

# Tissue Integrity and COVID-19

Subjects: Biochemistry & Molecular Biology

Contributor: Garry Kerch

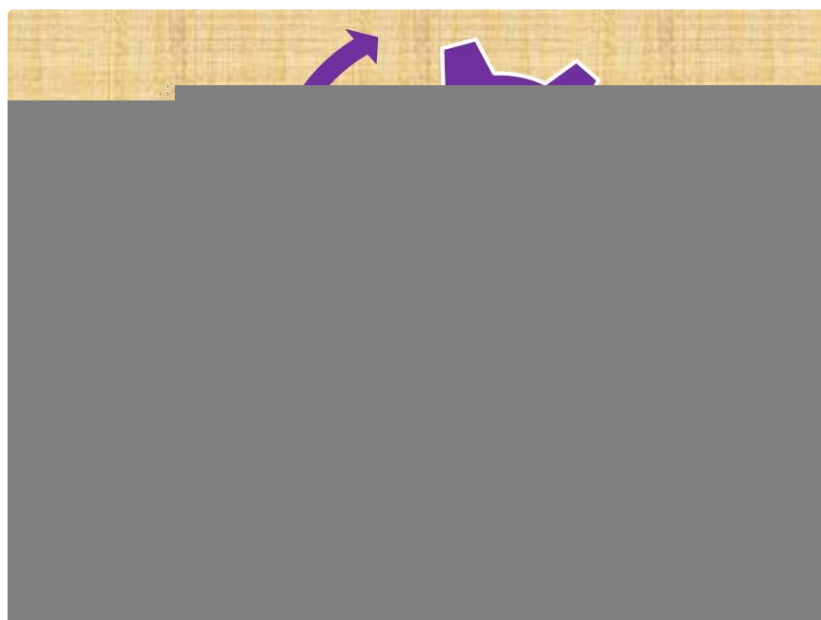
Tissue integrity depends on biological tissue stiffness. Tissue integrity can protect both against age-related diseases and against severity of COVID-19. The disruption of tight junctions and increase of tissue permeability with advancing age can be related with age-related diseases as well as with age-dependent COVID-19. Release of tightly bound water from collagen fibrils leads to the increase of extracellular matrix stiffness and to the associated with matrix stiffness increased tissue permeability. The link between arterial stiffness and oxidative stress has been reported and is expected to be studied in more detail in the future. Trehalose can be suggested for retardation of tightly bound water release and subsequent extracellular matrix crosslinking by advanced glycation end products. Increase in tissue permeability can be blocked by polyphenols that inhibit ICAM-1 expression and mitigate cytoskeleton reorganization. NF- $\kappa$ B activation as a result of increased stiffness and cytoskeleton reorganization can cause both cardiovascular pathologies and COVID-19. Increased cholesterol content in cell membrane leads to increased virus entry into cell and increase of cholesterol is linked with cardiovascular diseases. Statins and chitosan are known as cholesterol-lowering substances. Nrf2 inhibits NF- $\kappa$ B activation and NF- $\kappa$ B inhibits Nrf2 pathway.

Keywords: COVID-19 ; extracellular matrix ; release of bound water ; stiffness ; NF- $\kappa$ B ; Nrf2 ; polyphenols ; chi-tosan ; cholesterol

The pandemic of coronavirus disease 2019 (COVID-19) resulted in an unprecedented crisis in global economy and health-care services. There is no clinically approved antiviral drug available at present to be used in the fight against COVID-19. Much more clear understanding of novel coronavirus behavior is necessary in order to combat it.

Statistical data show that incidence of novel coronavirus SARS-COV-2 and severity of COVID-19 disease were very low in children <sup>[1][2]</sup>, but the chance to become infected and the fatality rate were very high for the older population, especially in patients aged 80 and older <sup>[2][3]</sup>.

Cellular processes depend on the mechanical properties of cellular environment <sup>[4]</sup> and changes of microenvironment with aging. Development of age-related diseases and age-dependent COVID-19 may be associated with changes in cellular processes as a result of gradual time-dependent biochemical and biophysical changes at molecular level in extracellular matrix, such as collagen crosslinking reactions, dehydration of collagen fibrils with decreasing binding energy between water molecules and functional groups, conformational changes of biological macromolecules. These changes increase stiffness of extracellular matrix with advanced age. Disruption of tissue integrity as a result of extracellular matrix stiffening and release of tightly bound water molecules from collagen is presented in **Figure 1**.



**Figure 1.** Release of tightly bound water from collagen fibrils increases biological tissue permeability as a result of increase in extracellular matrix (ECM) stiffness.

The aim of this entry is to discuss the potential of results based on mechanobiology of biomaterials to be used in the possible translation of emerging destiffening therapies from cardiology to the treatment of COVID-19 patients by repurposing already existing drugs.

Influence of age-related changes on incidence and severity of COVID-19 mentioned in the introduction is evident. Strong age dependence on disease severity may be related with commonly known increasing of tissue stiffness, and more specifically arterial stiffness, with advanced age. Cells are mechanosensitive and respond to the stiffness of their environment [5]. Immune cells are also mechanosensitive. The interaction and mutual relationship between immune cells and endothelial cells, vascular smooth muscle cells, platelets, and monocytes/macrophages were demonstrated [6]. So, the close link between decline in immune system with aging and arterial stiffening with advanced age can be suggested. Gradual release of tightly bound water molecules from collagen fibrils can be considered as a process driven by entropy. The change of water state from tightly bound to loosely bound and free water results in increase of entropy of a system. Water acts as a tissue plasticizer and loss of water leads to increase of tissue stiffness and disruption of tight junctions and decreased integrity, **Figure 1**. Extracellular matrix (ECM) stiffening in **Figure 1** may be replaced by immune system response decline because age-associated changes in the immune system are closely related with tissue integrity and barrier functions. There is a link between immune system function and ECM stiffness due to immune cells mechanosensitivity.

Exercise in a hot environment may be considered as a combination of mechanical forces and loss of water. The effect of exercise on circulating immune cell responses and immune cell function has been reported by researchers at Exercise Physiology Laboratory of Texas Christian University [7]. They found that exercise affects immune system and that the number of leukocytes, neutrophils, lymphocytes, and natural killer cells were higher as a result of exercise. It has been also demonstrated that dehydration is closely related with oxidative stress [8]. Evidently oxidative damage leads to disruption of tissue integrity and to the increase of tissue permeability.

It has been reported that platelet adhesion is higher on rigid chitosan coatings containing tightly bound water molecules if compared with softer chitosan coatings containing water molecules with lower binding energy to biological macromolecules [9].

---

## References

1. Wu, Z.; McGoogan, J.M. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020, 323, 1239–1242.
  2. Kerch, G. Role of changes in state of bound water and tissue stiffness in development of age-related diseases. *Polymers (Basel)* 2020, 12, 1362.
  3. Bonanad, C.; García-Blas, S.; Tarazona-Santabalbina, F.; Sanchis, J.; Bertomeu-González, V.; Fácila, L.; Ariza, A.; Núñez, J.; Cordero, A. The Effect of Age on Mortality in Patients With COVID-19: A Meta-Analysis With 611,583 Subjects. *J. Am. Med. Dir. Assoc.* 2020, 21, 915–918.
  4. Baumann, K. Environment dictates behaviour. *Nat. Rev. Mol. Cell Biol.* 2010, 11, 679.
  5. Janmey, P.A.; Fletcher, D.A.; Reinhart-King, C.A. Stiffness sensing by cells. *Physiol. Rev.* 2020, 100, 695–724.
  6. Lacolley, P.; Regnault, V.; Avolio, A.P. Smooth muscle cell and arterial aging: Basic and clinical aspects. *Cardiovasc. Res.* 2018, 114, 513–528.
  7. Mitchell, J.B.; Dugas, J.P.; McFarlin, B.K.; Nelson, M.J. Effect of exercise, heat stress, and hydration on immune cell number and function. *Med. Sci. Sports Exerc.* 2002, 34, 1941–1950.
  8. Jacobs, P.J.; Oosthuizen, M.K.; Mitchell, C.; Blount, J.D.; Bennett, N.C. Heat and dehydration induced oxidative damage and antioxidant defenses following incubator heat stress and a simulated heat wave in wild caught four-striped field mice *Rhabdomys dilectus*. *PLoS ONE* 2020, 15, e0242279.
  9. Kerch, G.; Zicans, J.; Merijs Meri, R.; Stunda-Ramava, A.; Jakobsons, E. The use of thermal analysis in assessing the effect of bound water content and substrate rigidity on prevention of platelet adhesion. *J. Therm. Anal. Calorim.* 2015, 120, 533–539.
-

