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TMPRSS2-Inhibitors Play a role in Cell Entry Mechanism of COVID-19: An Insight into Camostat and Nafamostat

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Camostat; Nafamostat; Trypsin; Mesylate.

Introduction

The enzymes trypsin, furin and other proprotein-convertasen, cathepsin, transmembrane proteases (TMPRSS) and elastases play a role by the cell entry of Coronaviren (Coronaviridae) [1]. The proteases TMPRSS2 and TMPRSS11a, which exist in the respiratory tract richly and become exprimed on cell surfaces, promote the entry of SARS-CoV-1-virus. For the TMPRSS-protease TMPRSS11d - also as protease similar to trypsin has confessed of the human respiratory tract - a proteolytic activation of the spike protein was proved by SARS-CoV [2]. TMPRSS2 again makes a complex reaction with the ACE2 receptor what allows an efficient penetration of the virus directly in the cell surface [2,3]. TMPRSS2 and TMPRSS11D activate the spike protein, while they split it in the S1 and S2 subunits by which an endosome independence cell entry is allowed in the cell membrane [2,3]. Virus-based therapies enclose monoclonal antibodies, anti-viral peptide which docks to the spike protein of viruses, inhibitors of the viral nucleic acid synthesis and inhibitors for docking to other viral structures and accessory proteins. Different known serine inhibitors do exist: Gabexate mesylate (Tokyo Chemical Industry, Tokyo, Japan), Nafamostat mesylate (Tokyo Chemical Industry), Camostat mesylate (Wako, Tokyo, Japan), Sivelestat sodium tetrahydrate (LKT Laboratories, St. Paul, MN, USA), rivaroxaban (Adooq Bioscience, Irvine, CA, USA) Telaprevir (Adooq Bioscience) and Simeprevir (TRC, Toronto, Canada) were dissolved in DMSO at a concentration of 10 mm Ulinastatin (Mochida Pharmaceutical Co. Ltd. Tokyo, Japan) was dissolved in PBS (-) which lacked Mg^{2+} and Ca^{2+}. The FDA approved drug library (L1300) was purchased from Selleck (Houston, TX, USA) and diluted

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in DMSO at a concentration of 100 μM. Especially in COVID-19, we took a closer look on two main serine protease inhibitors.

Camostat

Camostat (mesylate) is delivered as a crystalline solid state. A solution with shares can be produced by dissolving of Camostat (Mesylat) in the solvent of the choice which should be cleaned with sluggish petrol. Camostat (Mesylat) is dissolvable in organic solvents like DMSO and Di-methyl form amid [4]. The solubility of Camostat (Mesylat) in these solvents amounts to about 25 mg/ml. Camostat is an inhibitor of [2,5] Progat. It restrains Trypsin (Ki=1 nm), and passed inflammatory provoked, including Plasmin, Kallikrein and Thrombin per one. Camostat restrains the integration of the heavy acute respiratory distress syndrome (SARS-CoV) and the glycoprotein SARS-CoV-2 in pseudo-typed particles bubble-shaped Vero cells, Calu 3 cells and more primarily from human lung epithelium wide cells if it is given, with a concentration of 10 μM [6]. It reduces the number of the genome width correspondences of SARS CoV 2. Camostat restrains the function of the sodium canal in human epithelium wide cells of the respiratory tract (IC50=50 nm) [2]. The management of Camostat (1 mg/kg) restrains the production from TNF-α and the monocytes chemo attractant protein 1 by monocytes and the proliferation of pancreas star cells in the model of a rat of chronic pancreatitis [5].

Nafamostat

Nafamostat is a synthetic serine protease inhibitor which is usually formulated with hydrochloric acid due to its basic properties. It was introduced to the Japanese market in 1986 as futhan for the parenteral treatment of acute symptoms of pancreatitis and for use in certain bleeding complications. It has been used in studies on the prevention of liver transplantation and post-transplant syndrome. The use of Nafamostat in Asian countries is approved as an anticoagulant therapy for patients undergoing continuous renal replacement therapy due to acute renal injury. Nafamostat is administered clinically by intravenous infusion. In different former studies it has been speculated that the blood concentration of the serine protease inhibitor Nafamostat after administration exceeded the concentrations required experimentally to inhibit the membrane docking with the spike protein of COVID-19. As expected, Nafamostat prevents the virus SARS-CoV-2 from entering human cells. Nafamostat, the brand name is Fusan, the drug used to treat acute pancreatitis, can used to block the necessary virus entry process that COVID-19 uses to spread and cause the novel disease. The University of Tokyo announced these new results on 18 March 2020.

Conclusion

In conclusion, TMPRSS2 plays an important role in the viral spread of MERS-CoV-2 and SARS-CoV within the respiratory tract of mouse models and in murine immunopathology [2,3]. A study conducted by Markus Hoffmann and Hannah Kleine-Weber of the German

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Primate Center together with other researchers, confirms that the SARS-CoV-2 virus also requires the presence of the ACE2 receptor and the TMPRSS2 enzyme in the cell membrane of lung cells, which cleaves the S protein on the virus envelope in order to be able to enter the lung cell [2,3]. According to this study, the known inhibitor of TMPRSS2, camostat, significantly reduces the probability of penetration of SARS-CoV-2 in cell experiments in vitro and could be suitable for treatment [5]. According to studies, SARS-CoV-2, the virus responsible for COVID-19, needs the TMPRSS2 present in the human body to enter the host cell, which could be a starting point for treatment. The efficacy of the drug in cell cultures has already been demonstrated [2,5,6]. Therapeutic efficacy in COVID-19 patients still has to be tested in clinical trials. Likewise, the Primate Centre Gottingen will investigate whether the active substance can be injected directly into the lung. There are doubts whether camostat per se is sufficiently available in the lung. Foipan (camostat) is one of the drugs for which the German Federal Ministry of Health initiated centralized procurement in April 2020 for the treatment of infected and seriously ill COVID-19 patients in Germany. Since a COVID-19 therapy is an individual healing trial without clinical proof of efficacy, its use should be considered primarily for severe forms of COVID-19 on an individual patient basis. According to the new research, Nafamostat can prevent the fusion of the envelope of the virus with surface membranes of host cells, the first step in infection with the causative virus SARS-CoV-2. Nafamostat can inhibit membrane fusion at a concentration of less than one-tenth of that of camostat mesylate, which was recently identified by a German group as an inhibitor of SARS-CoV-2 infection [2]. Nafamostat seems to develop more effect in treating COVID-19 adequately compared to Camostat. Both serine protease inhibitors seem to be confident solutions in treating severe cases of COVID-19. Further clinical research (off-label trials) are necessary and were started at the University of Aarhus in Denmark and at the University of Tokyo, Japan.

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