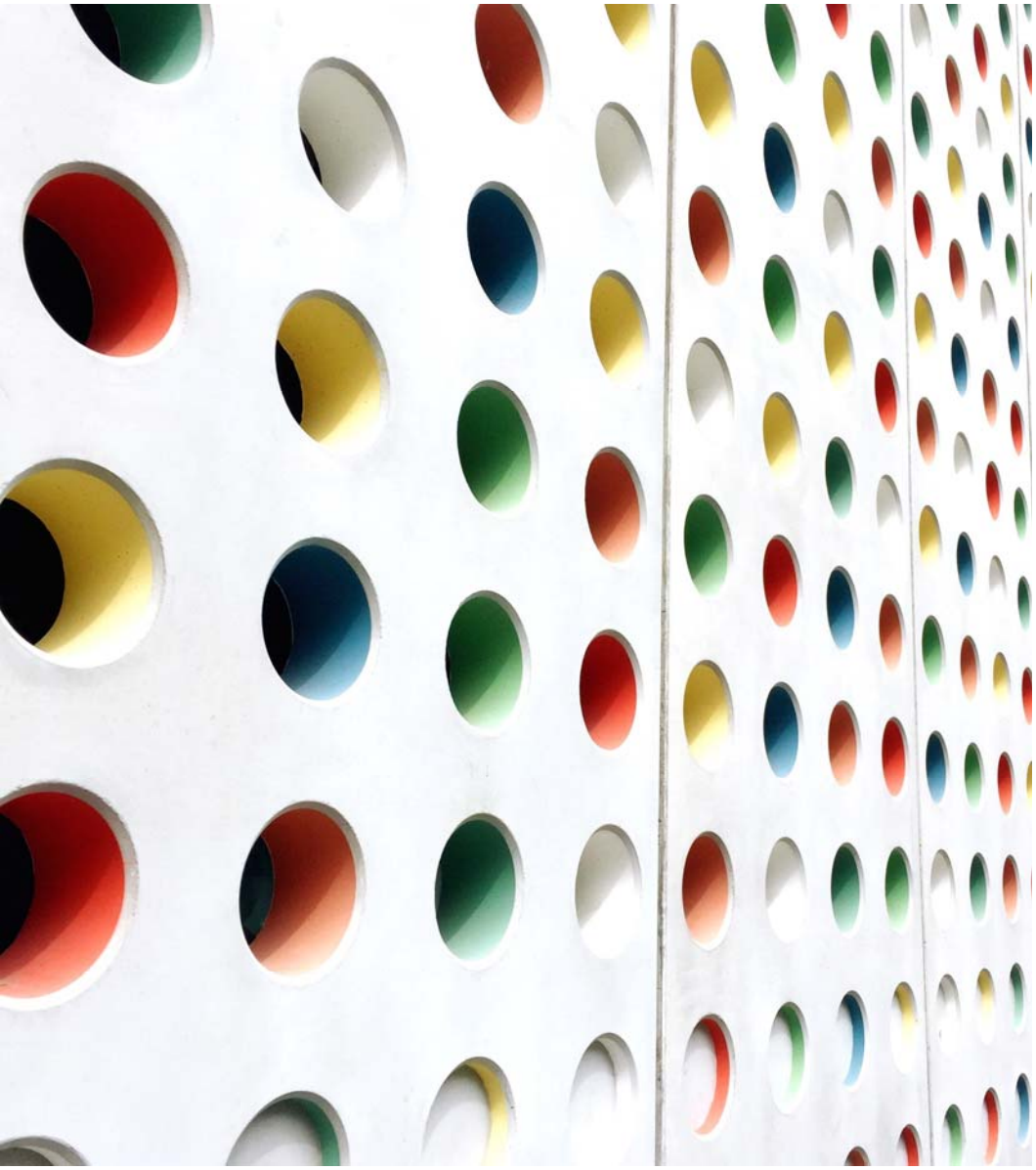

COVID-19 Acts Like Radiation Injury

LOCALIZED INVASIVE VIREMIA AND VASCULAR OXIDATIVE DAMAGE VERSUS FLOOD FIELD RADIATION-INDUCED INJURY

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"Long Hauler" Condition: The Role of ACE2 and Oxidative/ROS Generation

Oxidative Stress ➔ Injury and Disease ➔ *Similar to Radiation Injury*

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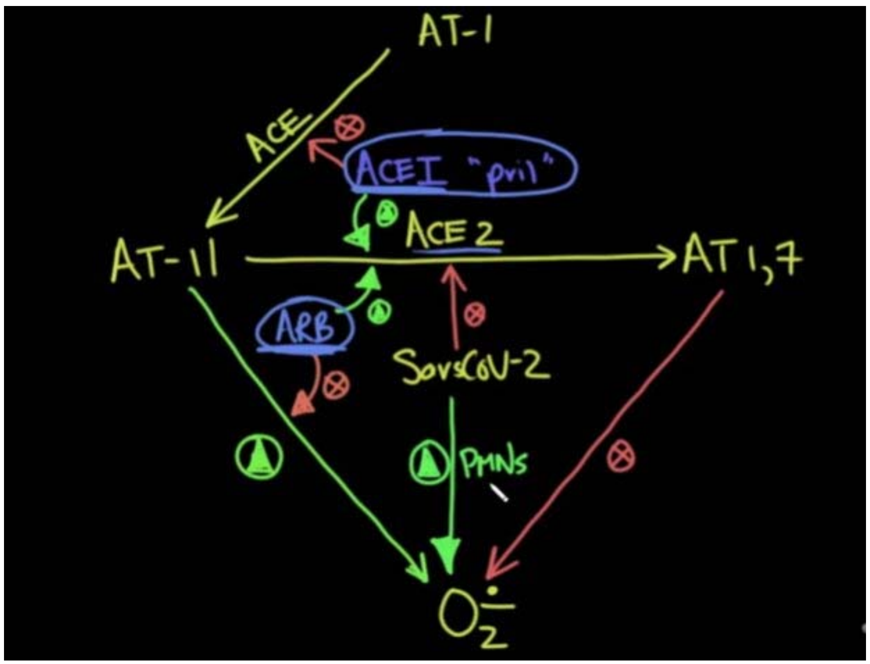

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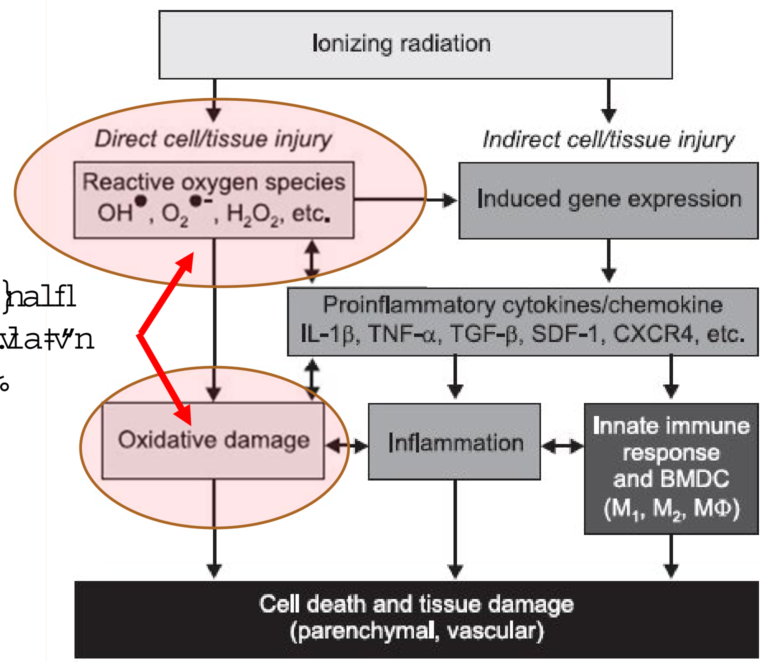

Kim, JH, et al., Radiat Oncol J 2014;32(3):103-115
http://dx.doi.org/10.3857/roj.2014.32.3.103

The Role of ACE2 and Oxidative/ROS Generation mimicking Radiation Injury

What Does the Body do to Clear Reactive Oxygen Products?

Cascade of enzymes: SOD, Catalase, Glutathione reductase (GSH), Glutathione peroxidase (GSHPX) and NADPH

E‥ⅵa‡√n Q‡fnffl ➔ :¡{·f‰ a¡l 0√fhafh a|√¡ ‡£ Pal√a‡√£¡ :¡{·f‰

.EY:0Đ˙Æ i√¡l√¡t ‡£ %.2˝ fnjn«‡£fii}£j|fl%C8 ˙Ĩ tn¡nfia‡√£¡ »u√ju fhfi'nfl afl a PEQ ifia|n

Oxidative Stress is the buildup of oxygen intermediates.

E‥‰tn¡ ËE·½√fl ·fhl s£fin¡nft‰ a¡l ~n‡aif}√fl~ ‡£ »a‡nfiafb

- E‥‰tn¡ ➔ nĐ ➔ Q·«nf£‥√n ËE·Ê½ if£|n¡ l£»¡ i‰ QE0 Ëfl·«nf£‥√n l√fl~ ·‡afh½Ëâ _¡ł.· a¡l B¡ s£finĐ ‡fia¡flsnf½

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- Q·«nf£‥√n ➔ nĐ ➔ u‰lf£tn¡ «nf£‥√n 9‥E‥ E·Ê➔ QE0 ➔ 9‥E‥ 8}·‡a‡u√£¡n «nf£‥√afh ➔ 9‥E M}·fl a .a‡a}afh «a‡u Ë7n j£·¡‡nfi√£¡½iaj| ‡£ E· a¡l 9‥E

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- 9‥E‥ ➔ nĐ ➔ u‰lf£‥‰}√£¡flé E9Đí

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- Z%S2P √fl a fl‡ai}nł¡n·‡fia}«9łs√¡a}finj£"nf‰«£√¡‡

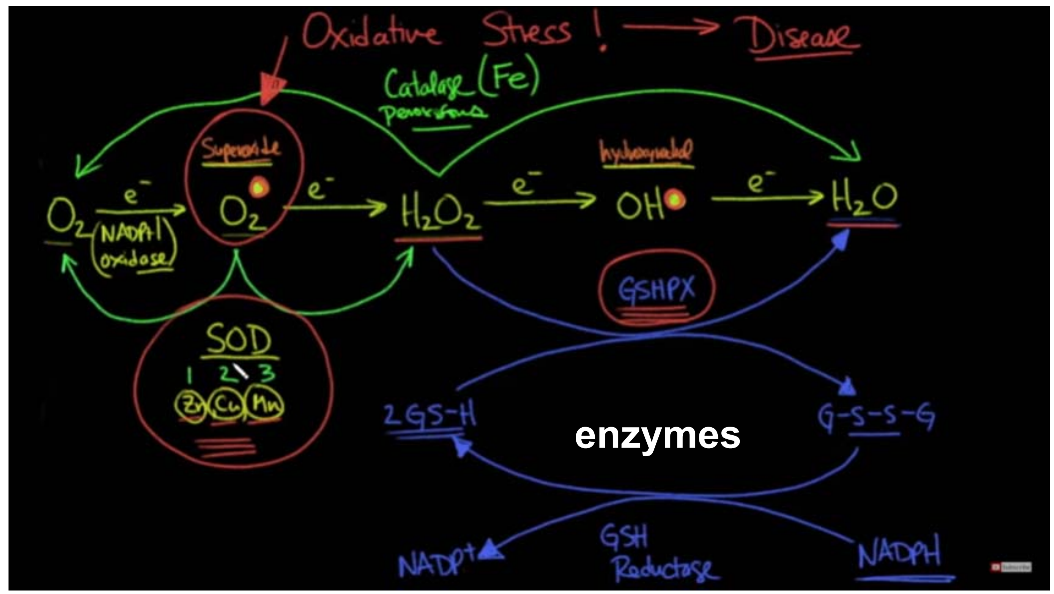

Figure from MedCram lecture No. 65. MedCram.com

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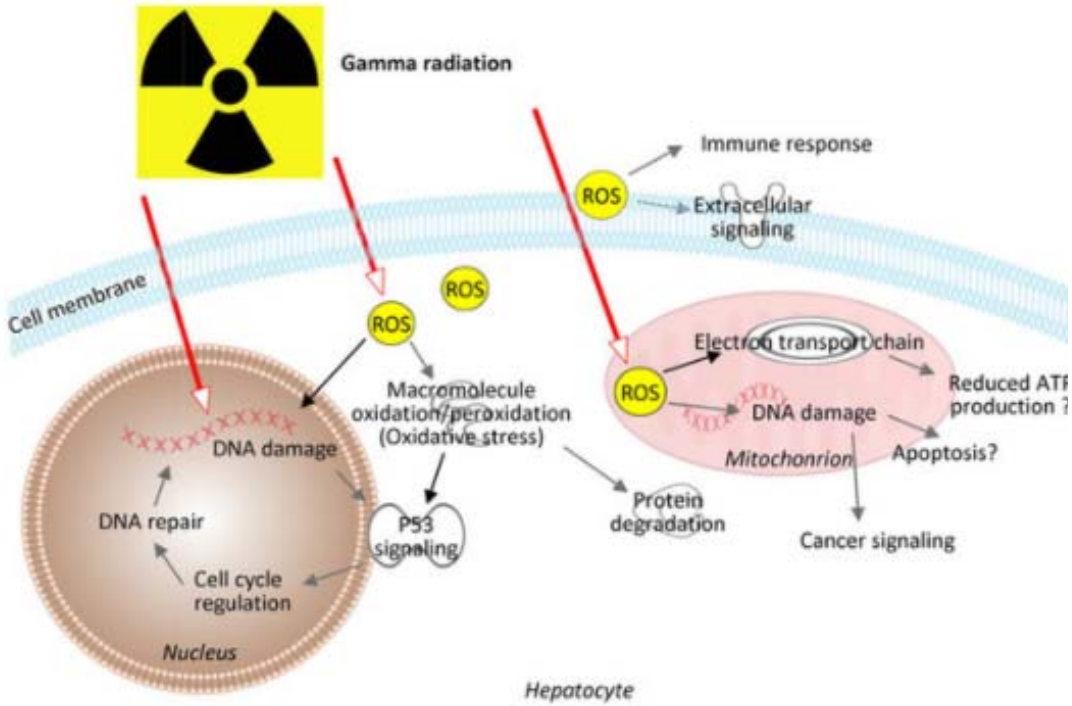
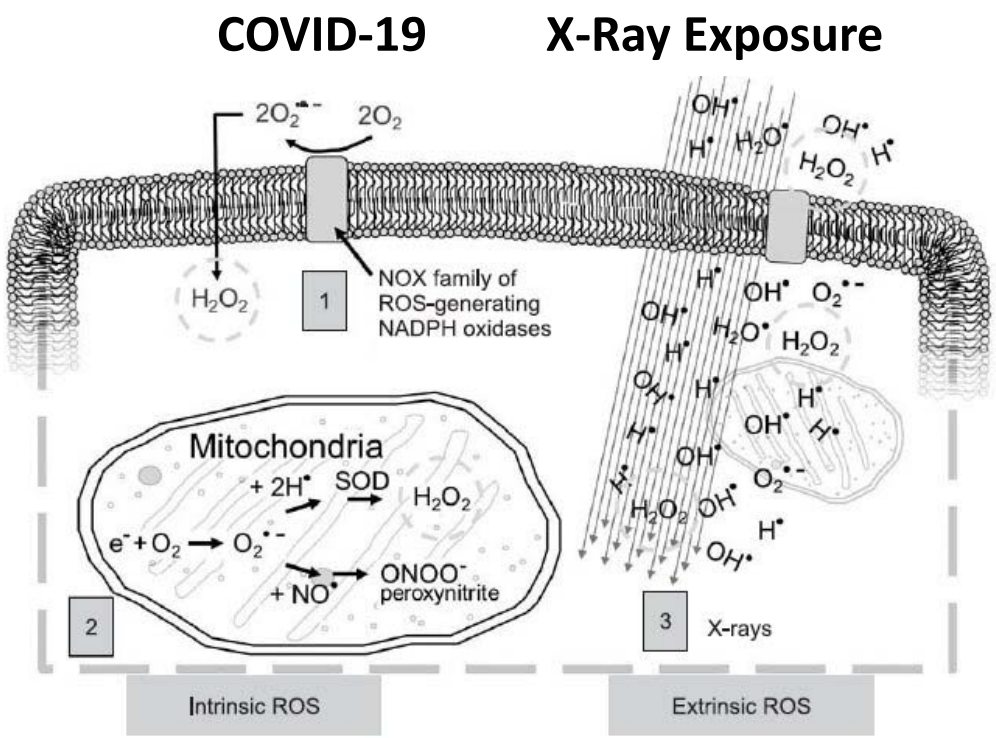
Reactive Oxygen Species (ROS) Generation = Oxidative Damage

The Virus generates vascular injury by local oxidative species



Radiation Injury Is Very Similar to the Mechanism of COVID-19



Radiation Injuries and COVID-19 Injuries:

Radiation creates a free radical environment and so does COVID-19

We may be treating COVID-19 with low dose radiation? Why? To stimulate the body's intrinsic ROS scavengers

What is Radiation Injury?

- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]

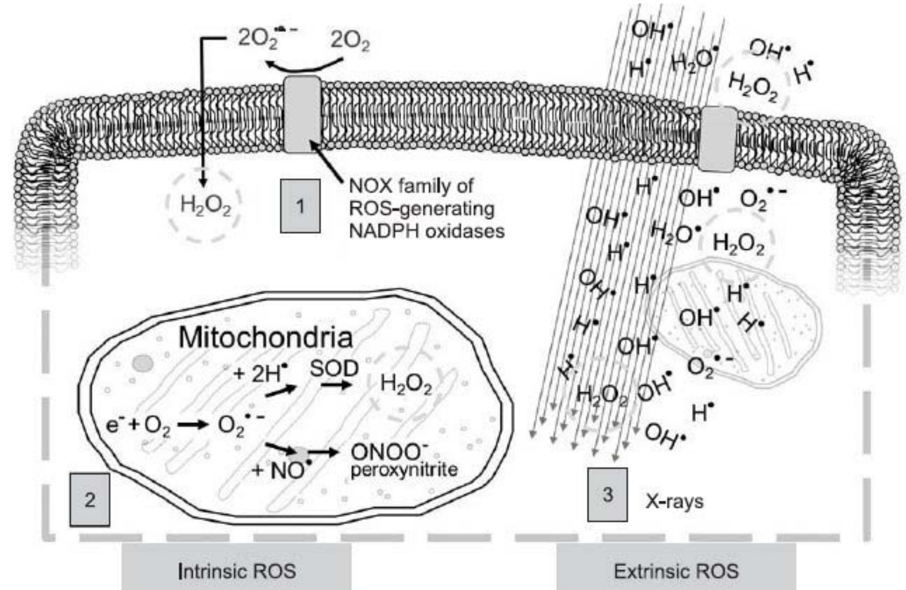
COVID-19 changes are similar:

- [illegible]
- [illegible]
- [illegible]
- [illegible] ***(see previous slide image)***

https://www.cyberknifemiami.com/could-low-dose-radiation-therapy-cure-covid-19/

COVID-19: **Viral exit = Cell lysis**

Ionizing Radiation: **Flood of ROS local ROS**



Intrinsic ROS resolution **NADPH, SOD, more**

Extrinsic Radiation **free radicals everywhere**

Kim, JH, et al., Radiat Oncol J 2014;32(3):103-115
http://dx.doi.org/10.3857/roj.2014.32.3.103

Radiation Injury and COVID-19 Injuries: They Look So Similar!

Commonalities Between COVID-19 and Radiation Injury, Carmen I. Rios, David R. Cassatt, et al., Radiation Research, 195(1):1-24 (2020). https://doi.org/10.1667/RADE-20-00188.1

- As the multi-systemic components of COVID-19 emerge, parallel etiologies can be drawn between SARS-CoV-2 infection and radiation injuries.
- As investigators begin to identify early markers of disease, we are seeing common threads with other pathologies.
- Interestingly, research in the field of radiation biology documents the complex multiorgan nature of exposure to high doses of radiation: the acute radiation syndrome (ARS).
- Inflammation is a key common player in COVID-19 as well as ARS. Inflammation drives the multi-system damage that dramatically alters biological homeostasis.
- The pathology of severe COVID-19 is characterized by a dysregulated inflammatory response, the so-called ‘‘cytokine storm,’’ along with a thrombotic response involving elevated D-dimer levels and coagulopathies ranging from small vessel thrombi to DIC.
    - The cytokine storm is manifested through high levels of pro-inflammatory cytokines such as IL-1b, IL-6, IL-18, and TNFa. The cumulative systemic effects of the hyperinflammatory response and dysregulated thrombotic activity can lead to multi-organ failure and death.
    - Radiation injury, mediated principally by reactive oxygen species (ROS) increasing after ionizing tissue fluids, leads to vascular injury, inflammation, and dysregulated clotting, all leading to organ failure and death.

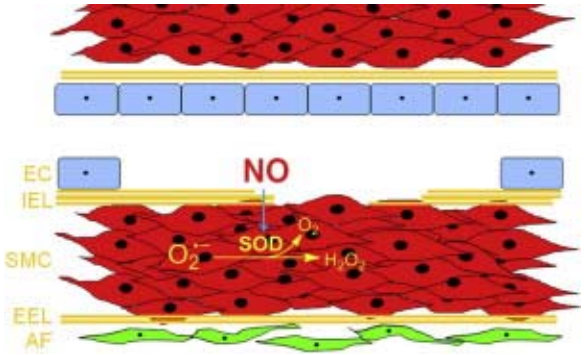
https://bioone.org/journals/radiation-research/volume-195/issue-1/RADE-20-00188.1/Commonalities-Between-COVID-19-and-Radiation-Injury/10.1667/RADE-20-00188.1.full

Radiation Injuries and COVID-19 Injuries: ACE2 Occupancy and ROS

Vascular injury is characterized by endothelial dysfunction, structural remodelling, inflammation and fibrosis.

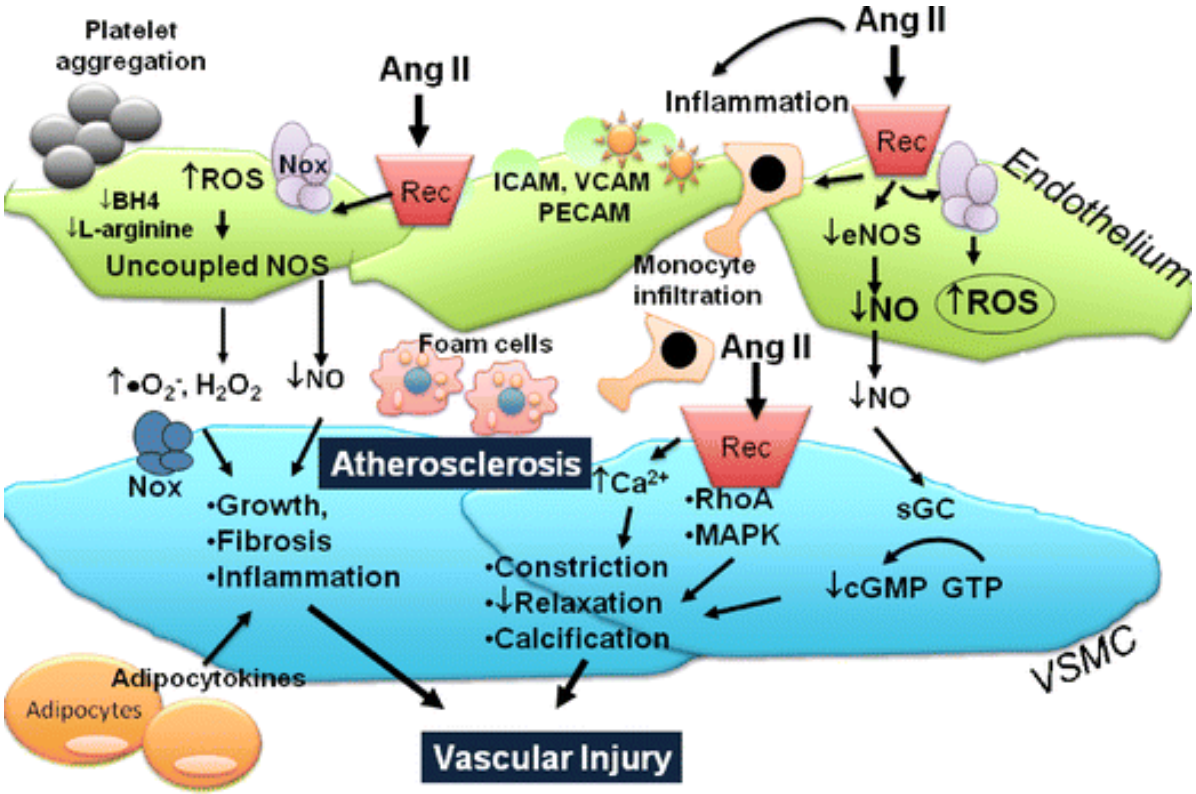
Radiation Injuries reduce eNOS (NO synthase) and NO by ROS generation (superoxide, peroxide) in endothelium and subsequent damage to the VSMC with increased Ca flux.

NO acts to mediate superoxidedismutase (SOD) conversion of ROS



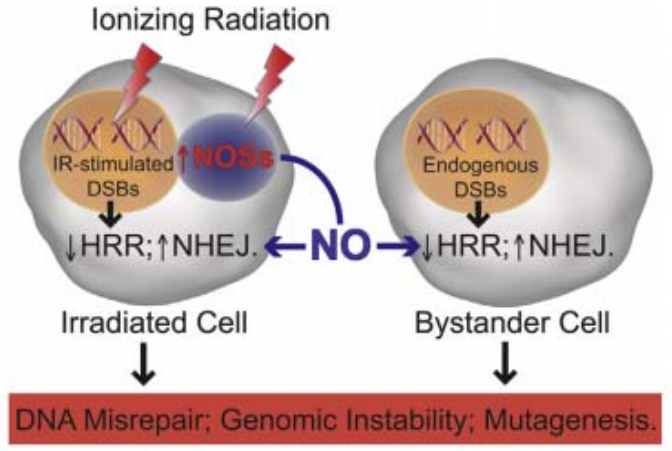
https://www.sciencedirect.com/science/article/abs/pii/S108986031400490X#f0010

COVID-19 occupancy of ACE2 = AngI ➔ ACE2 ➔ AngII (ROS braking interrupted)



https://link.springer.com/article/10.1007/s11906-014-0431-2

Radiation Injuries and COVID-19 Injuries: Nitric Oxide (NO) Involvement



Genomic instability changes:

u£~ £}£t£·flfinj£~ iv¡a+v£¡ fin«avïË9PP½1
¡£¡Du£~ £}£t£·fln¡lÐ{£v¡v¡t ËC92?

NO, generated from arginine by the activity of different isoforms of nitric oxide synthase (NOS), is a major signaling molecule in the immune, cardiovascular, and nervous systems.

Radiation-induced bystander effect (RIBE).

The hydrophobic properties of NO, which permit free diffusion through the cytoplasm and plasma membranes, allows NO to be a signaling molecule that can affect both irradiated cells as well as bystander (non-irradiated) cells.

- COVID generation of ROS can induce damage and also create a “bystander effect” through NO mechanisms

NO mediates cellular regulation through posttranslational modification of a number of regulatory proteins. The best studied of these modifications are S-nitrosylation (reversible oxidation of cysteine) and tyrosine nitration. These modifications can affect many signaling proteins.

NO-dependent effects include the **stimulation of genomic instability** (GI) and the **accumulation of DNA errors** in bystander cells even without direct DNA damage

https://reader.elsevier.com/reader/sd/pii/S2213231715001081

Myocyte (Heart Muscle)-Specific Upregulation of ACE2 in Cardiovascular Disease (CVD):

Implications for SARS-CoV-2–Mediated Myocarditis

The presence of cardiac injury has been shown to lead to a 5-fold increase in mechanical ventilation and a 51.2% mortality rate.

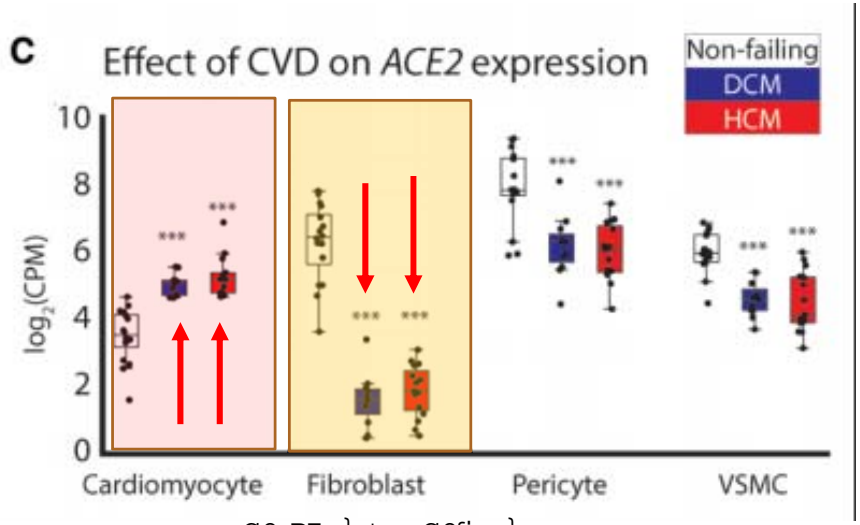
The effect of cardiovascular disease (CVD) on ACE2 receptor expression adds to the severity of COVID-19 infections.

The effect of CVD is to drive the ACE2 receptor into **a higher expression relative to normal subjects in cardiomyocytes (heart muscle cells)**. This is regardless of the type of CVD from dilated (thin cardiac walls), mitral valve prolapse, or hypertrophic (more muscle mass) heart conditions (red).

This is the opposite of FIBROBLASTS (yellow) where the ACE2 expression levels are LOWER.

Vascular smooth muscle (the vessel walls) are slightly lower in CVD ACE2 expression..

These findings may provide a **pathologic link** for COVID-19 associated viral myocarditis.



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9.B ç u‰«nfiff£«uvj jafilv£~‰£«a+u‰

Severe respiratory syndromes can occur when COVID-19 binds to the ACE2 receptor in different tissues of the body, especially abundant in the mouth cavity and the tongue.

It needs *the* serine protease, the transmembrane serine protease 2 (*TM*PRSS2), for cell entry and the Cathepsin L/B (CTSL/CTSB) protease for the next step of endosomal (*RNA translation*) pathway.

Tucker; et al. Nov 2020; https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.120.047911