DRUG DESIGN STRATEGIES FOR THE TREATMENT OF CORONAVIRUS INFECTION

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The increasing size and density of the human population is leading to an increasing risk of infectious diseases that threaten to spread yet another pandemics. The widespread use of vaccination has reduced morbidity and mortality associated with viral infections and in some cases eradicated the virus from the population entirely. Regrettably, some virus species retain the ability to mutate rapidly and thus evade the vaccine-induced immune response. New antiviral drugs are therefore needed for the treatment and prevention of viral diseases. Modern research into the structures and properties of viral proteases, which are of key importance in the life cycle of viruses, makes it possible, in our opinion, to turn these enzymes into promising targets for the development of effective viral disease control methods.

Keywords: antiviral drugs, viral proteases, protease inhibitors, prodrug design

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СТРАТЕГИИ ДИЗАЙНА ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ ДЛЯ ЛЕЧЕНИЯ КОРОНАВИРУСНОЙ ИНФЕКЦИИ

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Возрастающие с каждым годом численность и плотность человеческой популяции приводит к увеличивающемуся риску распространения инфекционных заболеваний, что грозит возникновением все новых эпидемий по всему миру. Широкое использование вакцинации снизило заболеваемость и смертность, связанные с вирусными инфекциями, а в некоторых случаях полностью уничтожило вирус среди населения. К сожалению, некоторые виды вирусов сохраняют способность к быстрой мутации и таким образом ускользают от вызванного вакциной иммунного ответа. В связи с этим для лечения и профилактики вирусных заболеваний требуются новые противовирусные препараты. Современные исследования в области структур и свойств вирусных протеаз, имеющих ключевое значение в жизненном цикле вирусов, позволяют, на наш взгляд, превратить эти ферменты в перспективные мишени для разработки эффективных методов борьбы с вирусными заболеваниями.

Ключевые слова: противовирусные препараты, вирусные протеазы, ингибиторы протеаз, дизайн пролекарств

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Together with cardiovascular and cerebrovascular diseases, infectious diseases caused by bacteria, viruses, parasites and fungi are the leading cause of death worldwide [1]. According to the World Health Organization, the global spread of coronavirus infection, which began in 2019 in China, has infected more than 600 million and killed more than 6.5 million people over three years [2]. The cause of the COVID-19 pandemic was a new coronavirus, SARS-CoV-2. Previously, members of the Coronaviridae family SARS-CoV and MERS-CoV caused outbreaks of severe acute respiratory syndrome (SARS) in 2002 and Middle East respiratory syndrome (MERS) in 2012 [3].

Several decades of studies of the family Coronaviridae have shown that the viral RNA genome is translated into two large polyproteins, pp1a and pp1ab, which, through their internal peptidase activity, are cleaved into several non-structural proteins (Nsps) required to enable transcription and replication of the viral genome [4]. Two cysteine proteases, papain-like peptidase (PLP) [5] and chymotrypsin-like peptidase (3CL), also known as the major coronavirus protease (M^{Pro}), are critical for proteolytic degradation of polyproteins [6]. MPro peptidase consists of three domains: domains I and II form a chymotrypsin-like fold containing a substrate-binding site located in the cleft between the two domains, while domain III is required for homodimer formation and plays a critical role in the catalytic activity of the protease as the M^{Pro} monomer is inactive [7]. M^{Pro} of different coronaviruses share highly conserved substrate-binding sites recognizing the amino acid sequence of the polyprotein (Leu-Gln)↓(Ser/Ala/Gly), where the peptide bond after the glutamine residue is hydrolyzed [7, 8].

The development of inhibitors of cysteine proteases involved in coronavirus (CoV) replication represent an effective strategy against COVID-19 and other diseases caused by coronaviruses. M^{Pro} is a promising target for the development of antiviral drugs targeting SARS-CoV-2 and other CoV because of its important role in post-translational processing

of polyproteins. Moreover, the absence of human proteases cleaving proteins after the Gln residue is one of the advantages of M^{Pro} as a target for inhibitor development, as it increases their specificity and limits the undesirable side-effects. Since the epidemic outbreaks caused by CoV in 2002 and 2012, various M^{Pro} inhibitors have been proposed [9], but not until 2021 that the first drug candidates that successfully passed clinical trials have appeared [10, 11].

Another interesting strategy for antiviral drug development is the use of proteolysis to activate prodrugs [12]. Prodrugs are inactivated derivatives of drug molecules that can undergo enzymatic transformation to release the active compound *in vivo* [12]. A number of protease-activated prodrugs (PAPs) have been developed and successfully used in cancer treatment to improve drug delivery to malignant neoplasms, where protease expression is higher than in healthy tissues [13]. However, the application of PAPs is not limited to the development of anti-cancer drugs; recent publications show that this approach can also be used to treat bacterial and viral infections [14, 15].

CONCLUSION

The combination of the two strategies could be a promising avenue in the development of drugs for the treatment of COVID-19. The use of inactivated cytotoxic and cytostatic drugs conjugated with both irreversible and reversible selective M^{Pro} protease inhibitors can provide the targeted delivery and release of the active agents in infected cells and reduce the systemic toxicity of the developed drugs.

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