



Title	Enhancement of IL-6 Production Induced by SARS-CoV-2 Nucleocapsid Protein and Bangladeshi COVID-19 Patients' Sera
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論文内容の要旨

Synopsis of Thesis

氏 名 Name	Md Abu Hasan
論文題名 Title	Enhancement of IL-6 Production Induced by SARS-CoV-2 Nucleocapsid Protein and Bangladeshi COVID-19 Patients' Sera (バングラデシュ国のCOVID-19患者の血清は、SARS-CoV-2のヌクレオカプシドタンパク質存在下でのIL-6産生を増強する)
論文内容の要旨 〔目的(Objective)〕 Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by severe acute respiratory syndrome coronavirus 2 that can have detrimental effects on multiple organs and accelerate patient mortality. This study, which encompassed 130 confirmed COVID-19 patients who were assessed at three different time points (i.e., 3, 7, and 12 days) after the onset of symptoms, investigated interleukin-6 (IL-6) enhancement induced by a viral nucleocapsid (N) protein from a myeloid cell line. IL-6 is the most notable pro-inflammatory cytokine which is responsible for pathogenesis of COVID-19 and increased IL-6 in early stage of SARS-CoV-2 infection indicates the disease severity of COVID-19. Disease severity was categorized as mild, moderate, or severe. The aims of the present study were to re-evaluate the enhancement of N protein mediated IL-6 production from myeloid cells induced by patient sera reported in our previous study and to clarify the roles of the anti-N antibody in this phenomenon. We also assessed untreated serum IL-6 levels, along with routine blood biomarkers, inflammatory markers, coagulation markers, and cardiac markers across mild, moderate, and severe COVID-19 cases. 〔方法ならびに成績(Methods/Results)〕 SARS-CoV-2 cases were confirmed by PCR method. Biochemical and hematological parameters were analyzed with automated systems. IL-6 was measured from heat-inactivated serum in myeloid cell line via ELISA and in untreated serum via an automated multiplex array. Anti-N and anti-Ep9 antibodies were also measured in heat-inactivated serum using in-house ELISA. Regarding the biochemical and hematological parameters of our study population, we observed significant increases in untreated serum IL-6, inflammatory markers such as CRP, ferritin, procalcitonin; coagulation marker D-Dimer, cardiac biomarkers, such as NT-proBNP and High-sensitivity Troponin-I and routine blood biomarkers such as WBC, creatinine, AST, and significant decreases in hemoglobin, hematocrit, and albumin values in severe cases. These results were consistent with numerous previous studies and confirmed our grouping of disease severity is appropriate. We re-evaluated the correlation between COVID-19 severity and the enhancement of IL-6 production caused by myeloid cells in the presence of the N protein. In previous study, sample collection dates were not consistent between mild and severe cases which is important for accurate assessment. Our present study ensured uniform sample collection dates for both mild and severe cases, with patient sera obtained from our tertiary care hospital just three days after symptom onset. To evaluate IL-6-inducing activity, serum samples collected at 3 days after symptom onset from these patients were incubated with and without the N protein. In presence of N protein, IL-6 production was enhanced by the heat inactivated patients' sera and this enhancement was greater in moderate and severe cases than mild cases. A longitudinal study with sampling at 3, 7, and 12 days after symptom onset showed that levels of IL-6 production increased daily, suggesting that anti-N antibody in patient serum plays a crucial role in increasing IL-6 production when the N protein is present. Our previous study did not show a correlation between anti-N antibodies and IL-6 induction from myeloid cells. However, in the present study, we observed a significant positive correlation between the anti-N antibody and IL-6 levels induced by patient sera in the presence of the N protein. The correlation remained statistically significant after dividing samples into 3, 7, and 12 days after onset of symptom. We also observed a significant positive correlation between the antibody concentration and N protein induced IL-6 levels from longitudinally collected sera. These results, together with our previous finding that healthy donor sera failed to enhance IL-6 production, indicate that the anti-N antibody in the patient sera enhances IL-6 production via myeloid cells in the presence of N protein produced by infected cells, which may aggravate the disease. 〔総括(Conclusion)〕 This retrospective study supports the hypothesis that elevated levels of different biomarkers and IL-6 may reflect disease severity and clinical outcomes. Anti-N antibody plays a crucial role in the pathogenesis of severe COVID-19 cases through the enhancement of IL-6 production from macrophages in the presence of the N protein. Our data also strongly support the current vaccine strategy, which targets the S protein only. Targeting the N protein may be a potential strategy for controlling the immune response and reducing inflammation in COVID-19 patients.	

論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

COVID-19はSARS-CoV-2によって引き起こされる呼吸器感染症であり、複数の臓器に有害な影響を及ぼす。本研究では、症状発現後3日、7日、12日の3時点においてCOVID-19患者130例の血清のウイルスヌクレオカプシド（N）タンパク質による骨髓系細胞株からのIL-6増強作用を調べた。骨髓系細胞株にこれらの患者の熱不活化血清を加えてNタンパク質存在下および非存在下で培養した結果、重症例ではNタンパク質刺激によりIL-6産生が増加することが示された。抗N抗体と、Nタンパク質および血清存在下における骨髓系細胞からのIL-6分泌量との間には強い相関が認められ、抗N抗体がIL-6産生誘導において重要な役割を果たすことが示唆された。制御不能なIL-6産生は疾患の重症度と死亡率を悪化させたため、Nタンパク質を効率的に標的化することは、重症例における免疫応答の調節と炎症の緩和を目的とした治療戦略として採用される可能性があり、学位に値するものと認める。