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Editorial

Self-Assembling Amyloids in Respiratory Virus Proteins

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Amyloidoses are encompass a wide range of incurable human and animal diseases associated with the aggregation of proteins into fibrils with their deposition in organs (including the brain) and systemic tissues. The amyloid state is known to be the most energetically stable conformation possible [1]. All proteins contain intrinsically disordered regions (IDRs) in addition to α-helixes and β-sheets. Besides, in some proteins aggregation-prone regions (APRs) are responsible for the amyloid formation. Partial unfolding of IDRs due to flexible protein conformation in solutions may cause APRs exposure with subsequent aberrant assembly into unbranched fibrils where the β-strands stack in perpendicular layers along the axis of the fibrils. The cross β-sheets, together with the connecting loops, constitute the "amyloid core" [2]. Amyloids are detected using fluorescent hydrophobic dyes: thioflavin T/S and Congo Red [2, 3]. X-ray diffraction analysis allows to reveal 2 reflexes: meridional 4,5–4,8 Å and equatorial 8–12 Å typical for the amyloid cross β–sheets [3]. Electron and atomic force microscopy show fibrils with diameters near 10 nm and lengths up to 10-15 μm. Initial slow nucleation stage of amyloid formation depends on APRs concentration with subsequent fast growth [3].

More than 50 human proteins involved in amyloid formation have been identified in association with neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease [2]. Approximately one third of human precursors of amyloidosises contain IDRs including Aβ peptides, α-synuclein and Tau proteins [2]. Disordered proteins may fibrillate either on their own or in cooperation with a cellular APR-containing protein. Cellular proteins can also be trapped into viral amyloids.

Both RNA- and DNA-containing viruses with single-stranded and double stranded genomic nucleic acids also encode amyloidogenic proteins that benefit the viruses. The E7 protein of human papillomavirus (HPV)-16 was the first viral protein found to have amyloidogenic properties. Subsequently, PB1-F2, an accessory protein encoded by an alternative open reading frame in PB1 segments of Influenza A virus was found to produce amyloids.

COVID-19 remains the public health concern because of substantial morbidity and mortality. At least one-third of COVID-19 patients have neurological symptoms (loss of smell, sensory confusion, memory loss, severe headaches, mood and anxiety disorders, cognitive impairment) and severe syndromes (Guillain–Barre Syndrome, encephalitis, encephalopathy, acute disseminated encephalomyelitis, intracranial hypertension) with possible ischemic or hemorrhagic strokes. The long persistence of neurological sequelae at the remission stages is called post-COVID-19 syndrome. SARS-CoV-2 can cross the blood–brain barrier and infect neuronal cells causing their death as well as destruction of vascular and immune cells of central nervous system [3]. Neuroinflammation and microvascular injury are known to be responsible for amyloid-related neurodegenerative diseases [3]. COVID-19 is caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2). The virions consist of genomic RNA and structural proteins: the spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. S protein is necessary for β-coronaviruses to attach to the host cell and enter. The SARS-CoV-2 nucleocapsid protein (N) responsible for packaging viral RNA and crucial for virus replication and assembly forms amyloids in phase separated droplets [2-4]. Self-assembling nanostructures from the SARS-CoV-2 recombinant proteins S1, S2, and N isolated from the transformed bacterial *Escherichia coli* cells and RBD glycoprotein fragment produced in the transfected human embryonic kidney cells Expi293F cells can interact with fluorescent dyes Thioflavin T and Congo Red suggesting amyloid-like fibers and nanoparticles [3]. The SARS-CoV-2 self-assembling nanoparticles (saNP) can affect both immunodiagnostics because of shielding of coroviral structural antigens inside solid NP and vaccinology with recombinant subunit vaccines with possible induction of Th1 immune response due to unspecific endocytosis of saNP and probable amyloidosises. Currently there are several vaccines against COVID-19 licensed for emergency usage based on mRNA, inactivated whole virus, or adenovirus vectors and more than 300 vaccine candidates in clinical and preclinical development. Currently available inactivated and live attenuated trivalent or quadrivalent vaccines against influenza are produced in eggs, cells or recombinant bacteria. Inactivated egg-based vaccines are still most commonly used. Possible amyloidogenic viral proteins should be carefully controlled in all the vaccines in order to avoid a risk of neurodegenerative conformational proteinopathies.

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