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Perspective

Shining Light on the COVID-19 Pandemic: A Vitamin D Receptor Checkpoint in Defense of Unregulated Wound Healing

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SUMMARY

SARS-CoV-2 pneumonitis can quickly strike to incapacitate the lung, leading to severe disease and sometimes death. In this perspective, we suggest that vitamin D deficiency and the failure to activate the vitamin D receptor (VDR) can aggravate this respiratory syndrome by igniting a wounding response in stellate cells of the lung. The FDA-approved injectable vitamin D analog, paricalcitol, suppresses stellate cell-derived murine hepatic and pancreatic pro-inflammatory and pro-fibrotic changes. Therefore, we suggest a possible parallel program in the pulmonary stellate cells of COVID-19 patients and propose repurposing paricalcitol infusion therapy to restrain the COVID-19 cytokine storm. This proposed therapy could prove important to people of color who have higher COVID-19 mortality rates and lower vitamin D levels.

The hallmark lethal complication of SARS-CoV pneumonitis is a remarkably rapid and severe respiratory syndrome that ignites an aggressive wounding response (Gralinski et al., 2013; Rockx et al., 2009) that strikes and incapacitates the lung. The combination of inflammation and fibrosis is the body's response to try to corral the process. However, the electrifying rate at which the virus spreads throughout the lungs makes it impossible to restrain. For many patients, this results in acute respiratory distress (ARD) with the only option being mechanical ventilation, and for many this is a losing battle. For unknown reasons, these complications are worse for people of color. The overarching goal is to create a safe, effective vaccine, but that may take a year or years to develop, produce, and distribute. So what can we do now? One way is *not to fight the virus* at all but rather to intercept the cytokine storm and damaging profibrotic response before it takes hold. This would open the door for T and B cells of the immune system to flood in and take the fight directly to the virus. As no specific antiviral treatment is available, this non-strain-specific approach may be able fend off severe complications of other viral infections or future coronavirus strains. Might study of vitamin D, discovered 100 years ago, provide a clue?

While benefits of sun- and ultraviolet (UV)-light exposure have been bantered about, this would not help any patient who is gowned, covered, and isolated with no exposure to natural light. However, a case can be made that vitamin D, long known important in calcium regulation, may have a much broader impact. Dietary vitamin D has an unusual form of metabolism. It is activated in the skin via UVB exposure, allowing it to become a short-acting but powerful hormone. Once activated, vitamin D seeks out select cells and organs that have a sensor known as VDR, a member of the nuclear hormone receptor (NHR) transcription factor family, the discovery of which changed everything about our understanding of *how* and *where* these pre-activated steroid hormones work (Evans, 1988). The *how* involves regulation of elaborate transcriptional programs such as differentiation, inflammation, cell fate, and function; the best way to find *where* vitamin D works is to locate the receptor.

Seven years ago during systematic organ- and cell-specific screens for dominant NHR expression patterns, we unexpectedly found high levels of VDR in hepatic stellate cells (HSCs), a rare lipid-loaded quiescent cell in the liver that is rapidly activated and expands ~100-fold in response to tissue injury, where it oversees a highly conserved, short-lived homeostatic wound-healing response (Foster et al., 2018). Repeated or persistent hepatic injury, however, elicits pathologic wounding with constitutive HSC activation and Cyp24a1 enzyme upregulation (rapidly degrading the natural ligand, creating an anatomic microenvironment of vitamin D deficiency), resulting in excessive cytokine and matrix-component release. Chronic liver disease, caused by obesity, alcohol, and viruses, is a major cause of global mortality. Currently, there is no FDA-approved anti-fibrotic liver therapy, as regulation of the wound-healing response process had been unknown for decades. Treatment options, therefore, are limited to transplant in advanced cases or supportive measures addressing complications of portal hypertension and liver failure. We uncovered a central mechanistic role of HSC VDR as an endocrine checkpoint, a type of molecular "brake," regulating the inflammation-repair balance in response to tissue injury. Vitamin D deficiency (or genetic deletion of VDR) in mice triggers a destructive combination of severe inflammation and fibrosis that, if caught early enough, could be curtailed by synthetic VDR agonist calcipotriol (Ding et al., 2013). In patients, severity of liver disease correlates inversely with VDR expression, levels of vitamin D, and metabolites (Oh et al., 2020), and hepatocellular injury directly with progressive COVID-19 (Henry et al., 2020; Ji et al., 2020).

In deconstructing the checkpoint, we discovered a previously unrecognized mechanism in which VDR, like a molecular zip code, locates and transcriptionally silences TGFβ signaling via genomic competition with Smad3 occupancy on pro-fibrotic and pro-inflammatory (e.g., IL-6) genes, thereby inducing a quiescent state (Ding et al., 2013). FDA-approved analog (generic name, paricalcitol) was the most potent VDR-agonist in NHR drug screens and HSC/injury models, and in recent comparative analog analyses in patients with chronic kidney disease (Geng et al., 2020). Acute lung injuries (ALIs) from closely related SARS-CoV and MERS-CoV RNA viruses share the TGFβ/Smad mechanism (Yeung et al., 2016; Zhao et al., 2008). For example, the SARS-CoV nucleocapsid (N)-protein directly stimulates Smad3 in human airway epithelial cell cultures (Zhao et al., 2008). This pathologic mechanism is likely to be relevant to SARS-CoV-2, which has 88.1% identity with the N-protein of SARS-CoV. Smad-dependent gene transcription is also facilitated by Ang II (see below). Remarkably, as in our HSC studies, VDR negatively regulates TGFβ signaling via transcriptional interference with Smad2/3, attenuating pro-fibroinflammatory changes in experimental cardiac, renal, and dermal models (Inoue et al., 2012; Meredith et al., 2015; Zerr et al., 2015). High levels of TGFβ have been detected in acute-phase SARS and COVID-19 (see below), related to the development of pulmonary fibrosis, observed in autopsy studies and a substantial proportion of SARS, MERS, and emerging COVID-19 survivors (George et al., 2020; Thille et al., 2013; Zuo et al., 2009). TGFβ blockade, a proposed COVID-19 therapy (Chen, 2020), has broad biological, including deleterious, effects. VDR disruption of N-protein-Smad3 interaction could selectively deter SARS-CoV-2-induced ALI.

Unexpectedly, we found that stellate cells, previously thought to be liver specific, in the pancreas were also VDR positive and in response to VDR ligands suppressed pancreatitis and pancreatic cancer progression in mice (Sherman et al., 2014, 2017). The former is important, as pancreatitis is a serious disease that lacks any mechanism-based therapy, associated with ALI and severe COVID-19 (Liu et al., 2020a; Zhang et al., 2013), and with pancreatic cancer risk. Though Cyp24a1 was very highly expressed in activated pancreas stellate cells, paricalcitol induced quiescence, reversing of immune exclusion, and fibrotic drug resistance. When coupled with standard gemcitabine chemotherapy, VDR signal-dependent stromal reprogramming greatly increased tumor drug levels, response, and survival, compared to gemcitabine alone. In addition to rodent models, we confirmed the functional presence of the VDR checkpoint in human cancer-associated fibroblasts (hCAFs) derived from pancreatic cancer patients. Together these studies helped to foster ten vitamin D-related (all paricalcitol, https://clinicaltrials.gov) early-phase clinical trials in pancreatic cancer therapy, including three of our own Stand Up To Cancer- and Lustgarten Foundation-supported trials to test this novel concept, coupling intravenous paricalcitol-VDR activation with chemotherapy (Helms et al., 2020; Sahai et al., 2020).

In pancreatic cancer and COVID-19 patients, inflammatory disruption of epithelial homeostasis typically precedes fibrosis. While not recognized initially, stellate-derived CAFs are not a monolithic cell population only laying extracellular fibrotic matrix. For example, a classic inflammatory signal of activated stellate cells is IL-6, the predominant source of this cytokine in pancreatitis and cancer models (Öhlund et al., 2017), reported to promote immune suppression via effects on monocyte precursors and metabolism. SARS-CoV increases IL-6 levels by various mechanisms (Wang et al., 2007), e.g., N-protein binding to the NF-kB regulatory element of the IL-6 promotor in human airway epithelial cell cultures (Zhang et al., 2007). Additional studies from our and Tuveson's group (Biffi et al., 2019; Shi et al., 2019) have shown that LIF, an IL-6 family member, is also highly expressed in inflammatory pancreatic stellate cells, and thus may be worth exploring in COVID-19 cytokine-storm pathogenesis.

SARS pneumonitis begins with diffuse alveolar damage-induced inflammatory and pro-fibrotic cytokine release, including IL-1β, IL-6, TNF, and TGFβ (Gubernatorova et al., 2020; Zuo et al., 2009), at the onset of ALI in lethal SARS-CoV infection mouse models (Gralinski et al., 2013; Rockx et al., 2009). The key inflammatory mediators and kinetics in SARS-CoV-infected mice parallel that in patients. Furthermore, sustained pro-fibroinflammatory cytokine elevation predicts a poor outcome (He et al., 2020; Henry et al., 2020; Lu et al., 2020; Manson et al., 2020). In this context, the unremitting wound-repair response highlights the potential of activating the VDR checkpoint. Vitamin D has been shown to suppress host immune-pathologic inflammatory responses to viral infections, including SARS-CoV-2 (Mok et al., 2020). The profound, highly consistent post-infection vitamin D effect dampening excessive host response to pathogenic viruses contrasts with the little, if any, ligand influence on the virus itself in studies of Dengue fever (Manion et al., 2017), respiratory syncytial virus, influenza, and coronavirus infections (Gui et al., 2017; Hansdottir et al., 2010; Khare et al., 2013; Telcian et al., 2017).

Epidemiological studies show that large numbers of people around the world are chronically vitamin D deficient, seasonally worse in the winter and at higher latitudes (compare NYC to Miami). While there are many reasons for this, poor diet, indoor work, and low sun exposure are the most common. Perhaps of relevance to late-stage COVID-19, rates of influenza complicated by pneumonia and death during the 1918–1919 pandemic were inversely correlated with estimated UVB exposure and implied vitamin D deficiency (Grant and Giovannucci, 2009). A strength of this ecologic analysis was the use of survey data collected over 100 years ago (by the US Public Health Service, from New Haven to San Francisco), *before* the isolation of vitamin D, and thus not confounded by supplement intake. Recently, similar vitamin D-related mortality patterns have been reported in ARD (Pham et al., 2019), including viral outbreaks; e.g., an estimated 4.4% increase in COVID-19 *mortality* was reported for each degree latitude north of 28 degrees North (Rhodes et al., 2020). Patient-level ARD data indicated that vitamin D deficiency (plasma levels) correlated with hyperinflammation, risk of ICU admission, advanced respiratory support, and death (Dancer et al., 2015; Parekh et al., 2013; Vo et al., 2018). Corresponding US and South Asian studies found that the more the deficiency in COVID-19 patients, the worse the outcome (Lau et al., 2020). Thus, mechanistic, therapeutic, and epidemiologic studies clearly show prognostic value of vitamin D deficiency in severe COVID-19, suggesting the gravity of measuring plasma 25(OH)D levels in hospitalized patients in

routine blood test biomarker panels (Henry et al., 2020; Manson et al., 2020). Furthermore, these data suggest that restoring vitamin D activity to critically ill patients to prime the VDR checkpoint may be crucial. In contrast, stellate cell Cyp24a1 degradation of natural vitamin D makes enteral supplements futile (Ginde et al., 2019, Schrumpf et al., 2017).

African Americans and other individuals with dark complexions have lower levels of plasma 25(OH)D due to increased skin pigmentation (Essien et al., 2013), which although protective against excess sunlight, comes at the cost of reducing vitamin D synthesis and activation in the skin. Vitamin D levels in Blacks are lowest as a group compared to all other ethnic groups (Lau et al., 2020). For example, a National Health and Nutrition Examination Survey found that over 80% of non-Hispanic Blacks were vitamin D deficient (25(OH)D levels < 20 ng/mL) relative to Hispanics (59.0%) and non-Hispanic Whites (39.5%); age and socioeconomic status were also associated with serum 25(OH)D levels < 30 nmol/L (Diaz et al., 2009; Orces et al., 2019). This deprivation is especially serious and severe in people of color who live in northern latitudes, associated with increased COVID-19 mortality among Blacks across the US (Kohlmeier, 2020). Not surprisingly, in the last several weeks as the COVID-19 curve flattens for most Americans and amid delayed and limited release of disaggregated demographic data (Abbasi, 2020; Millet et al., 2020), an alarming COVID-19 ethnic/racial mortality signal was exposed. Notably, the newly created COVID Racial Data Tracker (and other dashboards) revealed consistent and stunningly high US (and UK) COVID-19 mortality rates in Blacks—exceeding Whites in *every* city and state with relevant data available, as well as exceeding American Indians and Hispanics by ~2-fold. In fact, a first major peer-reviewed primary report was published just weeks ago—a large case series of Ochsner Health hospitalized patients finding that Blacks (~30% of their catchment area) comprised >80% of COVID-19 ICU admissions requiring mechanical ventilation (Price-Haywood et al., 2020). This was quickly followed by research reports from two other hotspots. A patient-level study from the Bronx Montefiore Health System (Golestaneh et al., 2020) found increased COVID-19 mortality in Blacks that, in contrast to Hispanics, persisted after controlling for relevant co-morbidities (e.g., diabetes, obesity) and socioeconomic (SES) factors. A population-based, cross-sectional study of COVID-19 hospital mortality in Brazil (Baqui et al., 2020) found increased mortality in Black and dark-skinned (previously shown to be vitamin D deficient) ethnicities. The racial disparity in rates of COVID-19 severity is consistent with reports of prior viral outbreaks, e.g., the 1862 smallpox, and 1918 and 2009 influenza pandemics. Despite the disproportionate ethnicity/race COVID-19 mortality, potential contributing biologic factors are unknown and largely unexplored (Chastain et al., 2020; Webb Hooper et al., 2020). Societal determinants and socioeconomic factors are clearly important (Evans, 2020), though these factors alone do not fully explain severity inequalities (Office for National Statistics, 2020), including mortality-rate differences between Blacks and Hispanics noted above in a recent study from New York.

While stellate cell activation may play a dominant role in promoting liver disease, pancreatitis, and cancer, other classes of inflammatory cells, such as monocytes and macrophages, could represent alternate therapeutic targets. Furthermore, VDR signaling may provide additional beneficial effects by regulating the renin-angiotensin system (RAS), a key player in SARS-CoV-2 infection and COVID-19 severity. Mechanistically, COVID-19 infection begins when the spike protein of SARS-CoV-2 binds ACE2 to enter the cell, then downregulates and degrades ACE2 itself in the lung and heart (Oudit et al., 2009), a pivotal early event in lethal SARS mouse models (Rockx et al., 2009). This pathologic process removes vital ACE2 restraint of Ang II levels, unleashing massive amounts of Ang II, mainly produced by stellate-derived fibroblasts (Zuo et al., 2009), as well as activated macrophages, which provoke a sinister set of events. This includes reactive oxygen species generation and diffuse alveolar (and blood vessel) damage (Ackermann et al., 2020), which can cause macrophage and neutrophil infiltration, inducing proinflammatory cytokine release. For example, Ang II can directly induce IL-6 expression, via NF-kB activation, the main stimulator of STAT3 *in vivo*. Ang II also drives adhesion molecule and extracellular matrix secretion, and ultimately ARD, fulminant fibroinflammatory multi-organ involvement (Gubernatorova et al., 2020; Liu et al., 2020b; Rockx et al., 2009), and unchecked wound healing (Rockx et al., 2009). In fact, Ang II induced hepatic injury, persistent HSC activation, TGFβ expression, inflammation, and progression to cirrhosis, a process reversed with ACE2 or Ang 1–7 in pre-cirrhotic mouse models (Abdul-Hafez et al., 2018). Interestingly, ACE2 protein administration suppressed SARS-induced ALI and viral spread. Estrogen-liganded NHR can also induce ACE2 expression, as well as suppress cytokine (e.g., IL-6) expression, mitigating H1N1 virus-induced immunopathology (Vermillion et al., 2018).

After lipopolysaccharide (LPS) challenge, VDR null mice exhibited more severe ALI and higher mortality compared with wild-type counterparts, manifested by increased pulmonary edema, neutrophil infiltration, and inflammation, caused by excessive induction of pulmonary renin and Ang II, partially ameliorated by Ang II receptor antagonist (Kong et al., 2013; Li et al., 2004). Chronic dietary vitamin D deficiency can lead to RAS activation with induction of TGF-β1 expression and activation of a pro-fibrotic cascade (Shi et al., 2017). Plasma 25(OH)D deficiency increased Ang II and renin levels in people with essential hypertension, consistent with increased expression of renin mRNA and Ang II in a VDR knockout hypertensive mouse model (Rostand, 2010). Vitamin D directly suppresses renin transcription by a VDR-dependent mechanism (Yuan et al., 2007). Paricalcitol and other vitamin D agonists alleviated LPS-induced ALI and preserved alveolar barrier function, reducing neutrophil recruitment (Shi et al., 2016) and RAS activation, the latter by inducing ACE2/Ang-(1–7) axis activity and inhibiting renin and the ACE/Ang II/AT1R cascade (Xu et al., 2017). Similar effects were observed in non-lung models; e.g., vitamin D deficiency (or VDR knockout) was associated with increased renin and Ang II (and IL-6 and TGFβ) levels in diabetic mice (Zhang et al., 2008). In contrast, activation of VDR has been shown to decrease Ang II and increase levels of ACE2 in tubular cells and enhanced expression of ACE2, MasR, and Ang(1–7) generation in microglial cells (Riera et al., 2016, Cui et al., 2019; Xu et al., 2017). Taken together, these observations provide evidence that VDR signaling prevents lung injury by negatively regulating RAS and the Ang-2-Tie-2-MLC kinase cascade. Human intestinal organoids (ACE2 expressing), suggesting a

gut enterocyte reservoir for SARS-CoV-2, fuel viral spread and cytokine response in COVID-19 pathogenesis, another potential enteric-phase inflammatory hurdle to oral vitamin D administration (Clevers, 2020). Heightened *basal* RAS (e.g., reduced ACE2 expression, higher Ang II levels) activation and inflammatory states (Ajilore and Thames, 2020; Albert and Ridker, 2004; Suthanthiran et al., 2000; Vinciguerra and Greco, 2020), reported in African Americans, are associated with severe COVID-19 outcomes and relevant risk co-morbidities (e.g., hypertension, diabetes), some linked to vitamin D deficiency (Rostand, 2010; Yancy, 2020).

Considering the above, could paricalcitol be repurposed to help patients with severe COVID-19 avoid mechanical ventilation or have a better response and thus increased hope of safely getting off the respirator? If so, what would be the appropriate dose and what might be the potential complications? First, parathyroid hormone (PTH) is naturally suppressed by vitamin D agonists and thus hypercalcemia is possible. So patients should have PTH and calcium levels monitored at the outset and once every 5–7 days. In our pancreatic cancer patients, our IND was for 25 μg intravenously 3 times weekly (NCT03520790) and was well tolerated. In the context of COVID, patients would most likely be receiving paricalcitol treatment at this dose for a relatively short time (1–2 weeks), increasing safety. Similar to classic steroids, in liver injury and pancreatitis models as well as patient-derived CAFs, paricalcitol can acutely activate the VDR checkpoint. While more science needs to be done, we suggest the major complications of SARS-CoV-2 pneumonitis may be aggravated by vitamin D depletion and corralled by VDR agonists. Thus, the promise of targeting the VDR transcriptional switch in pro-inflammatory and pro-fibrotic stellate cells is real. This therapeutic concept is fortuitously supported by the recent discovery of lung stellate cells in mouse models, directly linked to pulmonary wounding response (Xie et al., 2018). These exciting, potentially game-changing results suggest stellate cells in the lung may logically share the VDR regulatory mechanism and, if so, be primed for therapeutic intervention. In the COVID-19 era, there is an urgent need for new ideas on the origin and nature of the unusual collection of complications that arise following infection, and repositioning existing drugs (such as dexamethasone) given at FDA-approved therapeutic doses but for short-course infusions in the acute setting (Lane and Fauci, 2020). As we await further study and formal proof, the potential of paricalcitol to trigger the VDR transcriptional "brake" to restrain and reprogram the intense inflammatory response in COVID-19 is compelling. As paricalcitol is injectable, pre-activated, and stable, it is a prescription drug option that can be quickly repurposed for bedridden, intubated COVID-19 patients with negligible sun exposure in the hospital ICU setting. This could offer much needed restoration and activation of VDR activity to the body, and perhaps cool inflamed lungs and boost body health enough to give patients a fighting chance to, on their own, walk out of the darkness and into the light.

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