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Perspective

Neurological Sequelae of COVID-19: A Biochemical Perspective

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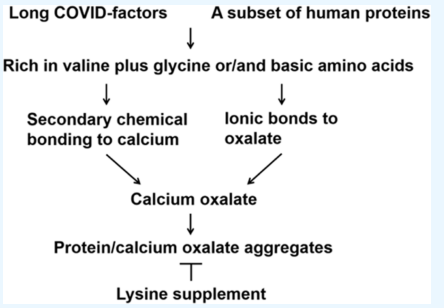
ABSTRACT: Exogenous factors can induce protein expression and modify the proteome which sustains for a certain period of time. The proteins of SARS-CoV-2 are high in valine plus glycine, which possess potent affinity to divalent cations such as calcium. Calcium buildup changes the protein expression profile by enabling the efficient synthesis of proteins rich in amino acids with calcium affinity. Subsequent formation of insoluble and stiff calcium oxalate and aggregates confers cellular stress and causes cell senescence. This scenario accounts for sequelae seen in some patients following recovery from COVID-19.



COVID-19 is triggered by SARS-CoV-2 infection, primarily involving the lungs, but studies have indicated that many other organ systems including the neurological system can be viral targets.[1,2] The sequelae of COVID-19 include neurological and neuropsychiatric symptoms that can affect both children and adults and even those who had mild illness. The link between infection and neurological disorders remains largely unknown, but recent research has suggested that SARS-CoV-2 can infect the nervous system. The high affinity of SARS-CoV-2 spike protein to the angiotensin-converting enzyme 2 (ACE-2) receptor may be one of the critical factors since ACE-2 has recently been detected on neurons and glial cells in several experiments.[3] Long-term adverse effects in the central and peripheral nervous system of COVID-19 remain to be explored. The sequelae of COVID-19, neurological or non-neurological, are now described as a global public health burden.[4]

BIOCHEMICAL ALTERATIONS IN LONG COVID AND HYPOTHESIS

Dry cough, fever, and loss of taste and smell are major symptoms of COVID-19. These manifestations can endure for long periods post-infection, and concomitant symptoms include fatigue, dyspnea, pain, neurological indications, and so forth. A chemical biological perspective might provide some clues to this perplexing issue.[5] For instance, dry cough can be caused by insoluble and water-free protein/small-molecule aggregates, which are solubilized via the use of a strong anion Cl^- as discussed later in this article.[6] Hydrogen bonding might be critical for senses like taste and smell, and insoluble and stiff calcium oxalate can block these processes via antagonizing the soluble states of cells.

CALCIUM BUILDUP INDUCES PROTEIN EXPRESSION AND MODIFIES THE PROTEOME

It was proposed that the high valine plus glycine content in the proteins of SARS-CoV-2 wreaks havoc on cells of certain patients, given the peculiar chemical properties of these amino acids (Figure 1).[7−14] Remarkably, glycine exhibited both senescence and anticancer effects[15,16] which can be attributed

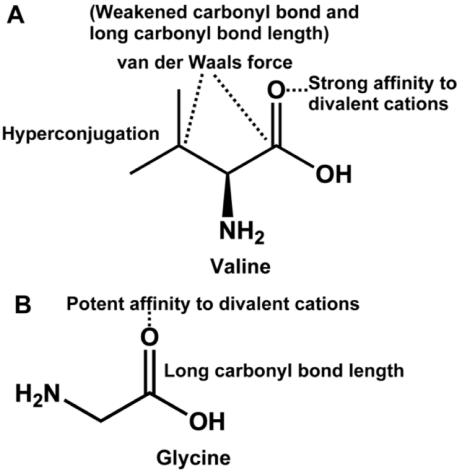


Figure 1. Chemical features of valine (A) and glycine (B).

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Table 1. Factors during Acute COVID-19 (% Amino Acids)

GENE	protein_name	UniprotID	F	L	hydrogen_bonding[72]	acidic_amino_acids	basic_amino_acids	V + G
SERPINF2	α-2-antiplasmin	P08697	5.91	15.27	42.57	9.57	10.39	12.42
SERPINA3	α-1-antichymotrypsin	P01011	5.91	13.95	39.95	12.77	12.06	9.46
ADIPOQ	adiponectin receptor protein 1	Q96A54	8	10.67	40.8	9.07	12	16.27
BST1	ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase 2	Q10588	3.77	12.89	42.14	11.01	13.84	10.06
SERPINF1	pigment epithelium-derived factor	P36955	4.31	13.64	41.87	11.96	12.68	11.48
SPP2	secreted phosphoprotein 24	Q13103	4.74	7.11	49.29	10.9	14.22	10.9
TNNT3	troponin T3, fast skeletal type	P45378	1.49	7.06	25.28	26.39	26.02	6.32
S100-A9	protein S100-A9	P06702	4.39	9.65	43.86	17.54	19.3	9.65

Table 2. Factors Predicting Long COVID/Post-acute Sequelae of COVID-19 (PASC) (% Amino Acids)[a]

GENE	protein_name	UniprotID	F	L	hydrogen_bonding[72]	acidic_amino_acids	basic_amino_acids	V + G
SERPINA1	α-1-antitrypsin	P01009	6.46	12.2	39.71	13.4	12.92	12.2
SERPINF2	α-2-antiplasmin	P08697	5.91	15.27	42.57	9.57	10.39	12.42
A2M	α-2-macroglobulin	P01023	4.21	9.7	44.37	10.65	11.87	15.6
ADIPOQ	adiponectin receptor protein 1	Q96A54	8	10.67	40.8	9.07	12	16.27
APOA4	apolipoprotein A-IV	P06727	3.03	14.14	33.08	17.17	15.66	9.85
B4GT1	β-1,4-galactosyltransferase 1	P15291	3.77	10.55	45.73	8.04	11.81	15.83
COL6A3	collagen α-3(VI) chain	P12111	4.69	8.88	37.87	11.52	12.34	18.73
CP	ceruloplasmin	P00450	4.88	6.95	46.38	13.9	13.8	13.15
CRISPLD1	cysteine rich secretory protein LCCL domain containing 1	Q9H336	2.4	4.4	51.8	9.6	15	14
CRP	C reactive protein	P02741	7.14	8.93	43.3	10.71	10.27	16.52
CYCS	cytochrome *c*	P99999	2.86	5.71	40.95	10.48	21.9	15.24
DCXR	L-xylulose reductase	Q7Z4W1	2.87	10.25	36.07	8.61	11.48	22.13
FGF21	fibroblast growth factor 21	Q9NSA1	2.87	13.88	42.58	11.48	10.05	14.83
HBE1	hemoglobin subunit epsilon	P02100	6.12	10.88	36.05	9.52	15.65	14.97
HPX	hemopexin	P02790	4.11	9.09	43.94	10.61	13.85	15.37
HSPA5	endoplasmic reticulum chaperone BiP	P11021	3.52	7.95	35.47	16.97	14.53	15.44
SERPING1	plasma protease C1 inhibitor	P05155	4.8	12.8	48.2	9.6	10.6	9.4
IGHE	immunoglobulin heavy constant epsilon	P01854	3.5	7.71	51.64	8.64	12.15	12.85
ITIH2	inter-α-trypsin inhibitor heavy chain 2	P19823	5.39	8.56	44.4	11.63	13.32	14.06
MASP2	Mannan binding lectin serine peptidase 2	O00187	4.52	8.02	46.06	11.81	11.52	14.58
MMP3	matrix metallopeptidase 3	P08254	6.71	9.01	39.62	13.84	14.47	13
NCAM1	neural cell adhesion molecule 1	P13591	2.91	5.94	45.45	14.45	10.84	14.34
CTSH	pro-cathepsin H	P09668	4.78	6.57	49.25	7.76	11.94	14.03
PEBP1	phosphatidylethanolamine-binding protein 1	P30086	1.6	10.16	41.71	12.83	16.04	16.58
SERPINF1	pigment epithelium-derived factor	P36955	4.31	13.64	41.87	11.96	12.68	11.48
PRDX3	thioredoxin-dependent peroxide reductase, mitochondrial	P30048	5.47	10.16	41.02	8.59	12.5	15.62
SAA1	serum amyloid A-1 protein	P0DJI8	7.38	6.56	32.79	13.11	14.75	14.75
TFEB	transcription factor EB	P19484	1.68	11.13	48.95	11.97	13.03	9.87

[a]The plasma proteome distribution triggered by SARS-CoV-2 infection spanned at least 6 weeks after the initial positive PCR assay.[19]

to its robust secondary chemical bonding to calcium, allowing the generation of stressful calcium oxalate and neutralization of mutagenic strong acids such as HCl, respectively.

A previous study demonstrated that the amino-terminus of the PrP^{C} protein harboring repeats of PHGGGWGQ possesses several sites that can chelate the divalent cation Cu^{2+} through glycine residues.[17] Valinate and isovalinate can associate with zinc and calcium giving rise to complexes.[18]

Tables 1 and 2 indicate that the host proteins induced during infection and post-infection[19−21] are high in either basic amino acids or valine plus glycine or both, attracting ions such as oxalate, calcium, or some ionic substances collectively.[7−9,14] The tissue-specific expression profiles of the aforementioned factors are summarized in Tables S1 and S2.[22,23]

The valine plus glycine contents in the envelope proteins of SARS and SARS-CoV-2 are 21.1 and 18.7%, respectively.[14,24−26] The envelope protein of SARS-CoV-2 alone, free of any viral nucleic acids, caused acute respiratory distress syndrome-like damages in vitro and in vivo,[26] whereas the envelope protein of SARS is a confirmed virulence factor.[25]

Previous studies demonstrated that the amino acid supplement induces changes in the proteome profile[27,28] and so do calcium and other cations.[29] For instance, calcium induces the expression of calcium-binding proteins.[30,31] Pertinent to a biochemical mechanism, antagonism between HIV-1 and SARS-CoV-2 on mortality rates was assumed to be mediated via the competition between hydrogen bonding and secondary chemical bonding to divalent cations, as strong acids and

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insoluble and stiff salts are two extremes of cellular states and counteract mutually.[32] Waterfowls do not often develop Avian Influenza but chickens and humans do, which is speculated to be the result of extensive hydrogen bonding and attendant weak acids in aquatic animals that modulate proton traffic and the formation of strong acids and solubilize insoluble and rigid salts. As another case in point, high humidity in south coastal China and Southeast Asia likely underlies the onset of nasopharyngeal carcinoma, and reduced humidity resulted from escalating global warming crisis accounts for the declining incidences of this type of cancer in south China in recent years.[33−39] Proteins with extensive hydrogen bonding can be induced in highly humid weather, and they are capable of bonding with both water and protons, enhancing the formation of acids, particularly the mutagenic strong acids such as HCl. Valine as well as glycine in viral proteins bind calcium present in calcium oxalate via secondary chemical bonding[7−9] and subsequently accumulated calcium induces the expression of calcium-binding host proteins high in valine and glycine and perhaps also arginine.[5] These host proteins persist and trigger cellular stress after disease recovery, despite that the human body has already cleared the virus. Calcium oxalate is stressful and a major component of renal stones, shortening the lifespan after buildup in cells.[40] Oxalate is mostly produced via energy metabolism, which might account for the favorable effects of calorie restriction in health and longevity.[14]

ENVIRONMENTAL, DIETARY, AND LIFESTYLE FACTORS INFLUENCE PATHOGENIC MECHANISMS

COVID-19 is particularly severe in cold winter due to the overdrive of energy metabolism, where oxalate can be produced from the shunt of Krebs cycle and other pathways.[8,9,14] Some meat-heavy diet is high in essential amino acids such as valine, thus detrimental to patients with SARS-CoV-2 infections by promoting protein synthesis, viral proliferation, and virulence.[14] Lifestyle factors such as intense exercise generate excess of lactic acid as well as stressful oxalate which accounts for the death of some post-recovery COVID-19 patients.[41] Church-goers have lower disease risks due to attenuated ion traffic, consequently reducing acid formation and calcium oxalate generation.[42]

There are also influences of germline genetic variations,[43] which affect every cell of a descendant. Unlike somatic mutations, germline variations are transmitted to offspring. Gene-by-environment interactions are evident when numerous genes in energy metabolism pathways are induced by low temperatures and down-regulated at higher temperatures.

A molecular pathological epidemiology study[44,45] demonstrated that microclots in long COVID plasma samples, harboring $\alpha(2)$-antiplasmin, several fibrinogen chains, and serum amyloid A, are more recalcitrant to fibrinolysis versus that of controls.[21]

CROSSTALK AMONG CALCIUM, α-SYNUCLEIN, AMYLOID β, TAU, AND LONG-COVID FACTORS

Neurodegenerative risk factors such as α-synuclein, amyloid β, or tau are all rich in valine plus glycine residues.[8,9,39] Together with long-COVID factors, they form extensive aggregates with calcium oxalate, compounding neurological and perhaps non-neurological symptoms (Figure 2). Aβ40 and Aβ42, two peptide fragments of amyloid β, possess nearly 30% valine plus glycine.[8] Biochemical aggregates consisting of proteins and small, insoluble, and stiff molecules generate stresses and result in cell death.

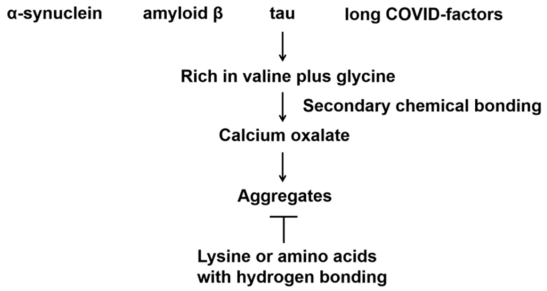

Figure 2. Crosstalk among risk factors for neurodegenerative disorders and long-COVID factors and intervention strategies.

The neurological sequelae of COVID-19 include ischemic and hemorrhagic stroke, cognition and memory disorders, peripheral nervous system disorders, migraine and seizures, mental health disorders, sensory disorders, and so forth.[46] Many neurological functions could be mediated at least in part by hydrogen bonding, as these functions are compromised by buildup of divalent cations which are prone to form insoluble and stiff salts in the brain that antagonize hydrogen bonding.[8,39] Rigid calcium oxalate impedes blood flow and can trigger ischemic stroke. Together with hemolytic, high-level Cl^-, it may increase the risk for hemorrhagic stroke. Furthermore, constipation is a sign for the presence of insoluble and stiff salts and is commonly seen in patients with COVID-19, Alzheimer's disease, dementia, seizures, cognition impairment, heart disease, and so forth.,[7−9,14,39] suggesting that insoluble salts might be involved in the etiology of numerous disorders. Indeed, calcium oxalate was detected in the brains of patients with some neurodegenerative diseases.[8,13]

FUTURE OUTLOOK

SARS-CoV-2 can cause inflammatory response, including fever, redness, swelling, and pain.[46] Fever is caused by the buildup of proton channeled for the production of ATP via the respiratory chain. Proton flux can be enhanced by hydrogen bond donors and acceptors in viral proteins. Redness can be increased by blood circulation and blood vessel dilation. Augmented ion traffic through chemical bonding or secondary chemical bonding is responsible at least in part for tissue swelling. Pain may be triggered by abnormal levels of strong acids such as HCl or accumulated stiff calcium oxalate.

Immunological memory is derived from an adaptive immune system, including CD4 T cells, CD8 T cells, B cells, and enduring antibody responses. Altered immunity in long COVID enhances inflammatory process and impacts the release of cytokines .[47−51] According to a limited examination, many cytokines do share sequence features with those in long COVID factors, such as relatively high content of valine plus glycine, basic amino acids, or both, consequently reinforcing symptoms of COVID sequel by augmenting the formation of aggregates. Cytokine storm damages tissues which can lead to long COVID.[52] T cell perturbations continue for months after COVID-19 and are linked with long COVID manifestations.[53]

In the thyroids of 85.2% of the patients aged 70 years and above, calcium oxalate crystals were detected within 5 h of death,[54] a telltale sign of its involvement in the aging process

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and death. Oxalic acid was enriched in the COVID-19 patient serum metabolome.[55] Hypocalcemia was associated with mortality during the COVID-19 pandemic,[56] and calcium depletion is likely to be triggered by the augmented formation of stressful calcium oxalate.

One countermeasure initially proposed by Nobel Prize laureate Linus Pauline and his colleagues for heart disease can address the issue of long COVID,[5,39,57] which was confirmed during the pandemic.[14,58,59] As long-COVID factors possess a similar mechanism to that of viral proteins, lysine supplement can find use in the treatment of the sequelae.

The positively charged lysine attracts Cl^-, which solubilizes calcium oxalate or its aggregates with proteins via the disruption of primary and secondary chemical bonding between amino acid residues and calcium (Figure 2).[5,39] The supplement of amino acids with hydrogen bonding capacity can either weaken or strengthen aggregate structures by forming acids solubilizing insoluble salts or hydrogen bond networks, respectively.[8]

Supplement of leucine or phenylalanine attenuates both hydrogen bonding and secondary chemical bonding to divalent cations in cells, via reduced cation traffic with their negligible cation affinity of carboxyl oxygen (Figure 3).[60−62] However,

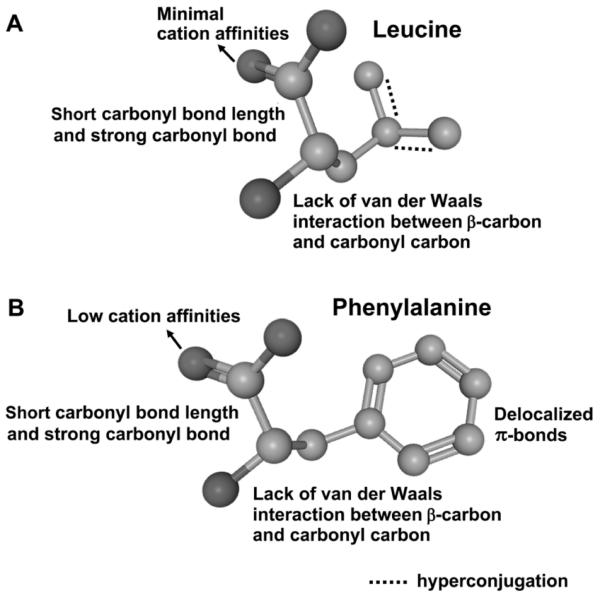

Figure 3. Chemical features of leucine (A) and phenylalanine (B).

leucine or phenylalanine supplement in some cases can enhance hydrogen bonding and secondary chemical bonding to divalent cations in proteins with very low content of acidic amino acids.[61] Acidic amino acids possess affinity to all cations, thus capable of modulating hydrogen bonding and secondary chemical bonding to divalent cations via the traffic of abundant, non-proton monovalent cations such as Na^+ and K^+.[61] When traffic of Na^+ and K^+ is attenuated in the presence of basic proteins with underrepresented acidic amino acids, the effects of protons and divalent cations become more pronounced with overrepresented leucine plus phenylalanine residues as they further diminish fluxes of cations including Na^+ and K^+, while amino acid residues with secondary chemical bonding to protons and divalent cations are preserved in these proteins. As regards to personalized molecular biomarkers, acidic amino acids, for instance, counteract lysine in the formation of acids or insoluble salts in a convalescent patient with particular long-COVID factors rich in basic amino acid residues.[39,61] The extent in the competition among these amino acids may suggest that different intervention tactics are better suited to different individuals. The biochemical antagonism between strong acids and protein/salt aggregates accounts for the inverse association of cancer and Alzheimer's disease.[39,63] Despite that all 20 amino acids are present in proteins, supplement of a particular amino acid enhances the synthesis of certain proteins overrepresented with this amino acid,[64] thus impacting ion traffic and consequently influencing acid and calcium oxalate formation.

Individuals on plant-based diets had 73% less likelihood of displaying moderate-to-severe COVID-19 symptoms.[65] When examining fasting blood glucose (FBG) levels set at <4.74, 4.74−5.21, 5.21−5.78, 5.78−7.05, and ≥7.05 mmol/L, the adjusted odds ratios for the risk of severe/critical condition in COVID-19 were 25.33, 1.00, 3.13, 10.59, and 38.93, highlighting a J-shaped response to FBG levels and the importance of calorie restriction.[66] The immunomodulatory role of divalent cation zinc on COVID-19 can be explained by its antagonism with calcium.[67−69] Acetic acid has a similar structure to oxalate and possesses preventive effects and treatment efficacy on COVID-19.[70,71] All these remedies can be valuable in the battle against long COVID.

CONCLUSIONS

In summary, the proteome profile can be modified by cations such as calcium or calcium-binding viral proteins upon SARS-CoV-2 infections. Strong anions, for instance Cl^-, antagonize calcium oxalate by disrupting secondary chemical bonding among proteins and insoluble salts and solubilize insoluble and stiff molecules.[5,14,39] To address changes in the proteome and sequelae of COVID-19, amino acids antagonizing valine plus glycine, for example, lysine or particular amino acids capable of hydrogen bonding, can be adopted in the dietary regimen at a modest amount to improve physical health.[5,14,58,59,61]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c04100.

Tissue-specific expression profiles of factors during acute COVID-19 and tissue-specific expression profiles of factors predicting the long-COVID/post-acute sequelae of COVID-19 (PASC) (PDF)

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Author Contributions

Q.L. contributed to the conception and design of the work. X.Z., Y.Z., L.W., J.L.O., W.Z., J.Z., Y.W., and Q.L. contributed to the analysis and interpretation of data and preparation of figures and gathering of references for the work. Q.L., Y.W., and X.Z. co-drafted the manuscript with input from all authors.

Notes

The authors declare no competing financial interest.

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