An Insight of comparison between COVID-19 (2019-nCoV) and SARS-CoV in pathology and pathogenesis

Xiaolong Cai[1,2,*]

1.Hanbio Research Center, Hanbio Tech Co. Ltd., Shanghai, P.R. China (www.hanbio.net)

2.R&D Center, GeneMedi Co.Ltd., Shanghai, P.R. China

*Corresponding authors: E-mail: cxl@hanbio.net

Abstract: COVID-19, a novel pathogenic coronavirus emerged in China and spread globally rapidly. COVID-19 shares above 85% identity in genome with SARS-CoV. Patients infected by COVID-19 and SARS-CoV also reveal similar clinical characteristics. Here we compare the clinical and pathological features between patients infected by COVID-19 and SARS-CoV respectively.

Conclusions:

1. Older patients refer to higher case fatality rate (CFR) than young.

2. Males show a higher CFR than females, and this difference may converge as age increase.

3.COVID-19 infection may have a kidney and testis damage. Combined with higher CFR in males, genitourinary system disorder caused by the COVID-19 infection need to be cautioned.

4. It is critical to control the cytokine release syndrome(CRS) in NCP. IL-6, IL-10 and their receptors may be the drugable target.

5.Consistently to decrease of CD4+T and CD8+T cells, spleen damage, and lymphocyte depletion may exist in NCP patients. Approaches for T cell rescued may be considered.

6. Compared with SARS-CoV's Spike protein, COVID-19 Spike protein present a higher binding affinity to ACE2, which suggests that soluble ACE2 might be a potential candidate for COVID-19 treatment. Other receptors, such as L-SIGN and DC-SIGN, need to be investigated in the future.

Introduction

A novel coronavirus pneumonia (NCP) caused by a novel coronavirus, 2019-nCoV, which named COVID-19 by WHO recently, emerged in Wuhan, Hubei province, China in December 2019. The NCP then broke-out aggressively in Jan 2020 following the human flow from Wuhan to other cities during the vocation of the Chinese Spring Festival.

Several coronaviruses can cause light respiratory disease in humans [1]. In contrast, the SARS-CoV, which emerged in 2003 in Guangdong Province, China, and MERS-CoV, in 2016, both proved host by bat and transmitted from other animals to humans, can cause severe respiratory diseases respectively[2].

Genetics Similarity of COVID-19 and SARS-CoV

The COVID-19 is also a novel coronavirus transmitted from uncertain wild animals, that can cause acute respiratory disease (ARD) with complicated clinical characteristics[3-7]. According to the whole genome sequence analysis, the COVID-19 is closer to the SARS-like bat CoVs (MG772933) than the SARS-CoV[8], which is descended from SARS-like bat CoVs However, COVID-19 share above 85% identity with SARS-CoV[8], but less related to MERS-CoV[9]. Importantly, within high similarity of RBD in Spike-protein, several analyses reveal that COVID-19 uses the same receptor of SARS-CoV - the angiotensin-converting enzyme 2 (ACE2)[10-12]. Meanwhile, DPP4 (dipeptidyl peptidase 4, also known as CD26), the MERS-CoV's primary receptor, is proved not to be a receptor of COVID-19[11].

Case fatality rate (CFR) of COVID-19 and SARS-CoV both affected by age and gender.

Age and gender distinction affect the CFR of NCP and SARS respectively(Table1). It is certain that older patients refer to higher CFR than young both in NCP[3] and SARS[13, 14] respectively. Consistently to SARS, Males seem to have a higher CFR than females in NCP3, 13, 14]. Meanwhile, a SARS related study in Hongkong indicates a gradual decrease of gender-depended difference in CFP as the age increase, which may also be likely to exist in NCP[14].

Comparison of Major Pathological Characteristics between COVID-19 and SARS-CoV

We summarize the major Major Pathological Characteristics between COVID-19 and SARS-CoV in Table2. Since lots of mentions in other articles, NCP induced acute respiratory distress syndrome(ARDS) will not be discussed in this article.

The high rate of renal impairment was observed in NCP patients, indicating the development of kidney dysfunction[15], which was consistent with SARS patients[16-20]. As is shown in Figure1, ACE2, the co-receptor of COVID-19 and SARS-CoV, presents a high expression level in the gastrointestinal tract, kidney, and testis. Since SARS induce severe testis damage[21], it holds a high risk that COVID-19 infection may also lead to testicular lesions in males,which need further clinical investigation. Considering the higher CFR of NCP and SARS in younger males than females, with the high ratio of kidney damage[12, 15](worthy of future investigation in gender), we should pay attention to the genitourinary system disorder caused by the COVID-19 infection.

Cytokine release syndrome(CRS) remains a core factor that aggravates disease progression[22]. A higher value of IL-6 and IL-10 was observed in NCP patients parallel with the severity of the disease[22]. IL-6 and IL-10 are the core cytokines that are consistently found to be

elevated in patients with CRS(23,24). Tocilizumab, a monoclonal antibody targeting the IL-6 receptor, was already registered for a Clinical Trials in Anhui Provincial Hospital now (Chinese Clinical Trials Registration number: ChiCTR2000029765).

Necrosis of the spleen and atrophy of the white pulp with severe lymphocyte depletion have been mentioned in SARS patients[16-18, 25, 26]. Consistently, the amount of various immune cells including CD4+T, CD8+T, dendritic cells(DCs), macrophages, and natural killer cells(NKCs) decrease respectively[26]. Since a significant decrease of CD4+T and CD8+T cells number were also found in NCP patients respectively[22], the spleen impairment needs to be further confirmed. Meanwhile, it was reported that CD4+T cells, but not CD8+T cells are Important in control of SARS-CoV infection[27]. We might further consider different approaches for T cell rescuing within the control of CRS.

Receptors

ACE2 is proved a co-Receptor of COVID-19 and SARS-CoV. Structure analysis of COVID-19 and SARS-CoV recently indicated that COVID-19 Sike protein(S-protein) binds ACE2 with above 10 folds higher affinity than SARS-CoV[28]. This discovery further explains the more rapid transmission characteristic of the COVID-19 in humans than SARS-CoV. Referring to the higher affinity of COVID-19 S-protein and ACE2, soluble ACE2 might be a potential candidate for COVID-19 treatment.

Recognized ACE2 as the receptor of COVID-19, now scientists find important an ACE2 downstream target-TMPRSS, which maybe drugable[11, 29]. Besides ACE2, the L-SIGN (CD209L, gene symbol: CLEC4M) and DC-SIGN (CD209, gene symbol: CD209) have been identified as alternative SARS-CoV receptors respectively [30, 31]. The organ-specific expression of L-SIGN and DC-SIGN is present in Figure1C, D respectively. It is unknown if L-SIGN and DC-SIGN can act as alternative receptors of COVID-19. Regarding 14 AA sequences of RBD of SARS-CoV , COVID-19 reveals 8 strictly conserved residues and 6 AA mutations, which may affect the tropism and transmission property. Excluding ACE2, other receptors may also be available.

Concluding remarks of COVID-19 compared with SARS

1. Older patients refer to higher CFR than young.
2. Males show a higher CFP than females, and this difference may converge as age increase.
3.COVID-19 infection may have a kidney and testis damage. Combined with higher CFR in males, genitourinary system disorder caused by the COVID-19 infection need to be cautioned.
4. It is critical to control the CRS in NCP. IL-6, IL-10 and their receptors may be the drugable target.
5.Consistently to decrease of CD4+T and CD8+T cells, spleen damage, and lymphocyte depletion may exist in NCP patients. Approaches for T cell rescued may be considered.
6. Other receptors, such as L-SIGN and DC-SIGN, need to be investigated in the future.

Acknowledgement

Tribute to the medical staff fighting against the COVID-19 in China. You are the angel.

Thanks for the helps from my colleagues from Hanbio Tech Co. Ltd., Shanghai, P.R. China (www.hanbio.net) and GeneMedi Co.Ltd., Shanghai, P.R. China (www.genemedi.net) respectively.

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Table 1

Age and gender distinction may affect the CFR of COVID-19 and SARS

		COVID-19 [3]		SARS in China Mainland [13]		SARS in China Hongkong [14]	
	R0	3.78				2-3	
		No.of case	CFR	No.of case	CFR	No.of case	CFR
	All	4021	3.06%	5327	6.40%	1755	17.04%
Gender	Male	2213	4.45%	2607	7.20%	776	21.90%
	Female	1808	1.25%	2720	5.60%	979	13.20%
Age group	<60	2969	1.43%	4777	4.35%	-	Age 0-44: CFR=7.7%(male); CFR=3.7%(female); Age 45-74: CFR=32.6%(male); CFR=24.5%(female)
	>=60	1052	5.30%	548	24.64%	-	Age>=75, CFR=64.7%(male); CFR=63.6%(female)

SARS, severe acute respiratory syndrome; CFR, case fatality rate; R0,reproductive number

Table 2

Comparation of Major Pathological Characteristics between COVID-19 and SARS-CoV

	COVID-19	SARS-CoV
Respiratory Tract	Pneumonia, ARDS	Pneumonia, ARDS
Gastrointestinal Tract	Diarrhea	Diarrhea
Kidney	Reported a 63% proteinuria, indicative of renal impairment.	Focal necrosis and vasculitis of small veins in the renal interstitial tissue.
Testis	Unknown, worthy of future investigation	Testes damage, germ cell destruction
Spleen	Unknown, worthy of future investigation	necrosis of the spleen with severe lymphocyte depletion
Immune system	Reduction of CD4+T,CD8+T, B cell,NK cell,especially CD4+T and CD8+	Reduction of CD4+T,CD8+T,Macrophages, DCs,NKCs cells; Increased size of macrophages
Cytokines & chemokines Release	higher value of IL-6, IL-10	IL-6,TNF-alpha,IL-2,IL-5,CXCL10,CCL2,CCL3,CCL5

ARDS, acute respiratory distress syndrome; DCs,dendritic cells; NKCs,natural killer cells;

Figure 1. ACE2, L-SIGN(CLEC4M), DC-SIGN(CD209) Protein & RNA expression in organs in Protein Atlas

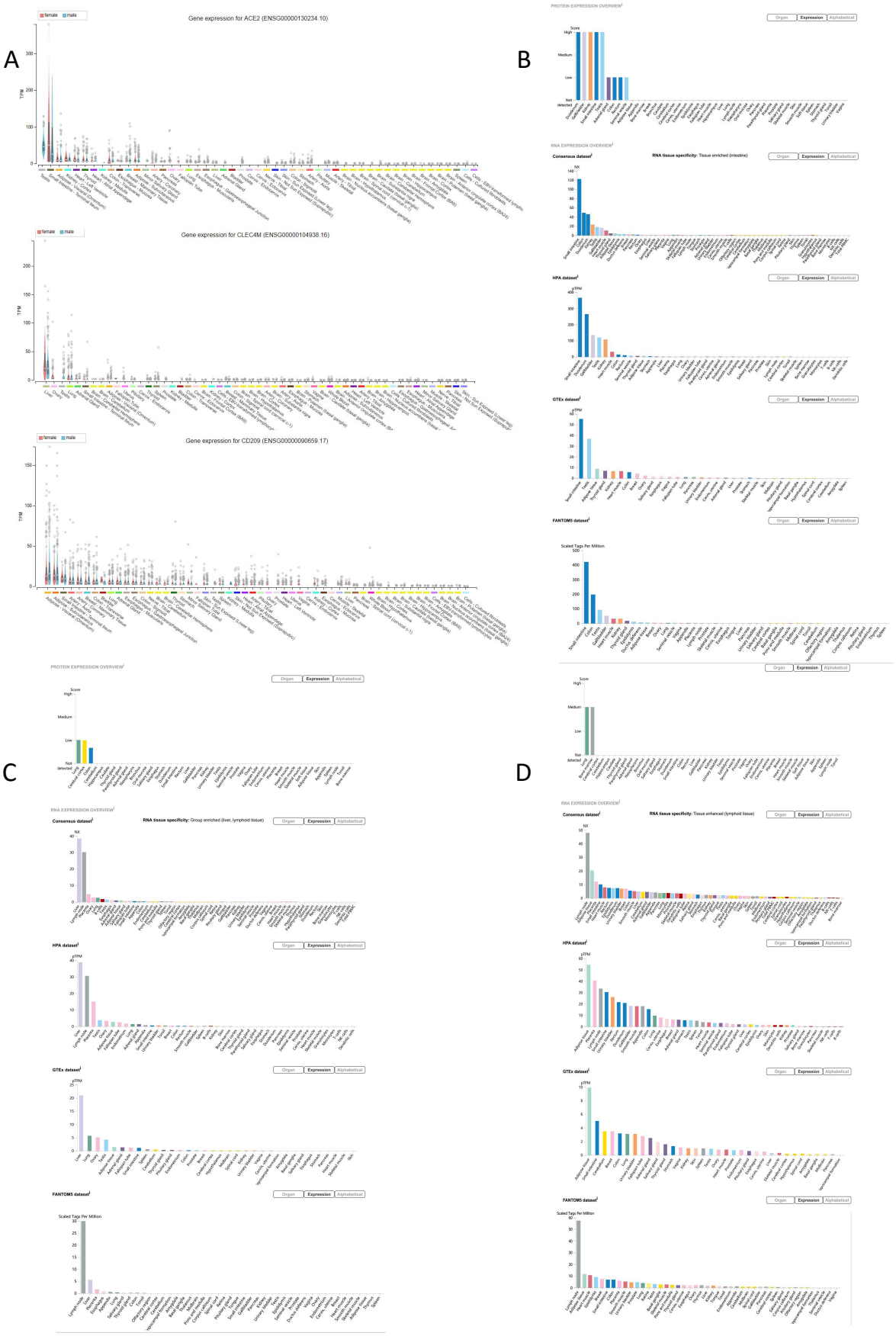
A. ACE2, L-SIGN(CLEC4M), DC-SIGN(CD209) gene expression in organs classified by gender;

B. ACE2 (the Co-receptor of COVID-19 and SARS-CoV) Protein & RNA expression in organs in Protein Atlas;

C. L-SIGN(CLEC4M, alternative SARS-CoV receptors) Protein & RNA expression in organs in Protein Atlas;

D. DC-SIGN(CD209, alternative SARS-CoV receptors) Protein & RNA expression in organs in Protein Atlas;

Figure 1


A
B
C
D
female
male
Gene expression for ACE2 (ENSG00000130234.10)
Gene expression for CLEC4M (ENSG00000104938.16)
Gene expression for CD209 (ENSG00000090659.17)
TPM
PROTEIN EXPRESSION OVERVIEW
RNA EXPRESSION OVERVIEW
Organ
Expression
Alphabetical
Consensus dataset
HPA dataset
GTEx dataset
FANTOMS dataset
RNA tissue specificity: Tissue enriched (intestine)
RNA tissue specificity: Group enriched (liver, lymphoid tissue)
RNA tissue specificity: Tissue enhanced (lymphoid tissue)
Scaled Tags Per Million