Racemization Hypothesis of COVID-19. Tip of the Iceberg

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Abstract

The impact of viral infections on the central nervous system is widely known. Virus-related neuropsychiatric and neurobehavioral syndromes are caused by the distortion of cognitive, affective, behavioral, and perceptual domains. Although it is a commonly known phenomenon, the mechanism behind it is not well-understood. The contagious and deadly features of coronavirus disease 2019 (COVID-19) have been associated with the virus-host cell interaction at the molecular level. However, there is no reliable biomarker characterizing the disease progression. Studies of the structure, function, and evolution of coronavirus transmembrane spike glycoproteins (S-, N-, and E-proteins) suggest an essential role of protein chirality in virus-cell membrane interaction. The virus-host interaction is the subject of multidisciplinary research from the biochirality and systems biology, to cell physiology and non-equilibrium thermodynamics of phase transitions in proteins. At the protein level, virus-host interaction is modulated by the amino acid sequence of viral proteins and cellular metabolism. Enzymatic and spontaneous post-translational modifications (PTMs) are two mutually influential mechanisms governing the dynamics of virus and host cell proteome. Among them, phosphorylation and racemization are the most inter-related and studied. The spontaneous phase transitions within viral glycoprotein impacts the cell-entry capability of the virus. The spontaneous racemization is a particular and highly specific metabolic event in virus-cell interaction that is the focus of our attention. Many viral proteins are characterized by a high proportion of the serine (Ser) residues, which are the common target of the host-cell glycosylation, phosphorylation, and racemization, and proteolytic enzymes. Particularly, coronavirus N proteins were found to be phosphorylated at multiple Ser residues, a portion of which are shown to be phosphorylation-prone by the Ser-associated kinases. Since Ser is known as one of the most racemization prone amino acids, we promote an idea of the specific impact of spontaneous racemization at Ser residues on virus-host interaction.

Keywords : Virus-host Cell Interaction, Virus Proteins, Post-translational Modification, Spontaneous Racemization, Spontaneous Phase Transitions

Abbreviations

Amino acids	:	AAs
D-amino acids	:	D-AAs
Carboxyl-terminal domain	:	CTD
Central nervous syste	:	CNS
Coronavirus	:	CoV
Coronavirus disease 2019	:	COVID-19
Herpes simplex virus type 1	:	HSV-1
Human immunodeficiency virus	:	HIV
Nucleocapsid protein	:	N protein
Post-translational modifications	:	PTMs
Serine	:	Ser
D-Serine	:	D-Ser
D-Aspartate	:	D-Asp

Threonine : Thr
Tyrosine : Tyr
Spike glycoprotein : S-proteins
Phase transitions : PhTs
Ribonucleic acid RNA, RNA polymerase II : RNAP II
Severe acute respiratory syndrome coronavirus 2 : SARS-CoV-2

Introduction

The intra-cellular protein-based metabolic network is an evolutionary conserved, but also a highly dynamic system. The main driving force of the network is a complex of canonical enzyme-catalyzed post-translational modifications (PTMs). The number of molecular side products and environmental stresses gives rise to many spontaneous non-canonical pathways of PTMs, that are involved in protein aging and human age-related disorders [1,2,3]. Enzymatic and spontaneous PTMs are two mutually influential mechanisms. For example, excessive phosphorylation of TAU is known as a cause of protein aggregation [4,5,6]. The mechanism is believed to be cell, protein, and residue specific. Post-translational phosphoproteins display significant age-related changes in the composition of amino acid's (AA's), and in their cross-linking, and racemization. A relevant example is the age-related loss of phosphoserine (SerPh) content in human phosphoproteins. This mechanism remains to be studied and presumably is associated with the interplay of enzymatic phosphorylation and spontaneous racemization [6]. The widespread role of non-enzymatic reactions in cell metabolism is also well documented [7]. In particular, it has been shown that the spontaneous modification of AAs in viral glycoprotein impacts the cell-entry capability of the virus [8]. The significance of biochirality is supported by a shared recognition that the spontaneous or induced mutations in viral genetic material may alter the disease's pathogenesis. This spontaneous racemization, a particular and highly specific metabolic events in virus-cell interaction, is the focus of the current short review.

Biochirality of Coronavirus

The origin, transmission, and clinical therapies of coronavirus disease 2019 (COVID-19) are a primary target of current medical and scientific investigation [1-30]. Coronavirus (CoV) is a group of enveloped RNA viruses causing respiratory diseases in both humans and animals. Many details of CoV-associated damage at the cellular and molecular levels are still unclear. Due to their inability to self-replicate, viruses have developed unique potentials to utilize and modify the metabolic and signaling pathways of the host cell. Recent development shows that the host cell entry and the replication cycle of coronavirus (CoV) employs a variety of forms of the cell's protein's PTMs including glycosylation and phosphorylation [24-28]. The fundamental physical mechanism underlying the translocation of viral genomes into the cells is traditionally identified as non-equilibrium phase transitions [31-36]. However, none of them gives attention to the essential role of the chiral determinants of molecular condensation, highlighted in several reviews [3]. The interplay of viral and host cell proteins PTMs is the subject of increasing attention. The interaction networks of viral and host proteins during early steps of infection is well known from immunodeficiency virus (HIV) related studies [29]. The knowledge about immune response induced by CoV is critical to patient treatment [37]. The mammalian innate and adaptive immune systems are under the control of AAs metabolism associated with the complex network of enzymatic and spontaneous racemization [38,39]. The pivotal role of D-amino acids (D-AAs), including D-Serine (D-Ser) and D-Aspartate (D-Asp) in the innate and adaptive immune systems, is a new-emerging and promising field of biochemistry [40-42]. However, in spite of the known role of D-AAs in immune system function, there is a void of information about the enzymatic and spontaneous racemization of CoV proteins and the impact of racemization on the virus-receptor coupling, membrane fusion, endocytosis and the host cell's protein racemization. The discovery of spontaneous PTMs in noroviruses suggests that the list of PTMs involved in this should include not only enzymatic but also spontaneous forms of PTMs including racemization and epimerization, which are common in the host cell physiology and pathology [3,30]. Notably, protein damage due to aberrant PTMs is a significant hallmark of lung aging[43]. The reductions of lung functions with age, at the molecular level, are associated with the cell type-specific protein aging and loss of functions related to aberrant PTMs. It is thus logical to assume that COVID-19 progression could be regulated by the aberrant PTMs.

The most accepted form of aberrant PTM associated with protein aging, aggregation, and dysfunction is spontaneous racemization [3]. The aberrant virus associated PTMs of proteins is well-known effect [28]. One particular example involves collagen nanofibers, which are the primary determinants of the biological and structural integrity of various tissues and organs, including bone, skin, tendon, blood vessels, cartilage, and the lungs [11]. Excessive deposition of collagen has previously been seen in virus-related pulmonary fibrosis [44]. Severe acute respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is associated with multi-modal lung dysfunction. At the protein level, SARS-CoV-2 is accompanied by collagen fibrosis [45]. The AA's chain of collagen contains multiple phosphorylation-prone and racemization-prone serine (Ser) residues [12-14]. The accumulation of fibrotic collagen is a well-known process that accompanies many pathological conditions [15-17]. The experimental results of lung proteomics in rodents revealed that collagen protein was increasingly racemized with age. Collagen is also a target of spontaneous racemization [18]. Most racemized AAs in lung collagen have been identified as Ser [19]. Although the details of the cellular responses to the coronavirus are unknown, the epithelial cells of the airway have been identified as a primary target [20]. Alterations in the composition of the extracellular collagen matrix have been shown in many pulmonary disorders [21,22].

Many viral proteins are characterized by a high proportion of Ser residues. Particularly, CoV nucleocapsid proteins (N

proteins) were found to be phosphorylated at multiple Ser residues, a portion of which is shown to be phosphorylation-prone by the serine-associated kinases [46-49]. Since Ser is one of the racemization prone AAs, we promote an idea concerning the specific impact of spontaneous racemization on virus-host interaction [3]. Viral Ser-targeting enzymes are traditionally used as a drug target in clinical practice [23]. This targeting strategy is in agreement with the several essential facts that point to the key role of Ser-associated enzymes in virus-host cell interactions including Ser kinases, Ser proteases, and Ser hydrolase enzymes [50-55,58].

The cell entry programs for CoV are mediated by the viral transmembrane spike glycoprotein (S protein) that bind cellular receptors and involves virus-cell membrane fusions. The interaction of S protein with the membrane receptor triggers a cascade of events including proteolysis, and acidification in endosomes [56]. It was found that S protein in viruses isolated from humans during the 2003–2004 outbreak had a Ser at position 360 (Ser-360) located in the α-helix region [57]. As a result, among the respiratory virus-activating membrane-anchored enzymes, the Ser protease family is of specific interest [58]. The function of the kinase-phosphatase PTMs at Ser, threonine (Thr), and tyrosine (Tyr) residues are well known from the studies of many human viruses including (HIV) [29,59]. Notably, Ser residues in this triad are classified as the most racemization- and phosphorylation-prone residues implicated in protein ageing and cellular disfunction [3,51]. The studies of herpes simplex virus type 1 (HSV-1) reveal that infection alters the phosphorylation of the carboxyl-terminal domain (CTD) of RNA polymerase II (RNAP II). CTD consists of a repeated heptameric sequence (YSPTSPS) containing three Ser residues (Ser-2, Ser-5, and Ser-7). Phosphorylation at Ser-2, Ser-5, and Ser-7 is essential for enzyme function and is vulnerable to the viral impact [60,61]. Protein phosphorylation on serine, threonine, and tyrosine (Ser/Thr/Tyr) is considered to be the major regulatory PTMs in eukaryotic cells from bacteria to mammal [62]. In mammals, the racemization-prone Ser residues are most closely linked to the post-translational phosphorylation (PTPh) of proteins Accordingly, Ser is among the key players in the rapid evolution of protein phosphorylation sites [3,63]. Also, PTPh of Ser serves for the rewiring and modulation of the cell signal pathways. Along with the Tyr and lysine (Lys), Ser phosphorylation is an essential regulator of NMDAR-associated neurotransmission [64]. From the broader biological scale, Ser associated phosphorylation is known as a mechanism involved in natural selection to fit the environment.

We hypothesize that the same Ser-centered mechanisms should be considered not only for the acute response to the environmental cues in general, but also for the immune response to the viral infection.

Conclusion

The coherent set of evidence discussed above, allows for the articulation of the hypothesis that COVID-19 triggers a cascade of spontaneous PTM. In this regard, the control of the level of D-AAs (including D-Ser) in the lung can serve as a reliable biomarker of COVID-19- related disease conditions. This hypothesis is supported by the newly derived line of facts including the finding that viral infection {herpes simplex virus type I (HSV-1)} of human-induced neural stem cells (hiNSCs) {3D bioengineered brain model} leads to the formation of the amyloid plaque-like aggregations [65]. The aggregates of amyloid plaque contain several D-AAs. It is also known that D-AAs-containing proteins are resistant to the metabolic and digestive enzymes, which usually recognize only proteins composed exclusively of L-AAs-based proteins or peptides [66]. As a result, unmetabolized D-AAs-containing brain peptides may be found in urine and blood, serving as the useful biomarker for associated diseases. The broad range significance of bio-chirality is exemplified in the studies of D-AAs role in kidney-related and neurodegenerative diseases [2,67,68]. Further investigation of the epidemiology, pathogenesis, and chiral proteomics of the virus is necessary for the proper understanding of acute and long-term consequences of CoV infections, as well as for nutritional support to patients , and the development of effective therapeutic and prophylactic [71].

Afterword

The multidisciplinary facets of virus-related research require attention to the physics of protein folding [3]. From a biophysics perspective, the capsid shell of the virus is seen as a two-dimensional crystal with a limited size closed surface comprising inside cargo space [70].

The capsid surface is the arrangement of the equivalent oligomeric sub-units. The chirality of virus proteins is a critical internal determinant of the handedness observed in capsid morphology. The chirality propagation from the protein to the morphological level is equally necessary for two different events [71]. The first: virus entry into the host cell and the second is the protection from unnecessary molecular invasions into virus DNA [72]. The spontaneous phase transitions (PhTs) within viral glycoproteins impacts the cell-entry capability of the virus. The spontaneous racemization is a particular and highly specific metabolic event in virus-cell interaction, and is the focus of our attention. Many viral proteins are characterized by a high proportion of the Ser residues, which are the common target of the host-cell glycosylation, phosphorylation, racemization, and proteolytic enzymes [58,73-76]. Particularly, CoV N proteins were found to be phosphorylated at multiple Ser residues, a portion of which are shown to be phosphorylation-prone by the Ser-associated kinases. Since Ser is known as one of the most racemization prone amino acids, we promote the idea of the importance of the specific impact of spontaneous racemization on virus-host interaction. While speculative, the above-considered arguments are convincing to expect that spontaneous racemization may also be involved in the development of neuropsychiatric and cognitive pathologies.

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Authors Conflict

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