Hypothesis

Hypothesis: HPV E6 and COVID spike proteins cooperate in targeting tumor suppression by p53

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ABSTRACT

Human Papilloma Virus (HPV) is a causative agent in several cancers including cervical cancer, head and neck cancer, anal cancer, penile, vulvar and vaginal cancers. HPV through its virus-encoded protein E6 and the cellular E6-Associated Protein (E6-AP) target the tumor suppressor p53 protein for degradation thereby contributing to cancer development after HPV infection. As viruses cause cancer, the author previously hypothesized that SARS-COV-2 virus may be associated with cancer. More recent insights on the present hypothesis have come from studies suggesting (1) Spike protein of SARS-COV-2 may suppress p53 function, (2) cancer has been associated with mRNA vaccines that produce Spike, and (3) a case mentioned by Dr. Patrick Soon Shiong of a patient who survived HPV-associated head and neck cancer, but the tumor recurred after COVID mRNA vaccination including with liver metastases. Thus, the present hypothesis is that virally encoded proteins such as HPV-E6 or SARS-COV-2 Spike may cooperate in suppressing host defenses including tumor suppressor mechanisms involving p53. The hypothesis can be further explored through epidemiologic and laboratory studies.

It is known that HPV E6 targets the tumor suppressor protein p53 for degradation through the E6-AP thereby contributing to the development of cervical cancer, head and neck cancer, anal cancer and others [1–17].

When the COVID-19 pandemic started, I pursued studies "to better understand and modulate the host immune response to SARSCoV-2 to prevent or reduce disease severity in the current COVID-19 pandemic. Some effort (was) directed at blocking ACE2, the receptor SARS-CoV-2 uses to enter cells." I further explained by March 24, 2020 (Figure 1) "while the host inflammatory response makes patients critically ill, the host innate immune system including natural killer (NK) cells is involved in fighting and eliminating virally infected cells. Over the last 25 years we have studied this innate immune system pathway that the immune system uses to eliminate transformed and cancer cells as well as virally infected cells. Natural killer cells secrete TRAIL which is involved in killing virally infected as well as transformed cells. This system can be triggered by p53 to suppress viral infection as well as cancer. Thus, our goal is to better understand and modulate the host immune response to increase the innate immune system early in SARS-CoV-2 infection while reducing the severe inflammation that occurs late. We further want to understand the impact of

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Reducing lethality of SARS-CoV-2 infection through immune modulation

Wafik El-Deiry, MD, PhD, FACP, Brown University 3-24-2020

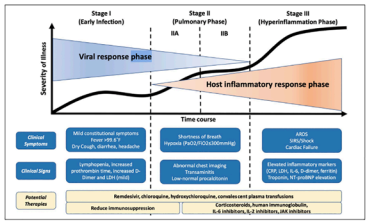
Coronavirus 2 (SARS-CoV-2) infection progresses to a rapidly lethal adult respiratory distress syndrome (ARDS) associated with high mortality especially among the elderly or those with multiple comorbid conditions (only ~1% of deaths are in individuals less than 50 years old). Patients with cancer are particularly vulnerable in part due to their weakened immune system and are further at risk due to the immune suppressive effects of chemotherapy. The lethality of SARS-CoV-2, the causative agent for the COVID-19 disease, involves a fulminant cytokine storm with bilateral lung infiltrates observed on chest X-rays and CT scans. Patients become critically ill and those at highest risk such as the elderly or those with comorbid conditions have a high mortality that can exceed 10% thereby overwhelming hospital and intensive care unit capacity as the virus spreads into the community during the pandemic. Current therapeutic approaches include a number of agents and this has led to a WHO-sponsored megatrial (SOLIDARITY) of the four most promising coronavirus treatments. These include:

- Remdisivir which inhibits RNA-dependent RNA polymerase,
- Chloroquine and hydroxychloroquine which reportedly reduce viral load in infected patients and reduce acidity of endosomes although the SARS-CoV-2 uses a different mode of entry involving spike protein to attach to a cell surface receptor,
- Ritoavir/lopinavir a combination drug used to treat HIV infection and that inhibits viral protease although initial clinical testing is not promising in very ill patients, and
- Ritonavir/lopinavir plus interferon-beta with the interferon-beta being added as an immune modulator.

Other approaches include use of

- Tocilizumab (anti-IL6) with recent approval by the FDA of a phase III trial of Tocilizumab in COVID-19 pneumonia (NCT04317092),
- Development of convalescent serum as a treatment for COVID-19.

It is becoming clear that men do much worse than women in the coronavirus pandemic in terms of mortality as more men than women become critically ill (in Italy among nearly 14K cases of COVID-19 and 803 deaths between 2-21-2020 and 3-12-2020, men accounted for 58% of all cases and 72% of deaths). The SARS-CoV-2 virus binds to angiotensin converting enzyme 2 (ACE2) receptors in the lower respiratory tract to enter the lungs leading to pneumonia and respiratory failure. Patients with hypertension who receive ACE inhibitors (ACEIs) or ARBs have increased ACE2 receptors and may be at increased risk for infection. Various vitamins including vitamin D and zinc have been suggested to boost the immune system in its fight against SARS-CoV-2.



https://twitter.com/weldeiry/status/1241028663228973057?s=20

Once SARS-Cov-2 enters into cells it triggers a host immune response that leads to pathogenesis and disease progression. The host inflammatory response phase of COVID-19 is the phase where patients become critically ill leading to high patient mortality.

The central thrust of our work is to better understand and modulate the host immune response to SARS-CoV-2 in order to prevent or reduce disease severity in the current COVID-19 pandemic. Some effort is directed at blocking ACE2, the receptor SARS-CoV-2 uses to enter cells.

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It is clear that while the host inflammatory response makes patients critically ill, the host innate immune system including natural killer (NK) cells is involved in fighting and eliminating virally-infected cells. Over the last 25 years we have studied this innate immune system pathway that the immune system uses to eliminate transformed and cancer cells as well as virally-infected cells. Natural killer cells secrete TRAIL which is involved in killing virally-infected as well as transformed cells. This system can be triggered by p53 to suppress viral infection as well as cancer. Thus, our goal is to better understand and modulate the host immune response to increase the innate immune system early in SARS-CoV-2 infection while reducing the severe inflammation that occurs late. We further want to understand the impact of current therapeutics used to treat COVID-19 on both the innate immune system as well as the cellular inflammatory response.

Experimental plans: The lab is set up to detect the host innate immune response that uses TRAIL and TRAIL death receptors to eliminate virally infected as well as transformed cells. Through our efforts to target and kill cancer cells, we have also set up immune killing assays that employ both NK as well as T-cells. Our immediate plans include:

- Study of chloroquine and hydroxychloroquine effects on NK- and T cell-mediated cell killing (including drug dose effects), and cytokine profiles
- the impact of suppression of p53 on IL6 production by normal lung fibroblasts and epithelial cells and effects of Tocilizumab in immune cell killing assays,
- the impact of commercially available SARS-CoV-2 Spike protein on p53 pathway in normal lung fibroblasts and epithelial cells,
- hormonal effects (estrogen and testosterone) and effects of vitamin D and zinc on the activity of NK cells and T cells as well as ACE2 expression, as well as cytokine profiles
- Effects of SARS-CoV-2 Spike protein on p53 pathway signaling, NFkB-mediated inflammation, TGF-beta signaling, and TRAIL-mediated cell killing
- Screen for compounds that block ACE2 expression as a way to reduce SARS-CoV-2 infectivity

We believe these and other efforts in the laboratory including expertise with organoids and in vivo models, and expertise with signal transduction, transcriptional control, tumor suppressor pathways that share control with virus response pathways (p53 was discovered in complex with SV40 T-antigen), immune signaling, interferon signaling, miR libraries, and combinatorial therapeutics will contribute to needed knowledge to help combat SARS-CoV-2 at various stages of its life cycle including the severity of COVID-19 disease. Our ability to perform these experiments should also open up opportunities for collaboration with colleagues based on ideas and relevant reagents they may have.

We intend to follow best practices for reducing risk to laboratory personnel while performing laboratory experiments including minimal time in the laboratory, minimizing number of personnel, keeping at 6 feet away from others as much as possible, wearing lab PPE to minimize risks and otherwise following laboratory guidelines for biosafety.

Figure 1: Original seed grant proposal dated 3-24-2020.

current therapeutics used to treat COVID-19 on both the innate immune system as well as the cellular inflammatory response."

The proposal received a Brown University COVID-19 Research Seed Award in the amount of $40,000 for "Reducing the lethality of SARS-CoV-2 infection through immune modulation and drug discovery" in the Spring of 2020. Four publications emerged subsequently from these efforts [18–21]:

2020: MEK inhibitors reduce cellular expression of ACE2, pERK, pRb while stimulating NK-mediated cytotoxicity and attenuating inflammatory cytokines relevant to SARS-CoV-2 infection.

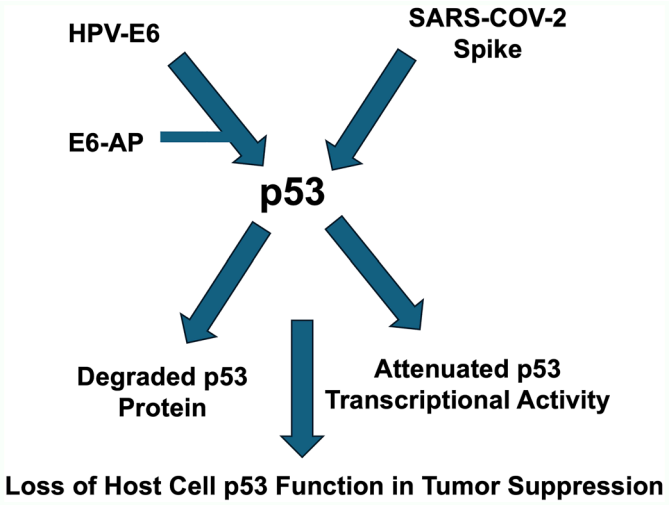

Figure 2: Schematic depicting hypothesized cooperation between HPV and COVID in suppressing p53 and contributing to cancer.

2021: Cytokine ranking via mutual information algorithm correlates cytokine profiles with presenting disease severity in patients infected with SARS-CoV-2.
2022: Integrin/TGF-β1 Inhibitor GLPG-0187 Blocks SARS-CoV-2 Delta and Omicron Pseudovirus Infection of Airway Epithelial Cells In Vitro, Which Could Attenuate Disease Severity.
2024: Transfected SARS-CoV-2 spike DNA for mammalian cell expression inhibits p53 activation of p21(WAF1), TRAIL Death Receptor DR5 and MDM2 proteins in cancer cells and increases cancer cell viability after chemotherapy exposure.

I listened to an interview (https://www.youtube.com/watch?v=tnVMjp9mCA0&t=2s) of Dr. Patrick Soon-Shiong by Chris Cuomo where I learned about a patient named Jim Johnson with a history of HPV-related head and neck cancer who by 2022 had survived his HPV-related cancer for 7 years and then he took the COVID vaccine. The "cancer was back with a vengeance," and the tumor had metastasized to his liver. After I listened to what happened in this case, it occurred to me that there may be cooperation between HPV and COVID infection or COVID vaccination and suppression of p53.

A search of the literature for "cooperation between HPV and COVID in suppressing p53" found per an AI overview that there is "no evidence of a direct molecular "cooperation" between HPV and COVID-19 in suppressing p53, research indicates they both target the p53 pathway independently, and a COVID-19 infection may indirectly accelerate HPV-related cancer progression by impacting the host immune system." I found a publication about "SARS-CoV-2 infection heighten[ing] the risk of developing HPV-related carcinoma *in situ* and cancer [22]," and a hypothesis that "COVID-19 can lead to rapid progression of cervical intraepithelial neoplasia by dysregulating the immune system [23]."

HYPOTHESIS

Based on existing literature discussed above, here is a schematic of the hypothesis that HPV E6 and COVID spike proteins may potentially cooperate in targeting tumor suppression by p53 (Figure 2). As depicted in Figure 2, the hypothesis put forth is that virally encoded proteins such as HPV-E6 or SARS-COV-2 Spike may cooperate in suppressing host defenses including tumor suppressor mechanisms involving p53. This hypothesis can be tested through epidemiologic studies looking at cancer incidence and recurrence among HPV-positive individuals who have either been infected by SARS-COV-2 or have been given COVID mRNA vaccines. Laboratory studies can test the impact of HPV-E6 combined with Spike protein on p53 expression and function.

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CONFLICTS OF INTEREST

W.S.E-D. is a co-founder of Oncoceutics, Inc., a subsidiary of Chimerix (Chimerix was acquired by Jazz Pharmaceuticals), p53-Therapeutics, Inc. and SMURF-Therapeutics, Inc. Dr. El-Deiry has disclosed his relationships and potential conflicts of interest to his academic institution/employer and is fully compliant with NIH and institutional policy that manage these potential conflicts of interest.

FUNDING

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EDITORIAL NOTE

The Editor-in-Chief, Dr. Wafik S. El-Deiry, was not involved in the peer-review process or the decision-making for this paper. Dr. El-Deiry shared the submitted manuscript with National Cancer Institute (NCI) Director Anthony Letai and NCI Deputy Director Doug Lowy in separate emails electronically on December 12, 2025.

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