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COVID-19

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Some Aspects of Mast Cells Carboxypeptidase A3 Participation in the Pathogenesis of COVID-19

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Abstract

Background: This study aimed to determine the involvement of carboxypeptidase A3 (CPA3) in developing lung damage in patients with COVID-19.

Methods and Results: The study included samples of autopsy material from the lungs of patients who died as a result of severe COVID-19 (the main group [MG] and persons who died from external causes (the control group [CG]). Immunohistochemical staining for CPA3 was carried out. A quantitative study of CPA3-positive mast cells (MCs) and the degree of their degranulation was carried out using a ×40 objective lens with an analysis of ≥50 fields of view with further conversion to 1 mm². Significant representation of CPA3-positive MCs per 1 mm² of CPA3-positive MCs, CPA3-positive MCs with signs of degranulation (SD), and co-adjacent MCs was found in the MG compared to the CG (P=0.01 in all cases). In the main group, positive correlations were identified between the total number of CPA3-positive MCs, CPA3-positive MCs with SD and the blood hemoglobin level shortly before death (r=0.491 [P=0.008] and r=0.521 [P=0.004], respectively). Co-adjacent CPA3-positive MCs were negatively correlated with blood eosinophils at the beginning of hospitalization (r=-0.420 [P=0.023]). Also, the number of separately lying, CPA3-positive MCs negatively correlated with the blood monocyte shortly before death (r=-0.384 [P=0.044]). A positive correlation was established between the total number of CPA3-positive MCs, CPA3-positive MCs with SD, and adjacent CPA3-positive MCs with total blood protein in patients at the beginning of hospitalization (r=0.431 [P=0.020], r=0.449 [P=0.015] and r=0.456 [P=0.013], respectively). In addition, the study demonstrated a positive correlation between CPA3-positive MCs with SD and the total number of CPA3-positive MCs with blood aPTT levels (r=0.304 [P=0.045] and r=0.375 [P=0.045], respectively). A negative correlation was also found between the total number of CPA3-positive MCs and the blood INR level (r=-0.812 [P=0.050]). Finally, in patients at the beginning of hospitalization, a negative correlation was found between CPA3-positive MCs with SD, CPA3-positive MCs without SD, separately located CPA3-positive MCs, adjacent CPA3-positive MCs, and the total number of CPA3-positive MCs with blood amylase (r=-0.550 [P=0.002], r=-0.452 [P=0.045], r=-0.485 [P=0.030], r=-0.622 [P=0.008], and r=-0.590 [P=0.006], respectively).

Conclusion: Our study identifies the potential involvement of CPA3 in the pathogenesis of severe COVID-19. However, many aspects of its participation remain unclear and require further study. **(International Journal of Biomedicine. 2023;13(4):301-305.)**

Keywords: COVID-19 • SARS-CoV-2 • carboxypeptidase A3 • mast cells

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Abbreviations

aPTT, activated partial thromboplastin time; **COVID-19**, coronavirus disease 2019; **CPA3**, carboxypeptidase A3; **CCL2**, chemokine (C-C motif) ligand 2; **G-CSF**, granulocyte colony-stimulating factor; **GBT**, general blood test; **INR**, international normalized ratio; **MCs**, mast cells; **SARS-CoV-2**, severe acute respiratory syndrome coronavirus 2; **SD**, signs of degranulation.

Introduction

COVID-19, an infectious disease caused by SARS-CoV-2, was first reported in 2019 and has already generated more than 700 million infections worldwide.[1] A hallmark of COVID-19 pathogenesis is a "cytokine storm" that causes elevated levels of pro-inflammatory cytokines and chemokines such as IL-6, TNF-α, CCL2, and G-CSF.[2] When a coronavirus enters the body, it primarily becomes attacked by innate immune cells—macrophages, lymphocytes, and mast cells (MCs)—strategically localized in the connective tissue of the membranes of the nasal cavity and lower respiratory tract.[3] MCs contain many biologically active substances packaged in cytoplasmic granules, such as a group of proteases, biogenic amines, and glycosaminoglycans. Many of them play a key role in the pathogenesis of COVID-19, exacerbating the inflammation process.[4] Carboxypeptidase A3 (CPA3) is also involved in the development of infectious and non-infectious diseases, and it is an important component of the MC's secret.[5,6] It has been found that CPA3 is involved in the pathogenesis of COVID-19. This may be explained by the abundant expression of CPA3 by MCs in various organs, including human lungs.[7,8]

This study aimed to determine the involvement of CPA3 in developing lung damage in patients with COVID-19.

Materials and Methods

The study included 30 patients (13(43%) men and 17(57%) women with an average age of 61.1±11.9 years) with a diagnosis of severe and extremely severe COVID-19, accompanied by bilateral, viral, community-acquired pneumonia, acute respiratory distress syndrome (ARDS) (diagnosed by the Berlin definition criteria),[9] who were treated at Voronezh Regional Clinical Hospital No. 1 in the COVID-19 departments from September 2021 to March 2022 and those who died as a result of COVID-19. Autopsy material from the lungs of patients in the main group (MG) was collected at the bases of pathology departments. The control group (CG) included 9 persons who died from external causes (4(44%) men and 5(56%) women; an average age of 60.9±10.1 years). Demographic indicators and the presence of comorbidities are presented in Table. 1.

The study did not include patients with chronic respiratory diseases (bronchial asthma, chronic obstructive pulmonary disease, chronic bronchitis, occupational lung diseases, other (except COVID-19) infectious respiratory diseases), cancer, hepatitis and cirrhosis, chronic kidney disease stage 3a and higher.

The collection of autopsy material from the lungs was carried out at the Voronezh Regional Bureau of Medical Examinations. The autopsy material was fixed in 10% neutral buffered formalin, a sample preparation procedure and embedded in paraffin, followed by the preparation of 5 μm thick sections for staining with H&E and Giemsa solution and ultrathin sections 2 μm thick for immunohistochemical analysis. Immunohistochemical staining was carried out according to the standard protocol[10] using polyclonal rabbit antibodies to CPA3 from Abcam (catalog number ab251685) at a dilution of 1:1000; after the application of secondary antibodies, sections were placed in a mounting medium. Microspecimens were analyzed using a Zeiss Axio Imager microscope A2 (Carl Zeiss, Germany) with a photo documentation system for images and a digital camera, Axiocam 506 color (Carl Zeiss, Germany). Images were processed in the ZEN 2.3 program. A quantitative study of CPA3-positive MCs and the degree of their degranulation was carried out using a ×40 objective lens with an analysis of ≥50 fields of view with further conversion to 1 mm². In patients of the MG, upon admission to the hospital and at least once over time, GBT and blood biochemistry were performed.

Table 1.

Patient demographic indicators and the presence of comorbidities.

Parameter	MG (n=30)	CG (n=9)
Sex, n (%) • male • female	 13 (43.3) 17 (56.7)	 4 (44.4) 5 (55.5)
Age, years	61.1 ± 11.9	60.9 ± 10.1
PCR SARS-CoV-2 «+», n (%)	30 (100)	0 (0)
Bilateral pneumonia, n (%)	30 (100)	0 (0)
ARDS, n (%)	30 (100)	0 (0)
Type 2 Diabetes, n (%)	1 (3.3)	0 (0)
Arterial hypertension, n (%)	25 (83.3)	8 (88.9)
Ischemic heart disease, n (%)	2 (6.7)	1 (11.1)
Ischemic stroke, n (%)	4 (13.3)	1 (11.1)
Chronic heart failure, n (%)	7 (23.3)	3 (33.2)
Obesity, n (%)	8 (26.7)	0 (0)
Chronic kidney disease, n (%)	2 (6.7)	1 (11.1)

Statistical analysis was performed using STATGRAPHICS Centurion XV software. The normality of data distribution was assessed using skewness, kurtosis, Kolmogorov–Smirnov, and Shapiro-Wilk tests. For descriptive analysis, results were presented as mean±standard deviation (SD), median (Me), lower quartile (Q1) and upper quartile (Q3). The Mann-Whitney U test was used to compare the differences between the two independent groups. Pearson's and Spearman's correlation coefficients were calculated to measure the strength and direction of the relationship between two variables. A probability value of $P<0.05$ was considered statistically significant.

Results and Discussion

The study determined the average number of CPA3-positive MCs per 1mm² in the MG and the CG. In addition, the number of CPA3-positive MCs with SD, CPA3-positive MCs without SD, MC fragments, and joint adherence of MCs were assessed (Table 2).

In the lung tissues of patients with COVID-19, it was found wide representation of CPA3-positive MCs with variable

degrees of degranulation activity or without it (Figure 1). Significant representation of CPA3-positive MCs per 1mm² of CPA3-positive MCs, CPA3-positive MCs with SD, and co-adjacent MCs was found in the MG compared to the CG (*P*=0.01, *P*=0.001, and *P*=0.0001, respectively).

Table 2.

CPA3-positive MCs in lung tissues of patients in MG and CG.

Parameter	Main group (n = 30)	Control group (n = 9)	*P*
CPA3-positive MCs without SD, per 1 mm²	4.35 (1.8;7.2)	3.48 (2.3;4.1)	0.796
CPA3-positive MCs with SD, per 1 mm²	6.49 (1.1;11.1)	2,07 (1.0;2.7)	0.001
MC fragments, per 1 mm²	1.52 (0.1;2.3)	1.27 (0.57;1.7)	0.779
Co-adjacent MCs, per 1 mm²	0.41 (0.1;0.5)	0.06 (0.0;0.1)	0.0001
Total number of MCs, per 1 mm²	10.84 (3.5;19.8)	5.56 (4.2;6.8)	0.01

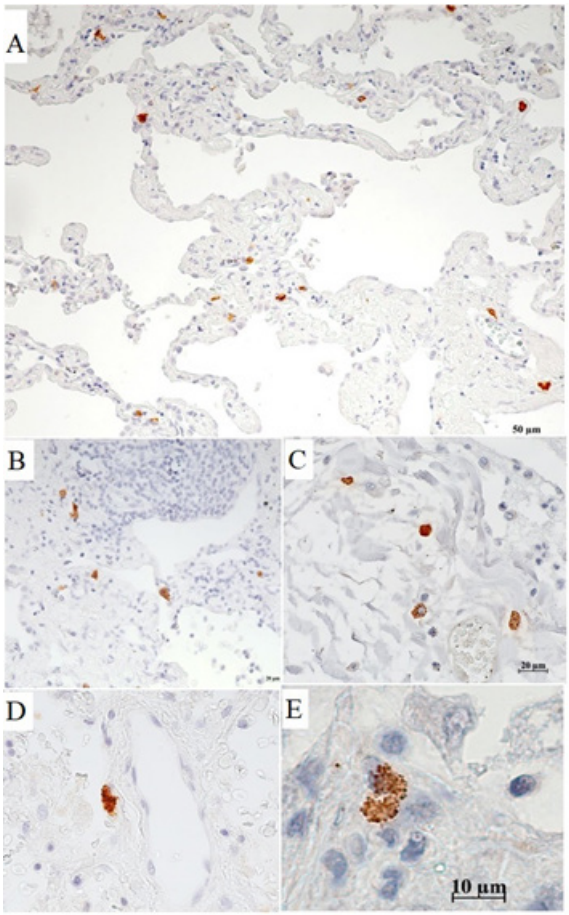

Fig. 1. *Histo-topographic features of CPA3-positive MCs in the lung tissues of patients without COVID-19 (A) and with COVID-19 (B-D). Immunohistochemical reaction: specific brown staining, nuclei stained blue with Mayer's hematoxylin.*
A – MCs with carboxypeptidase granules, with different levels of secretory activity (without degranulation and with signs of degranulation); B – interalveolar septa are deformed and thickened due to inflammatory cell infiltration, surrounded by CPA3-positive MCs with SD; C - area of developing pulmonary fibrosis, modified by CPAZ-positive MCs; D – perivascular localization of a CPAZ-positive MC; E – intercellular interaction of CPAZ-positive MC. Magnification: A – x200; B, C, D – x400, D – x1000.

Positive correlations were identified between the total number of CPA3-positive MCs, CPA3-positive MCs with SD and the blood hemoglobin level in GBT performed on the patient shortly before death (r=0.491 [*P*=0.008] and r=0.521 [*P*=0.004], respectively). CPA3-positive MCs in autopsy lung material also showed correlations with blood eosinophils. The average number of co-adjacent CPA3-positive MCs per 1mm² was negatively correlated with blood eosinophils at the beginning of hospitalization (r=-0.420 [*P*=0.023]). Also, the number of separately lying, CPA3-positive MCs negatively correlated with the blood monocyte shortly before death (r=-0.384 [*P*=0.044]). A positive correlation was established between the total number of CPA3-positive MCs, CPA3-positive MCs with SD, and adjacent CPA3-positive MCs with total blood protein in patients at the beginning of hospitalization (r=0.431 [*P*=0.020], r=0.449 [*P*=0.015], and r=0.456 [*P*=0.013], respectively). In addition, the study demonstrated a positive correlation between CPA3-positive MCs with SD and the total number of CPA3-positive MCs with blood aPTT levels (r=0.304 [*P*=0.045] and r=0.375 [*P*=0.045], respectively). A negative correlation was also found between the total number of CPA3-positive MCs and the blood INR level (r=-0.812 [*P*=0.050]). Finally, in patients at the beginning of hospitalization, a negative correlation was found between CPA3-positive MCs with SD, CPA3-positive MCs without SD, separately located CPA3-positive MCs, adjacent CPA3-positive MCs, and the total number of CPA3-positive MCs with blood amylase (r=-0.550 [*P*=0.002], r=-0.452 [*P*=0.045], r=-0.485 [*P*=0.030], r=-0.622 [*P*=0.008], and r=-0.590 [*P*=0.006], respectively).

The results of our previously published study revealed that in patients with COVID-19, the average number of tryptase-positive MCs without SD and the total number of CPA3-positive MCs was statistically significantly higher, and tryptase fragments and CPA3-positive MCs were lower than in the CG. Negative correlations were established between the number of tryptase-positive MCs and the content of erythrocytes in GBT. A negative correlation was found between the number of non-degranulating tryptase-positive MCs and the hemoglobin content. Positive correlations were found between tryptase-positive MCs and the content of leukocytes in GBT, and negative correlations between the number of CPA3-positive MCs and the platelet content (*P*=0.0436 and *P*=0.0334, respectively). A direct correlation was established between the number of co-adjacent and fragments of tryptase-positive MCs with the erythrocyte sedimentation rate. A negative correlation was found between the number of CPA3-positive MCs without SD and the level of blood C-reactive protein (*P*=0.0278). In patients with COVID-19, reduced degranulation activity of tryptase-positive MCs was found, along with an increased representation of CPA3-positive MCs.[11] It was also revealed that the total number of CPA3-positive MCs per 1mm² in autopsy lung material obtained from patients with COVID-19 was significantly higher than in the CG, which may indicate the involvement of CPA3 in the pathogenesis of patients with COVID-19.

In the current study, negative correlations were observed between separately lying, CPA3-positive MCs and the content

of blood monocytes. Evidence suggests that in SARS-CoV-2 infection, monocytes, macrophages, and MCs can produce large amounts of multiple types of proinflammatory cytokines and chemokines, causing a cytokine storm with local tissue inflammation and a dangerous systemic inflammatory response. Low expression of ACE2 by monocytes/macrophages in COVID-19 patients may also contribute to the development of pathological reactions due to the proinflammatory properties of angiotensin II and dysfunction of the renin-angiotensin system. Both local tissue inflammation and cytokine storm play a fundamental role in the development of complications associated with COVID-19, such as ARDS, which is the leading cause of death in patients infected with SARS-CoV-2.[12] In addition, chymase and CPA3 can also interact in the enzymatic cleavage of angiotensin II, in which each enzyme has its catalytic activity toward specific substrate proteins.[13] Co-adjacent CPA3-positive MCs in autopsy lung material showed positive correlations with the content of eosinophils in SGBT. Subsets of MCs containing CPA3 have previously been reported to be involved in major airway diseases, such as asthma, COPD, and pulmonary fibrosis.[8,14,15]

The identified positive correlations between the total number of CPA3-positive MCs and CPA3-positive MCs with SD with the blood hemoglobin level are consistent with existing data that SARS-CoV-2 infection significantly affects the structural membrane homeostasis of erythrocytes at the levels of protein and lipids. In the red blood cells of COVID-19 patients, the levels of glycolytic intermediates were increased, accompanied by oxidation and fragmentation of membrane proteins. In patients with COVID-19, red blood cells may be unable to respond to changes in hemoglobin oxygen saturation as they move from the lungs into the bloodstream and may have a reduced ability to transport and deliver oxygen.[16]

Noteworthy is the established positive correlation between the number of CPA3-positive MCs with SD and the total number of CPA3-positive MCs with the aPTT level and the negative correlation between the total number of CPA3-positive MCs and the blood INR level. The transition from mild to severe disease in patients with COVID-19 may be caused by a cytokine storm and increased hypercoagulability with a significant risk of thromboembolic complications.[17] COVID-19 causes endothelial damage, coagulation activation, and intravascular fibrin deposition. Patients experienced thrombocytopenia, elevated D-dimer levels, and prolonged aPTT, suggesting that death in patients with COVID-19 may be related to disseminated intravascular coagulation.[18]

The data obtained are in line with data confirming that CPA3 has potential significance for pulmonary fibrosis, COPD, as it regulates the contraction of smooth muscles, regulates blood vessel tone and vascular blood flow through proteolytic modification, for example, angiotensin I, apolipoprotein B and neurotensin. Even with the proposed role of CPA3 in homeostasis, activated CPA3 mRNA may also have pro-inflammatory effects and is essential for the biogenesis of extracellular matrix components.[19]

Finally, the discovered negative correlation between CPA3-positive MCs with SD, CPA3-positive MCs without SD, separately located CPA3-positive MCs, adjacent CPA3-positive MCs, and the total number of CPA3-positive MCs with blood amylase is confirmed by the data that SARS-CoV-2 infection contributes to pancreatic damage. The virus infects the endocrine part of the pancreas and, to a lesser extent, the exocrine part. It has been shown that there is a bidirectional relationship between COVID-19 and diabetes; patients with COVID-19 and concomitant diabetes mellitus had a severe and extremely severe course of the disease and increased mortality; in other patients with COVID-19, without concomitant diabetes mellitus, the earlier development of COVID-19 was observed.[20]

In conclusion, our study identifies significant correlations between CPA3-positive MCs and the level of monocytes, eosinophils, hemoglobin, amylase, total protein, INR, and aPTT. A statistically significant increased total number of CPA3-positive MCs, CPA3-positive MCs with SD, and co-adjacent MCs was found in the MG compared to the CG. The potential involvement of CPA3 in the pathogenesis of COVID-19 was considered, namely in changes in hematological parameters and blood coagulation parameters, inflammation, pulmonary fibrosis, and organ failure observed in COVID-19.

Competing Interests

The authors declare that they have no competing interests.

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