solving such a pandemic viral infection as soon as possible. Here we introduced the pre-existing natural or synthetic compounds known to inhibit PAK1 directly or its up-stream, thereby potentially blocking coronaviral infection or pathogenesis. Among these PAK1-blockers, at least CQ and Ivermectin have been proven to block the replication of COVID-19 in Vero cell culture with IC_{50} ranging 1–3 μM, and a combination of HQ and AZ or ciclesonide alone have been shown clinically to ease the pathogenic symptom of this virus. Thus, we would urgently encourage world-leading viral experts to test whether the rest of PAK1-blockers listed here also directly block the replicaion of this virus in cell culture, and if so, test their anti-COVID-19 efficacy clinically in an attempt to save over 2 million victims world-wide. . In this context, it should be worth noting that a recent large-scale clinical trial of a propolis for COVID-19 patients in Netherlands appears to be successful for easing their viral pahthogenesis: https://osaka20420.blogspot.com/2020/04/propolis-therapy-of-covid-19-letter.html.

Furthermore, in addition to its promotion of viral infections in general, PAK1 contributes to the suppression of both B-cell and T-cell based immune systems which normally produce a series of specific antibodies against viruses [9]. Thus, PAK1-blockers could knock-out each virus with "double" punches (Fig. 2). Lastly it should be high-lighted that the major purpose of PAK1-blockers for clinical application such as therapy of viral infection is to reduce the virus-induced abnormally activated PAK1 to the "normal" level (instead of "null" level) in patients suffering from PAK1-dependent diseases. Thus, it is very unlikely that such a cautious measure/approach would cause any serious side effect.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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