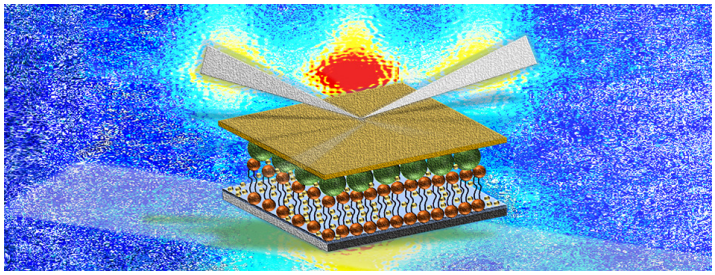

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The influence of the SARS-CoV-2 spike protein on red blood cells

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Almost 4 years into the Covid-19 pandemic, its repercussions go far beyond a simple respiratory infection. A current study estimates that more than 13 % of Covid-19 patients develop Long Covid (LC) with symptoms such as shortness of breath, memory loss and, most prominently, a debilitating, chronic fatigue (CF). Similar post-viral complications (PVC) including CF have also been observed after other viral infections. Micro-blood clots including red blood cell (RBC) stacks ("rouleaux") found in Covid-19 patients' blood samples appear to contribute to LC/CF, e.g. by interfering with oxygen transport. Evidence suggests that the SARS-CoV-2 surface spike protein ("Spike"), which circulates in the bloodstream after a Covid-19 infection binds to RBC membranes [1] and triggers blood coagulation [2]. A detailed investigation of the structural aspects of spike protein binding to RBCs is the 1st part of this study: To address this question, we performed SAXS/ SANS experiments with RBCs at different ionic strength of the buffer solution and studied the effect of spike protein binding on cellular RBC properties. From the measured protein-protein structure factors we determined the intracellular hemoglobin concentration that is informative on morphological shape of the RBCs. Our results reveal a swelling of RBCs upon spike protein binding under all investigated conditions. Effectively, an osmotic counter pressure of around 50 mOsm is needed to counterbalance the swelling effect caused by the spike protein under physiological conditions. A 2nd part of our project zooms in on the role of the stiffness of biological RBC membranes and the effect of the spike protein on RBC membrane bending stiffness. We performed NSE experiments on liposomes prepared from entire RBC membranes and determined the RBC membrane bending modulus within the Zilman-Granek model. Our results demonstrate that RBC membrane stiffness is not affected by spike protein binding. However, an additional dynamic mode at low q-vectors could be observed in native RBC membranes that is suppressed upon pathological conditions induced by spike protein binding. Our study reveals molecular effects of spike protein binding on RBC membranes that affect cellular RBC properties which might lead to impaired oxygen transport and an increased thrombosis risk of Covid-19 patients.

[1] Himbert et al. PLoS ONE 17(3): e0263671 (2022); [2] Zheng et al. Int J Biol Macromol, 193, 1124 (2021)

Hauptautor: STADLER, Andreas

Co-Autoren: WU, Baohu (JCNS-4); Frau DELAUNAY, Clara (Univ. Grenoble Alpes, CNRS, CEA, CNRS, IBS, 38000 Grenoble, France); Prof. FIESCHI, Franck (Univ. Grenoble Alpes, CNRS, CEA, CNRS, IBS, 38000 Grenoble and Institut Universitaire de France (IUF), 75005 Paris, France); Frau MATSARSKAIA, Olga (Institut Laue-Langevin (ILL), Grenoble, France); Dr. CZAKKEL, Orsolya (Institut Laue-Langevin (ILL), Grenoble, France)

Vortragende(r): STADLER, Andreas

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