

Supplementary Information for

IL-6 trans-signaling induces plasminogen activator inhibitor-1 from vascular endothelial cells in cytokine release syndrome

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Figure S1

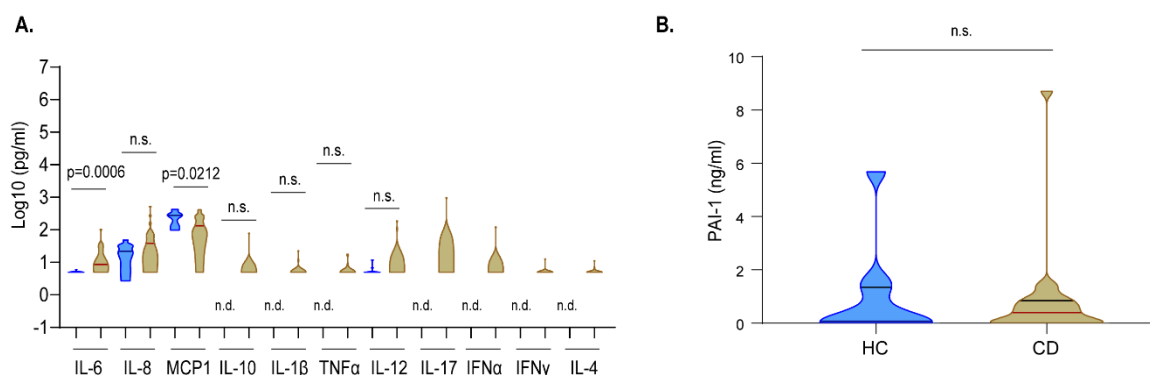
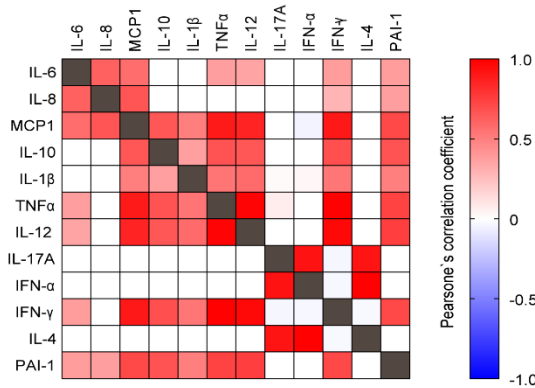


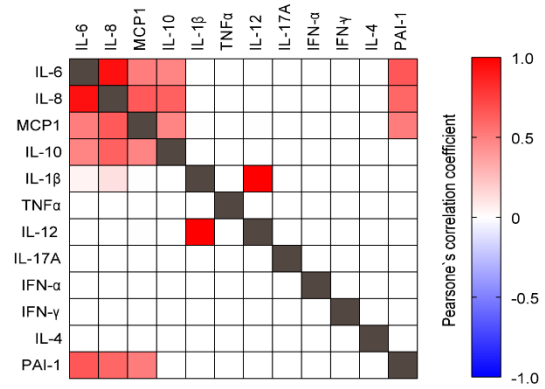
Fig. S1. Cytokine and chemokine profiles of chronic disease patients. Nineteen patients with chronic diseases included 8 with rheumatoid arthritis, two each with polymyositis/dermatomyositis, systemic sclerosis, and polymyalgia rheumatica, and one each with adult-onset Still disease, Behçet disease, systemic lupus erythematosus, IgG4-related disease, and mixed connective tissue disease, and healthy control (n=10) (A, B) Cytokine, chemokine (A) and PAI-1 (B) levels were measured in sera of patients with cytokine release syndrome. Comparisons were made by the Mann-Whitney U-test followed by correction (A), and the unpaired two-tailed *t*-test (B). Statistical comparisons are indicated, ns: non-significant; nd: non-detectable. Bar indicates the median.

Figure S2

A.



B.



C.

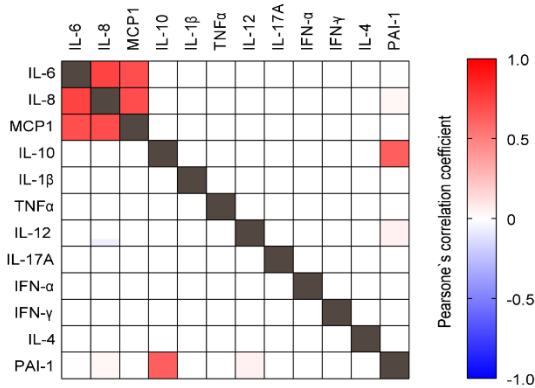


Fig. S2. Pearson's correlation of each cytokine in CRS patients. Hierarchical clustering of Pearson's correlations between cytokines and PAI-1 in patients with each cytokine release syndrome (Sepsis, A; ARDS, B; burns, C). r , Pearson correlation of determination. All data with $p < 0.05$ was shown.

Figure S3

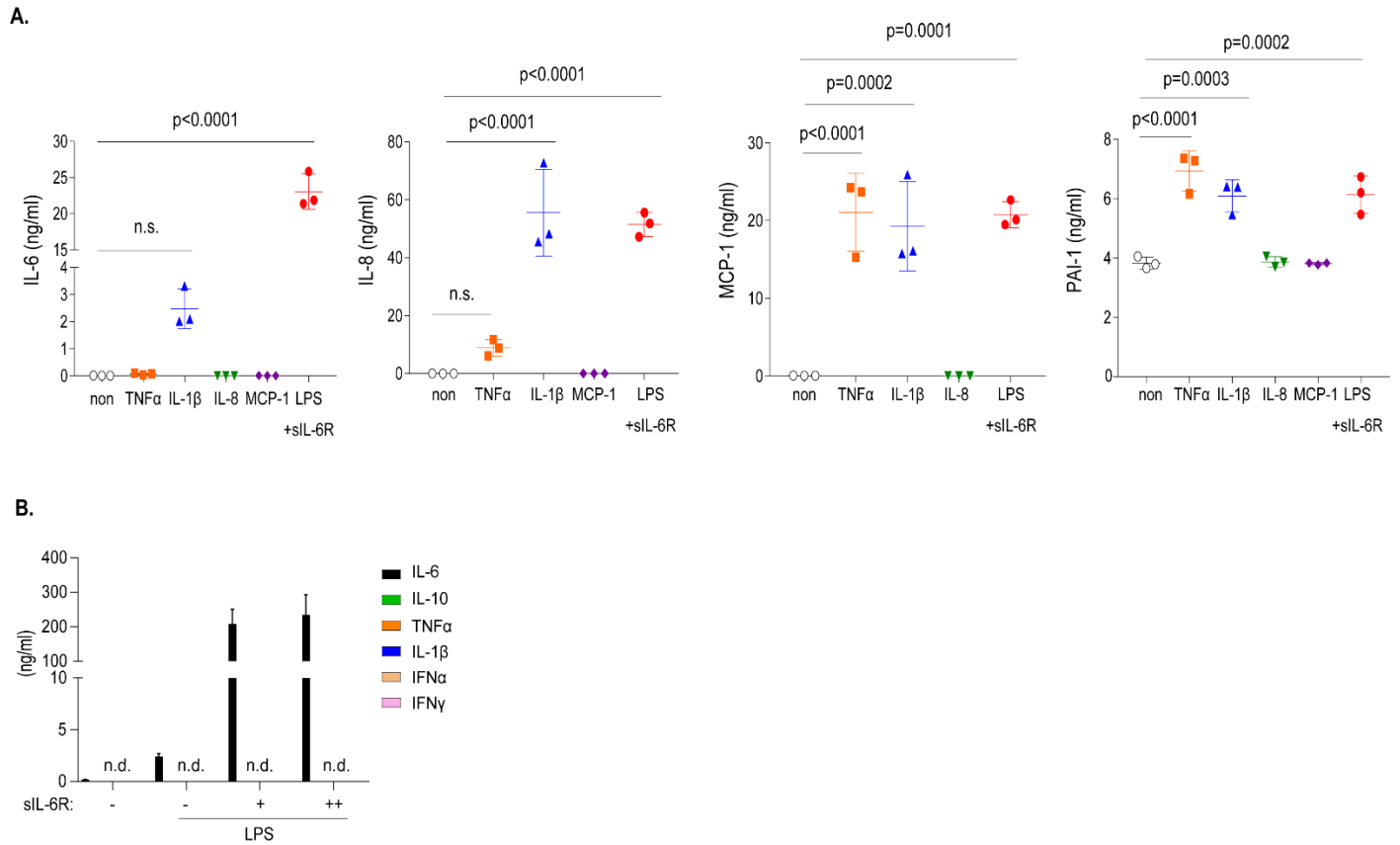


Fig. S3. Responses of HUVECs by stimulation of several cytokines or LPS with sIL-6R. HUVECs were treated with TNF α (10 ng/ml), IL-1 β (5 ng/ml), MCP-1 (100 ng/ml), IL-8 (50 ng/ml) LPS and sIL-6R. Levels of IL-6, IL-8, MCP-1 and PAI-1 in the culture supernatants after 48 h are shown. n.s., not significant. *P*-values were determined by unpaired one-way ANOVA (A). The indicated cytokines in the supernatant of HUVECs of Fig. 3A were detected by ELISA (B). Statistical comparisons are indicated, ns: non-significant; nd: non-detectable. Data are representative of three independent experimental replicates, and are presented as means \pm SD [*n* = 3 samples per group (A)].

TABLE S1

Healthy control (n=36)	
Male gender (n, %)	35/3 (88%)
Sepsis (n=37)	
Age	67 (53–78)
Male gender (n, %)	25/12 (67%)
Mortality (%)	14 (37.8%)
APACH II score	19 (15–27)
SOFA score	9 (5.5–11.5)
ARDS (n=19)	
Age	70 (60–80)
Male gender (n, %)	12/7 (63%)
Mortality (%)	7 (36.8%)
APACH II score	25 (22–28)
SOFA score	9 (7.5–12)
PaO ₂ : FiO ₂ ratio	126.3 (91.5–177.7)
Burns (n=35)	
Age	56 (41–77)
Male gender (n, %)	18/17 (51%)
Mortality (%)	5 (14%)
SOFA score	3 (0.75–6)
% TBSA	30 (33–52)
BI	25 (30–35)
PBI	82 (70.5–98)

Table S1. Characteristic features and clinical course of patients with sepsis, ARDS and burns. %TBSA, percentage of the total body surface area; APACHE, Acute Physiology and Chronic Health Evaluation; BI, burn index; PBI, prognostic burn index; SOFA, Sequential Organ Failure Assessment. PaO₂, partial pressure of arterial oxygen; FiO₂, percentage of inspired oxygen. Data are shown as group number or median (interquartile range). Missing values were not included in the table.

TABLE S2

Case	Age/Gender	Complications	Anti-viral drugs combined with TCZ	Requiring O2 conc. and laboratory findings before TCZ	Clinical features and laboratory findings after TCZ	Patient condition
1	72/M	NTM, COPD, Lower pharyngeal cancer	F+C	O2 3L/min, Lym 175/ μ L, CRP 8.62 mg/dL, Ferritin 153.1 ng/mL	Day 5: CRP 0.30, Lym 470 Day 8: O2 2L/min Day 21: CRP 0.05, Lym 970, Ferritin 77.2 Day 25: SARS-CoV-2 (-) Day 27: Discharge with HOT	Cure
2	41/M		F+C	O2 2~3 L/min, Lym 530/ μ L, CRP 13.51 mg/dL, Ferritin 1522 ng/mL	Day 5: O2 free Day 5: CRP 1.07, Lym 1150, Ferritin 889.4 Day 11: CRP 0.10, Lym 1580, Ferritin 652.9 Day 11: SARS-CoV-2 (-) Day 12: Discharge	Cure
3	63/M	HT	F+C	O2 3~5 L/min, Lym 1280/ μ L, CRP 11.53 mg/dL, Ferritin 1531.8 ng/mL	Day 3: CRP 1.98, Lym 990, Ferritin 943.9 Day 7: O2 free Day 10: CRP 0.12, Lym 1664, Ferritin 592.5 Day 15: SARS-CoV-2 (-) Day 16: Discharge	Cure
4	68/M	DM	F+C	O2 2~6 L/min, Lym 999/ μ L, CRP 2.33 mg/dL, Ferritin 880.6 ng/mL	Day 5: O2 free Day 7: CRP 0.17, Lym 1400, Ferritin 828.5 Day 13: CRP 0.06, Lym 1350, ferritin 1120.8 Day 14: SARS-CoV-2 (-) Day 15: Discharge	Cure
5	71/M	DM	L/R+C	Under artificial ventilation (FiO2 0.35~0.8), Lym 2130/ μ L, CRP 7.47 mg/dL, Ferritin 4383.4 ng/mL	Day 4: CRP 1.13, Lym 1010 Day 12: Under artificial ventilation (FiO2 0.3) Day 25: SARS-CoV-2 (-)	Improvement
6	79M		F+C	O2 4L/min, Lym 860/ μ L, CRP 8.57 mg/dL, Ferritin 1110.7 ng/mL	Day 2: Intubation and transfer to other hospital Day 2: CRP 3.9, Lym 660, Ferritin 1505.6 Day 13: Extubation and transfer to our hospital Day 13: CRP 0.46, Lym 581, Ferritin 800.4 Day 15: O2 free	Recovery from deterioration
7	48/M	DM HT Obesity SAS	F+C	O2 6L/min, Lym 82/ μ L 0, CRP 3.78 mg/dL, Ferritin 3355.4 ng/mL	Day 1: Intubation and transfer to other hospital Day 9: Extubation and transfer to our hospital Day 13: CRP 0.12, Lym 278, Ferritin 3700.9 followed by mPSL pulse	Recovery from deterioration

Table S2. Characteristic features and clinical course of patients with COVID-19 treated with tocilizumab. TCZ: tocilizumab; DM: diabetes mellitus; HT: hypertension; NTM: non-tuberculous mycobacteriosis; COPD: chronic obstructive pulmonary diseases; F: favipiravir; C: ciclesonide; L/R:lopinavir/ritonavir.