The Long Haul of COVID-19 Recovery: Immune Rejuvenation versus Immune Support

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Abstract

With the COVID-19 pandemic still affecting communities all over the world and "Long Haul" chronic health issues emerging, it is time for us to look back at past multi-symptom health conditions that required a different approach to their treatment, beyond just managing symptoms. It is important for us to consider how to apply what we have learned about immune rejuvenation and its impact on conditions associated with chronic immune dysfunction. We know more than we ever have before about how to reduce chronic inflammation at its source through the support of selective immune cell autophagy/mitophagy and improved immune cell mitochondrial activity, followed by remodeling of the immune epigenome, and—ultimately—a reset of immune function.

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Thousands of people have not felt well since recovering from the acute phases of COVID-19 infection. Principal residual symptoms include brain fog, shortness of breath, chronic cough, muscle and joint pain, and unremitting fatigue. It's becoming known as "The Long Haul" and *Science* magazine prominently featured an article by that title in their August 7, 2020 issue. A sub-headline effectively highlighted the challenge of the situation: "Some COVID-19 survivors are still sick months later. Doctors want to learn why and what they can do."[1]

We have seen a similar constellation of symptoms before. In 1985, the picturesque ski town of Incline Village, Nevada experienced a very bad flu season. Two local physicians—Paul Cheney, MD, PhD, and Charles Lapp, MD—saw these trends emerge in their patient population and started to closely follow those who were affected. Ultimately, Cheney and Lapp would publish a seminal article about the condition they had studied and named: "The Chronic Fatigue Syndrome."[2] In collaboration with Anthony Komaroff, MD, further research had been undertaken that revealed chronic fatigue syndrome was associated with an alteration in immune system function and a state of chronic inflammation.[3,4]

I began a correspondence with Dr. Cheney shortly after his publications about chronic fatigue syndrome started appearing in the medical literature. I was leading a research group of my own in Washington state at that time and I had two close associates—Scott Rigden, MD, and Graham Reedy, MD—who were eager to study and understand the origins of this post-viral chronic fatigue issue. During that same era—the 1990s—we observed that many veterans returning from the Gulf War were seeking help for symptoms that included serious fatigue, myalgia, and cognitive deficits. This was happening all over the country and the condition eventually came to be called "Desert Storm Syndrome." My research group did work with local veterans. Our findings indicated these debilitating issues appeared to be associated with induced mitochondrial defects in biochemical energy production, and that this state of impairment could have a lasting deleterious impact on immune function.[5]

Michael Maes, MD, PhD, and Martin Pall, PhD, are two researchers who have independently spent years studying chronic fatigue syndrome. Their work confirmed that this condition is associated with functional mitochondriopathy, immune dysfunction, and oxidative stress that results in a state of sustained tissue-specific inflammation and gives rise to the complex multi-organ symptomatology of this syndrome.[6-10] Now, long-haul post-COVID-19 infection recovery is making headlines. Although it has not been officially named a syndrome, the similarities in clinical

presentation to chronic fatigue syndrome and Gulf War syndrome are striking. Can a similar immunopathology be inferred? If so, what course of therapy should be pursued given this shared putative immune mechanism? Lastly, are there diet and lifestyle factors that contribute to the degree of immunopathology following the SARS-CoV-2 infection?

Nutritional Recommendations for Immune Protection Against Viral Infections

Optimal nutritional status is very important for maintaining a well-functioning immune system, which in turn can protect an individual from illness caused by exposure to viral and other infectious organisms.[11] Philip Calder, PhD, has been writing extensively on this topic, and in May 2020 he published an article in *BMJ Nutrition, Prevention & Health* with the following title: "Nutrition, Immunity and COVID-19." This very helpful review provided insights into the daily dietary intakes of specific nutrients that support immune system function. These include vitamin A, vitamin C, vitamin D, vitamin E, and zinc, as well as omega-3 fatty acids and specific probiotic organisms.[12]

Are these recommendations to support a healthy immune system sufficient enough to meet the needs of an individual who has suffered immune injury as a consequence of infection with COVID-19 or other viral pathogens? That is the question of the moment, and it comes with some urgency. Based on my past experience with chronic fatigue syndrome, advanced medical nutrition therapy may be required in this situation.

It is now recognized that infection with the SARS-CoV-2 virus results in injury to the immune system and a residual "memory" of the infection, as observed in the types and activities of various immune cells.[13] This results in an imbalanced immune system state that is characterized by overactivation of the NLRP3 inflammasome, as well as a heightened activation of inflammatory cytokines. It has been demonstrated that this situation can create "bystander" damage to hematopoietic stem cells (the cells from which all immune cell types are produced).[14] This damage can take the form of mutational and epigenetic changes to the progenitor immune cells. The mutational injury that follows a serious viral infection resembles changes that are seen in a condition known as clonal hematopoiesis of indeterminate potential (CHIP).[15] In long-haul COVID-19 patients, the alteration of genes in the CHIP-driver sequence in hematopoietic stem cells resulting from SARS-CoV-2 infection could create a long-term inflammatory phenotype associated with mitochondrial and immune system dysfunction that results in the complex symptom profile noted in this population.

Studies of COVID-19 patients indicate that aging and comorbidities linked to alterations in immune system function are associated with increased disease severity, including the cytokine storms that have become a hallmark of SARS-CoV-2 infection.[16] Immunosenescence is a term used to describe the aging of the immune system. It is now known that infection with the virus can accelerate this process and cause damage to immune cells. Additionally, the type of immune system imbalance an individual has prior to exposure to the virus, as well as pre-existing increased activities in certain immune cells, are two factors that may influence disease severity in the event of infection with SARS-CoV-2.[17] When the underlying status of the immune system is unknown, non-specific "boosting" immune activity can result in adverse outcomes among people with altered immune system function.

What about seemingly healthy individuals? Recently, a large collaborative study involving investigators from the Karolinska Institute, the University of North Carolina, and Stanford University School of Medicine demonstrated there is considerable variation in immune system status and function among healthy populations. Importantly, the differences were not genetically determined, but rather they were driven by lifestyle, diet, and environmental factors to which the immune system had been exposed.[18]

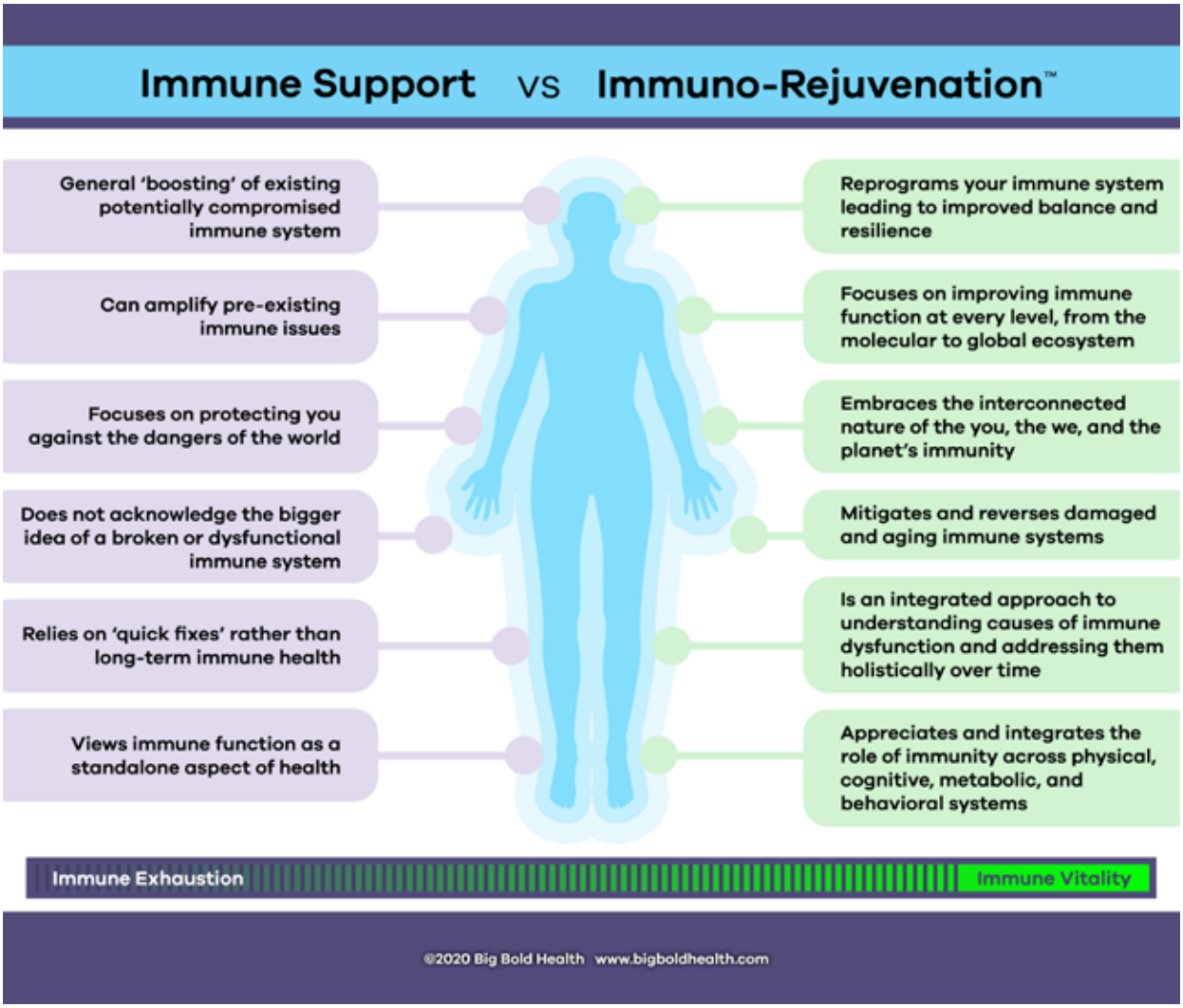
These researchers measured 204 different immune parameters, including immune cell types, cytokine responses, and serum proteins derived from the immune system, of which 77% were dominated and 58% were almost completely determined by non-heritable factors. Some of these factors were found to become variable and accumulate at different rates with age. This suggests the cumulative influence of environmental, diet, and lifestyle exposures could lead to differing immune identities. Furthermore, the accumulation of immune cells that have undergone mutational injury and epigenetic changes as a result of lifestyle and environmental factors may increase the inflammatory state of the individual.

This perspective indicates that an objective for improving immune function should be focused on reducing the production rate of damaged immune cells, the elimination of immune cells that carry messages from past exposures, and the replacement of those cells with new immune cells not imprinted with those memories. In other words: immune rejuvenation.

Immune Rejuvenation and Autophagy

Identifying immune identities. Rejuvenating the immune system. These are objectives that have existed in medicine for some time. Recent discoveries related to the structure and function of the immune system have opened the door to these objectives becoming realities. Here is a brief timeline chronicling the evolution of our understanding of the immune system over the past 60 years: T and B cell differentiation in the immune system was discovered in the early 1960s; natural killer cells were discovered in the 1970s; Th1 and Th2 immune cell types and their connection to inflammation were discovered in the 1980s; regulatory T cells were discovered in the 1990s; and characterization of M1 and M2

Figure 1. Immune Support Vs Immuno-Rejuvenation Diagram



macrophage types came about in the early 2000s. in 2006, the Nobel Prize in Physiology and Medicine was awarded to Yoshinori Ohsumi, PhD, for his discovery of the mechanism of autophagy. This year—2020—Leo Swadling, PhD, discovered a population of T cells in the liver that can switch on autophagy to renew organelles like mitochondria to maintain their fitness.[19-21]

Autophagy has dominated immune system research in recent years, and for good reason. Back in 2009, an article was published in *Nature Review of Immunology* with a provocative title: "The Ageing Immune System: Is It Ever Too Old to Become Young Again?"[22] That article described work that promoted immune system renewal through selective activation of autophagy and mitophagy in immune cells. Since then, considerable progress has been made in understanding how various lifestyle and dietary factors can influence the autophagy process, both positively and negatively.

It has now been demonstrated that autophagy is clinically connected to the activation of immune rejuvenation through the application of fasting physiology, as well as the consumption of diets that are low in refined starch and sugar, high in omega-3 fatty acids, and high in specific dietary polyphenols and flavonoids.[23,24,25,26,27] It has also been found that the diet-related composition and activity of the intestinal microbiome influences immune autophagy.[28] In addition, there is evidence that specific prebiotic and probiotic formulations may be important in supporting immune autophagy.[29] The trajectory of the current research indicates that personalized lifestyle medicine can play an important role in supporting immune system rejuvenation by reducing damage to hematopoietic stem cells, which are progenitor cells that produce new immune cells and improve immune function, and encouraging the replacement of damaged cells with more resilient immune cells.[30,31]

Immuno-Rejuvenation versus Immune Support

With this increased understanding of the factors that influence autophagy and immune system function, there

is evidence that an important clinical approach to treating patients who are struggling with COVID-19 recovery is rejuvenation of their immune system. These long-haulers have experienced immune injury as a result of SARS-CoV-2 infection, and they may require more than immune support to recover.[32] The application of an Immuno-Rejuvenation Program™ may be the best course of action. This program would identify specific immune identities, which would lead to intervention with personalized strategies for reducing immunosenescence and chronic inflammation. In turn, improvement could potentially be achieved for the following variables: impaired immune autophagy, inflammasome activity, genomic instability, immune mitochondrial dysfunction, epigenetic alterations, and telomere attrition.

The contrast between immune support and immuno-rejuvenation can be seen in Figure 1.

A growing body of work validates that lifestyle, along with dietary components such as specific phytochemicals found in various foods and herbs, have a positive impact on immune rejuvenation.[33] With the COVID-19 pandemic still affecting communities all over the world and "Long Haul" chronic health issues emerging, it is time for us to look back at past multi-symptom health conditions that required a different approach to their treatment, beyond just managing symptoms. It is important for us to consider how to apply what we have learned about immune rejuvenation and its impact on conditions associated with chronic immune dysfunction. We know more than we ever have before about how to reduce chronic inflammation at its source through the support of selective immune cell autophagy/mitophagy and improved immune cell mitochondrial activity, followed by remodeling of the immune epigenome, and—ultimately—a reset of immune function.

References

1. Couzin-Frankel J. The long haul. *Science*. 2020 Aug 7;369(6504):614-617. doi: 10.1126/science.369.6504.614. PMID: 32764050.
2. Lapp CW, Cheney PR. The chronic fatigue syndrome. *Ann Intern Med*. 1995 Jul 1;123(1):74-5. doi: 10.7326/0003-4819-123-1-199507010-00015. PMID: 7762921.
3. Buchwald D, Cheney PR, Peterson DL, Henry B, Wormsley SB, Geiger A, Ablashi DV, Salahuddin SZ, Saxinger C, Biddle R, Kikinis R, Jolesz FA, Folks T, Balachandran N, Peter JB, Gallo RC, Komaroff AL. A chronic illness characterized by fatigue, neurologic and immunologic disorders, and active human herpesvirus type 6 infection. *Ann Intern Med*. 1992 Jan 15;116(2):103-13. doi: 10.7326/0003-4819-116-2-103. PMID: 1309285.
4. Caligiuri M, Murray C, Buchwald D, Levine H, Cheney P, Peterson D, Komaroff AL, Ritz J. Phenotypic and functional deficiency of natural killer cells in patients with chronic fatigue syndrome. *J Immunol*. 1987 Nov 15;139(10):3306-13. PMID: 2824604.
5. Bland JS. Chronic Fatigue Syndrome, Functional Mitochondriopathy, and Enterohepatic Dysfunction. *Integr Med (Encinitas)*. 2017 Oct;16(5):18-21. PMID: 30936800; PMCID: PMC6438100.
6. Myhill S, Booth NE, McLaren-Howard J. Chronic fatigue syndrome and mitochondrial dysfunction. *Int J Clin Exp Med*. 2009;2(1):1-16. Epub 2009 Jan 15. PMID: 19436827; PMCID: PMC2680051.
7. Anderson G, Maes M. Mitochondria and immunity in chronic fatigue syndrome. *Prog Neuropsychopharmacol Biol Psychiatry*. 2020 Dec 20;103:109976. doi: 10.1016/j.pnpbp.2020.109976. Epub 2020 May 26. PMID: 32470498.
8. Smirnova IV, Pall ML. Elevated levels of protein carbonyls in sera of chronic fatigue syndrome patients. *Mol Cell Biochem*. 2003 Jun;248(1-2):93-5. doi: 10.1023/a:1024176016962. PMID: 12870659.
9. Pall ML. Elevated, sustained peroxynitrite levels as the cause of chronic fatigue syndrome. *Med Hypotheses*. 2000 Jan;54(1):115-25. doi: 10.1054/mehy.1998.0825. PMID: 10790736.
10. Pall ML. Nitric oxide synthase partial uncoupling as a key switching mechanism for the NO/ONOO- cycle. *Med Hypotheses*. 2007;69(4):821-5. doi: 10.1016/j.mehy.2007.01.070. Epub 2007 Apr 19. PMID: 17448611.
11. Calder PC, Carr AC, Gombart AF, Eggersdorfer M. Optimal Nutritional Status for a Well-Functioning Immune System Is an Important Factor to Protect against Viral Infections. *Nutrients*. 2020 Apr 23;12(4):1181. doi: 10.3390/nu12041181. PMID: 32340216; PMCID: PMC7230749.
12. Calder PC. Nutrition, immunity and COVID-19. *BMJ Nutrition, Prevention & Health* 2020;bmjnph-2020-000085. doi: 10.1136/bmjnph-2020-000085
13. Wu Y, Huang X, Sun J, Xie T, Lei Y, Muhammad J, Li X, Zeng X, Zhou F, Qin H, Shao L, Zhang Q. Clinical Characteristics and Immune Injury Mechanisms in 71 Patients with COVID-19. *mSphere*. 2020 Jul 15;5(4):e00362-20. doi: 10.1128/mSphere.00362-20. PMID: 32669467; PMCID: PMC7364211.
14. Ratajczak MZ, Kucia M. SARS-CoV-2 infection and overactivation of Nlrp3 inflammasome as a trigger of cytokine "storm" and risk factor for damage of hematopoietic stem cells. *Leukemia*. 2020 Jul;34(7):1726-1729. doi: 10.1038/s41375-020-0887-9. Epub 2020 Jun 1. PMID: 32483300; PMCID: PMC7262681.
15. Abplanalp WT, Mas-Peiro S, Cremer S, John D, Dimmeler S, Zeiher AM. Association of Clonal Hematopoiesis of Indeterminate Potential With Inflammatory Gene Expression in Patients With Severe Degenerative Aortic Valve Stenosis or Chronic Postischemic Heart Failure. *JAMA Cardiol*. 2020 Jul 8:e202468. doi: 10.1001/jamacardio.2020.2468. Epub ahead of print. PMID: 32639511; PMCID: PMC7344831.
16. Zheng Y, Liu X, Le W, Xie L, Li H, Wen W, Wang S, Ma S, Huang Z, Ye J, Shi W, Ye Y, Liu Z, Song M, Zhang W, Han JJ, Belmonte JCI, Xiao C, Qu J, Wang H, Liu GH, Su W. A human circulating immune cell landscape in aging and COVID-19. *Protein Cell*. 2020 Oct;11(10):740-770. doi: 10.1007/s13238-020-00762-2. Epub 2020 Aug 11. PMID: 32780218; PMCID: PMC7417788.
17. Yao C, Bora SA, Parimon T, Zaman T, Friedman OA, Palatinus JA, Surapaneni NS, Matusov YP, Cerro Chiang G, Kassar AG, Patel N, Green CE, Aziz AW, Suri H, Suda J, Lopez AA, Martins GA, Stripp BR, Gharib SA, Goodridge HS, Chen P. Cell type-specific immune dysregulation in severely ill COVID-19 patients. *medRxiv* [Preprint]. 2020 Jul 24:2020.07.23.20161182. doi: 10.1101/2020.07.23.20161182. PMID: 32743611; PMCID: PMC7386732.
18. Brodin P, Jojic V, Gao T, Bhattacharya S, Angel CJ, Furman D, Shen-Orr S, Dekker CL, Swan GE, Butte AJ, Maecker HT, Davis MM. Variation in the human immune system is largely driven by non-heritable influences. *Cell*. 2015 Jan 15;160(1-2):37-47. doi: 10.1016/j.cell.2014.12.020. PMID: 25594173; PMCID: PMC4302727.
19. Zhou XJ, Zhang H. Autophagy in immunity: implications in etiology of autoimmune/autoinflammatory diseases. *Autophagy*. 2012 Sep;8(9):1286-99. doi: 10.4161/auto.21212. Epub 2012 Aug 14. PMID: 22878595; PMCID: PMC3442876.
20. Jiang GM, Tan Y, Wang H, Peng L, Chen HT, Meng XJ, Li LL, Liu Y, Li WF, Shan H. The relationship between autophagy and the immune system and its applications for tumor immunotherapy. *Mol Cancer*. 2019 Jan 24;18(1):17. doi: 10.1186/s12943-019-0944-z. PMID: 30678689; PMCID: PMC6345046.
21. Swadling L, Pallett LJ, Diniz MO, Baker JM, Amin OE, Stegmann KA, Burton AR, Schmidt NM, Jeffery-Smith A, Zakeri N, Suveizdyte K, Froghi F, Fusai G, Rosenberg WM, Davidson BR, Schurich A, Simon AK, Maini MK. Human Liver Memory CD8$^+$ T Cells Use Autophagy for Tissue Residence. *Cell Rep*. 2020 Jan 21;30(3):687-698.e6. doi: 10.1016/j.celrep.2019.12.050. PMID: 31968246; PMCID: PMC6988113.
22. Dorshkind K, Montecino-Rodriguez E, Signer RA. The ageing immune system: is it ever too old to become young again? *Nat Rev Immunol*. 2009 Jan;9(1):57-62. doi: 10.1038/nri2471. PMID: 19104499.
23. Cuervo AM, Macian F. Autophagy, nutrition and immunology. *Mol Aspects Med*. 2012 Feb;33(1):2-13. doi: 10.1016/j.mam.2011.09.001. Epub 2011 Oct 1. PMID: 21982744; PMCID: PMC3996457.
24. Madeo F, Carmona-Gutierrez D, Hofer SJ, Kroemer G. Caloric Restriction Mimetics against Age-Associated Disease: Targets, Mechanisms, and Therapeutic Potential. *Cell Metab*. 2019 Mar 5;29(3):592-610. doi: 10.1016/j.cmet.2019.01.018. PMID: 30840912.
25. Shen L, Yang Y, Ou T, Key CC, Tong SH, Sequeira RC, Nelson JM, Nie Y, Wang Z, Boudyguina E, Shewale SV, Zhu X. Dietary PUFAs attenuate NLRP3 inflammasome activation via enhancing macrophage autophagy. *J Lipid Res*. 2017 Sep;58(9):1808-1821. doi: 10.1194/jlr.M075879. Epub 2017 Jul 20. PMID: 28729463; PMCID: PMC5580895.
26. Pallauf K, Rimbach G. Autophagy, polyphenols and healthy ageing. *Ageing Res Rev*. 2013 Jan;12(1):237-52. doi: 10.1016/j.arr.2012.03.008. Epub 2012 Apr 6. PMID: 22504405.

27. Prieto-Domínguez N, Garcia-Mediavilla MV, Sanchez-Campos S, Mauriz JL, Gonzalez-Gallego J. Autophagy as a Molecular Target of Flavonoids Underlying their Protective Effects in Human Disease. *Curr Med Chem*. 2018;25(7):814-838. doi: 10.2174/0929867324666170918125155. PMID: 28925866.
28. Keller MD, Torres VJ, Cadwell K. Autophagy and microbial pathogenesis. *Cell Death Differ*. 2020 Mar;27(3):872-886. doi: 10.1038/s41418-019-0481-8. Epub 2020 Jan 2. PMID: 31896796; PMCID: PMC7205878.
29. Zaylaa M, Alard J, Kassaa IA, Peucelle V, Boutillier D, Desramaut J, Rosenstiel P, Nguyen HTT, Dabboussi F, Pot B, Grangette C. Autophagy: A Novel Mechanism Involved in the Anti-Inflammatory Abilities of Probiotics. *Cell Physiol Biochem*. 2019;53(5):774-793. doi: 10.33594/000000172. PMID: 31647207.
30. Fang Y, An N, Zhu L, Gu Y, Qian J, Jiang G, Zhao R, Wei W, Xu L, Zhang G, Yao X, Yuan N, Zhang S, Zhao Y, Wang J. Autophagy-Sirt3 axis decelerates hematopoietic aging. *Aging Cell*. 2020 Sep 20:e13232. doi: 10.1111/acel.13232. Epub ahead of print. PMID: 32951306.
31. Chang NC. Autophagy and Stem Cells: Self-Eating for Self-Renewal. *Front Cell Dev Biol*. 2020 Mar 4;8:138. doi: 10.3389/fcell.2020.00138. PMID: 32195258; PMCID: PMC7065261.
32. Salimi S, Hamlyn JM. COVID-19 and Crosstalk With the Hallmarks of Aging. *J Gerontol* A Biol Sci Med Sci. 2020 Sep 16;75(9):e34-e41. doi: 10.1093/gerona/glaa149. PMID: 32544216; PMCID: PMC7337690.
33. Wang C, Ling S, Xu JW. Effect of Active Ingredients of Chinese Herbal Medicine on the Rejuvenation of Healthy Aging: Focus on Stem Cells. *Evid Based Complement Alternat Med*. 2020 Jul 8;2020:7307026. doi: 10.1155/2020/7307026. PMID: 32724327; PMCID: PMC7366228.