Chapter

The Role of Vitamin D in the Restriction of the Progress and Severity of COVID-19 Infection

Alakesh Bharali, Bhargab Deka, Himangshu Sarma, Ashique Ahmed, Bedanta Bhattacharjee, Santa Sarma, Suman Kumar, Susankar Kushari and Rajlakshmi Devi

Abstract

SARS-CoV-2 has affected socio-economic activity in every country around the world since its outbreak began in 2019. 3.5 million people have died worldwide as of now, including 3.2 lakh in India. The cytokine storm significantly contributes to COVID mortality. To put it simply, the virus causes an uncontrolled release of cytokines, which results in severe inflammation, multi-organ failure, and death. Vitamin D was discovered to be a significant risk factor for cytokine storm in COVID patients. Numerous studies have demonstrated that those with deficient serum vitamin D levels have a significant mortality rate. The current understanding of the role of vitamin D in immune modulation in the innate and adaptive immune systems and how this may relate to COVID-19 is discussed in this article. Additionally, we evaluated the most recent clinical information about vitamin D deficiency, cytokine storm, and COVID-19 mortality.

Keywords: Covid-19, cytokine storm, immune regulation, pandemic, vitamin D

1. Introduction

As with SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome), the rapid spread of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) wrecked global health and economics. As of May 13, 2022, the SARS-CoV-2 outbreak has caused more than 519.9 million infections with over 6.3 million deaths [1] (https://www.worldometers.info/coronavirus). The SARS-CoV-2 infected or COVID-19 patients may develop various clinical manifestations,including severe acute pulmonary disease [2, 3], heart damage [4], kidney injury [4], hepatic dysfunction [4], pancreatic symptoms [5], gastrointestinal [6] and olfactory dysfunction [7]. However, the impact of COVID-19 may have long-lasting effects on the physiological systems. Nevertheless, these numbers are increasing at a frenetic pace [8]. In certain people, COVID-19 infection is accompanied by a "cytokine storm." The cytokine storm is a phenomenon in which

pro-inflammatory cytokines are released at an abnormally rapid rate, allowing for the recruitment of additional immune cells to the injury site, resulting in organ damage. Numerous investigations evaluating COVID-19 patient cytokine profiles discovered that the cytokine storm is associated with significant lung injury and potentially multi-organ failure in COVID-19 patients [9].

Recent research has revealed that different people's bodies respond differently to the infection. Despite sharing the same race, culture, age, and sex, some people contract the virus while others do not exhibit the core symptoms/remain asymptomatic. According to studies, some people's immune systems handle COVID-19 better than others. COVID-19 is more prevalent in those with pre-existing health disorders such as cardiovascular disease, diabetes, respiratory disease, or hypertension, particularly those over 60. These comorbidities/factors impair the immune system, hence raising the severity of the disease [10]. Vitamin D deficiency and cytokine storm have been identified as risk factors; more studies have shown that vitamin D deficiency causes chronic illness and mortality in COVID-19 patients. Vitamin D supplementation has been proven to reduce the likelihood of a cytokine storm, although the molecular mechanism is unknown [11]. Additionally, vitamin D has been identified to dampen cytokine storms during the 1918–1919 viral influenza pandemic and prior coronavirus pandemics [12]. Thus, vitamin D's astounding quality draws our attention to authoring this review on its role in lowering the COVID-19-associated cytokine storm.

2. Pathology of SARS-CoV-2 infection

Chinese researchers utilized Cryo-electron microscopy to demonstrate how SARS-CoV-2 infects humans. The virus targets angiotensin-converting enzyme II (ACE II), located in human cells and tissues such as the lungs, heart, kidneys, and intestines [13]. According to Mark Fielder, a scientist at Kingston University, the virus appears to target two types of lung cells: goblet cells, which coat the respiratory

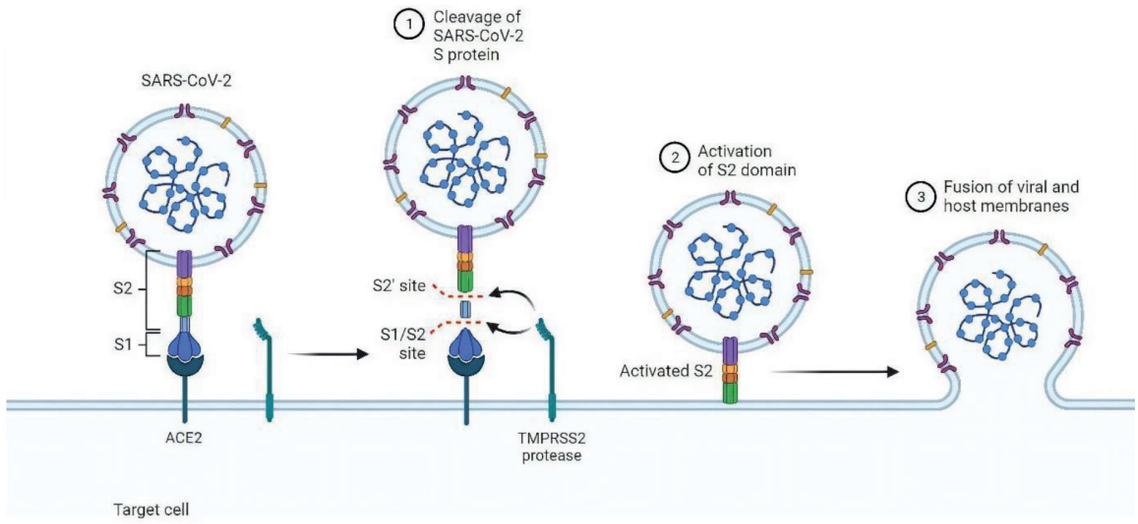

Figure 1.
Steps in the infection of SARS-CoV-2. The spike protein on the surface of the new coronavirus serves as the principal mechanism by which the virus enters the cell. A protein termed transmembrane protease serine-2 (TMPRSS2) cleaves spike protein into two subunits, S1 and S2. It is a cell surface protein that epithelial cells express in various organs, including those of the aerodigestive tract. TMPRSS2 aids the virus in infecting the host cell.

tract with mucus, and ciliated cells, filtering out debris [14]. Two receptor-binding domains (RBD) are present on the viral spike protein, one pointing downward and the other facing upward. As a result, the virus can bind to and infect human cells. The virus interacts with upward-facing RBD via spike proteins. Once inside the cell, the virus breaks down its protein coat and releases its Ribonucleic acid (RNA) payload, according to the British Society for Immunology. It replicates itself by taking control of the endoplasmic reticulum and the host cell structure. As a result of hijacking, the Golgi bodies of hijacked cells become encased in a protein shell that caps viral RNA and proteins, creating new viruses that exit the infected cell via the membrane. Coronavirus infection disturbs the host cell, according to a study published in Frontiers in Microbiology. Apoptosis, or cell death, occurs when an infection overwhelms the host cell's ability to sustain homeostasis (**Figure 1**) [15].

3. Role of vitamin D in immune regulation

Vitamin D is produced by the skin when it is exposed to sunshine. To begin, cholesterol is converted to 7-dehydrocholesterol by an enzyme called DHCR7 (7-Dehydrocholesterol Reductase). It is then converted to pre-vitamin D by the sun's ultraviolet B (UV-B) light, which spontaneously turns into vitamin D at body temperature. Although nature contains five different forms of vitamin D, only vitamin D_3, also known as cholecalciferol, is synthesized by the human body [16]. Cholecalciferol is an inactive form of vitamin D that the body must activate. It is converted to calcidiol in the liver by the enzyme vitamin D 25-hydroxylase. Calcidiol is then converted in the kidney to calcitriol (1,25-dihydroxycholecalciferol), the active form of vitamin D [17]. It is primarily regulated by parathyroid hormone, blood calcium/phosphorus levels, and calcitriol levels. Its active form aided in calcium absorption in the small intestine and was historically used to treat osteoporosis and rickets.

Additionally, it assists in the form of calcium deposits in the bones. Vitamin D has been recognized as a critical immune modulator and is also implicated in various

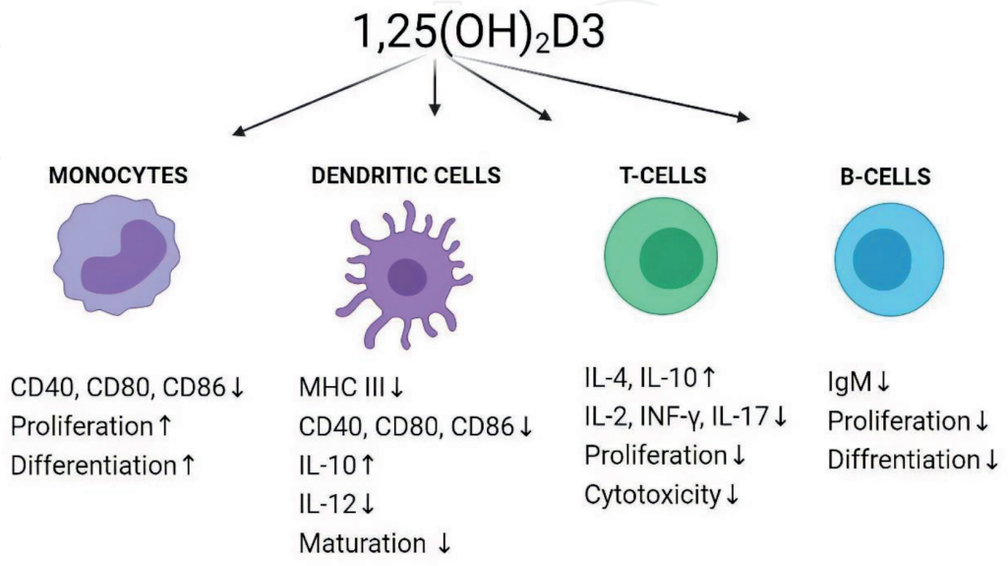

Figure 2.
Role of vitamin D in immune regulation. It down-regulates pro-inflammatory substances and up-regulates anti-inflammatory substances.

diseases, including autoimmune illnesses. The significant 1969 discovery that vitamin D, like other steroid vitamins such as vitamin A, may act on various cell types via activation of the vitamin D receptor (VDR) revealed a new window into understanding its role in health and disease [18]. As a result, vitamin D has been discovered as an immunomodulator, and VDR is detected in nearly all immune cells. Vitamin D increases IL-10 and T regulatory cells while decreasing T helper cytokines like IL-2, IL-32, Interferon-gamma (IFN-γ), and IL-17 [19]. This results in a change in damage-associated molecular pattern signaling, which is linked to numerous disorders (**Figure 2**).

4. Vitamin D as a regulator of the innate immune system

Vitamin D can augment the innate immune system's antimicrobial defenses. This role was discovered 30 years ago. Previous research has revealed that our immune cells, notably macrophages and monocytes, may synthesize vitamin D on their own and boost the development of an antimicrobial protein called cathelicidin, enhancing the intracellular clearance of *Mycobacterium tuberculosis* [20]. In epithelia, similar processes that contribute to barrier function have been discovered. Vitamin D receptor complexes enhance the transcription of cathelicidin by binding to vitamin D response sites in the cathelicidin gene promoter [21]. Cathelicidin is a significant antimicrobial protein with additional functions, including chemotaxis stimulation, generation of pro-inflammatory cytokines, recruitment of T-lymphocytes to the site of infection, and clearance of respiratory pathogens by apoptosis and autophagy infected epithelial cells. Vitamin D levels in the blood regulate macrophages' ability to generate cathelicidin.

Additionally, vitamin D appears to influence another intrinsic antibacterial compound, called β-defensin 2. β-defensin 2 induces the release of antiviral cytokines and chemokines that recruit macrophages, neutrophils, natural killer cells, and T cells, resulting in strong host defense [22]. Vitamin D can also serve as an antibacterial by regulating cellular iron metabolism. The survival of bacteria is dependent on intracellular iron. During an infection, hepcidin is formed, which blocks transcellular iron export via ferroportin, increasing cellular iron levels. Vitamin D is a potent hepcidin suppressor, increasing ferroportin and decreasing intracellular iron levels, inhibiting bacterial growth [23].

5. Vitamin D as a regulator of adaptive immune response

The adaptive immune system responds to threats based on the characteristics of the adversary, hence the name. In comparison to the innate immune response, it takes time to mature. A unique type of cell triggers this form of immune response called an antigen-presenting cell (APC). These cells next activate B and T lymphocytes, which are in charge of subsequent antigen identification. After a priming period, T and B cells are activated in body tissues such as lymph nodes, often located far from the original antigenic substance exposure site. The proliferation of activated T and B cells and post-translational alterations of immunoglobulin synthesis utilize this time, allowing the cell to respond uniquely to an antigen. An antigen's context and the surrounding environment, including serum vitamin D levels, determine the type of T-cell activated, CD4 or CD8, or within the helper T-cell class Th1, Th2, Th17, or T-regulatory cells

(Treg). There is evidence that vitamin D suppresses inflammatory T-cells and increases regulatory T-cell activity (Tregs) [24]. Tregs are a critical component of the immune system. Its essential purpose is to reduce the immunological response after removing the threat from the body. Because the immune response persists after the threat has been eradicated, collateral damage to healthy cells and tissues may occur. Tregs are crucial in COVID-19 for preventing the cytokine storm associated with severe respiratory distress. Additionally, vitamin D is a potent suppressor of macrophage activation mediated by IFN-γ, which is likely to play a role in COVID-19 [25].

6. COVID-19 and its link to vitamin D and cytokine storm

As previously acknowledged, vitamin D deficiency has been found as a possible risk factor for COVID-19. Vitamin D acts as an immunological modulator, and its lack results in a reduced innate immune system. COVID-19's severity is determined by an individual's immune system's state. This virus severely impacts individuals with weakened immune systems, whilst those with more robust immune systems remain asymptomatic or exhibit mild-to-moderate symptoms. As a result, we could establish a link between vitamin D deficiency and the severity of COVID-19 [26].

Vitamin D's antibacterial activity was found three decades ago [27]. Besides antibacterial function, vitamin D promotes antiviral activity, which is particularly relevant in COVID-19. It possesses/promotes antiviral activity by preventing viruses from entering cells and inhibiting viral reproduction via induction of cathelicidin and defensins [28]. Additionally, vitamin D may increase antiviral activity via a critical cellular process called autophagy. Autophagy contributes to the creation of a hostile cellular environment for viruses such as coronavirus [29].

In some individuals, COVID-19 infection is accompanied by a "cytokine storm," in which several pro-inflammatory cytokines, such as IL-1, colony-stimulating factor (granulocyte CSF, macrophage CSF, granulocyte-macrophage CSF), and tumor necrosis factor-alpha (TNF-α), are released in large quantities, allowing for the recruitment of additional immune cells to the site of injury. The coronavirus causes damage by infecting both the upper and lower airways, leading to fast viral replication and extensive infiltration of immune cells, resulting in a significantly increased release of pro-inflammatory cytokines and chemokines. This results in a condition known as acute respiratory distress syndrome (ARDS) [30]. The epithelial cells of infected airways secrete cytokines that further disrupt the innate immune system. Furthermore, it stimulates the inflow of inflammatory cells such as monocytes, neutrophils, and macrophages, exposing healthy lung cells to apoptosis [31]. The lungs' microvascular and alveolar epithelial barriers are damaged by apoptosis, contributing to vascular leakage and alveolar edema. In addition, T-cell response to viral clearance is slowed, which reduces their capacity to regulate cytokine storms [32].

Vitamin D is critical for regulating the pathophysiological manifestations of the cytokine storm. Along with 1,25-$(OH)_2$D and CYP27B1, vitamin D receptors are expressed on the airway epithelia. In addition, pulmonary alveolar macrophages express vitamin D receptors as well as CYP27B1. As a result, by boosting/activating the innate immune system and increasing local 1,25-$(OH)_2$D synthesis, vitamin D can slow down the cytokine storm and chemokine production. This increases viral neutralization and clearance while moderating pro-inflammatory reactions that follow. Vitamin D also inhibits the adaptive immune system from becoming hyperactive, facilitating a quick response to viral loads [22].

6.1 Clinical evidence between COVID-19 and vitamin D

UV-B radiations are negligible at the earth's surface throughout the winter at latitudes over 40°. In a study, Rhodes et al. discovered a link between COVID-19 deaths and countries based on latitude. He discovered that countries with latitudes less than 35° North have low death rates. This could be related to the fact that persons living in regions north of 35° North do not receive enough sunlight during the winter, resulting in vitamin D insufficiency [33].

According to D'Avolio et al., 107 numbers of COVID-19 nasopharyngeal swabs were obtained from March 1 to April 14, 2020 [34]. He determined that those who tested positive for the virus suffer from severe vitamin D insufficiency. In contrast, those who tested negative have an average or insufficient vitamin D level in their blood. The median 25-OHD concentration in the 27 individuals tested positive for SARS-CoV-2 was 11.1 ng/ml, compared to 24.6 ng/ml in those who tested negative. Gennari et al. reported reduced 25-OHD levels in COVID-19 patients hospitalized in Italy [35]. Bergman et al. performed a meta-analysis of randomized controlled trials (RCTs) evaluating vitamin D to prevent respiratory tract infections (RTI). They established that preventive vitamin D treatment decreases the risk of developing RTIs [36].

Ahmed's research incorporated bioinformatics and system biology techniques to gain a deeper understanding of the SARS-CoV-2-induced cytokine storm. Vitamin D inhibits the synthesis of pro-inflammatory cytokines by inhibiting the TNF-α induced NFkB1 signaling network. It activates the IFN-α induced Jak–STAT signaling route, promoting interferon-alpha stimulating genes (ISGs) for antiviral defense [11].

According to Daneshkhah et al., Italy, Spain, and France have the highest COVID-19 age-specific case fatality rate as well as the lowest 25OHD levels (0.25 ng/l) compared to other countries. Italians and Spaniards are heavily affected by COVID-19 and have the highest rate of hypovitaminosis D in Europe (142 according to endocrinology) [37]. According to a study of 700 Italian women aged 60 to 80, 76% had 25-OHD levels less than 12 ng/ml. (154). Over 80% of postmenopausal women have hypovitaminosis D in summer, whereas only 32% have it during the winter [38, 39].

Lau et al. evaluated the levels of 25OHD in twenty COVID-19 patients admitted to an intensive care unit. Vitamin D insufficiency was detected in 11 participants and all patients under the age of 75. Seven of these individuals exhibited 25OHD concentrations of at least 10 ng/ml. According to this study, vitamin D deficiency worsened COVID-19 infection [40]. The highest rates of vitamin D deficiency were associated with the highest rates of infection and mortality, according to a study of COVID-19 severity in Europe. Further, a preliminary investigation conducted in the United States revealed a high correlation between vitamin D deficiency and mortality and other risk factors for adverse outcomes [12]. Carpegnano et al. demonstrated in a retrospective and observational investigation that vitamin D insufficiency predicts poor prognosis in patients with acute respiratory failure caused by COVID-19 [41].

In COVID-19 patients, vitamin D deficiency is associated with a high risk of hospitalization. A team of investigators undertook a recent study on elderly patients on a sample of 105 persons aged 65 and up who displayed COVID-19-like symptoms. They discovered that 35 (33.3%) of the participants tested negative for SARS-CoV-2 (vitamin D level = 52 nmol/l) when tested. Whether or not, 70 (66.7%) of individuals tested positive for SARS-CoV-2 (vitamin D level = 27 nmol/l). Among the 70 (66.7%) people, 39 (55.7%) had vitamin D levels below 30, whereas the remaining 31 (44.3%) had Vitamin D levels above 30, and their D-dimer value was lower (D-dimer is considered a risk factor for blood clots in COVID-19) [42].

The production of IL-6 by monocytes, dendritic cells, and macrophages during COVID-19 infection resulted in producing a large number of pro-inflammatory cytokines and C-reactive protein (CRP). CRP is a nonspecific inflammatory marker that becomes more specific to the bioactivity of IL-6. It can generate significant inflammation, which is critical in the development of cytokine storms in individuals with severe COVID-19 [43]. Guan et al. reported that approximately 44.5% of severe COVID-19 patients with high CRP levels had a higher risk than patients with mild COVID-19 [44]. Vitamin D deficiency promotes the release of cytokines such as TNF-α and IL-1, leading to increased inflammation and elevated CRP [45]. This could explain the concurrent reduction in CRP and inflammatory cytokines ($CD4^+$ and IFN) in hemodialysis patients following calcitriol treatment, as well as the elevation of both CRP and cytokines in severe COVID-19 patients. Experiments have shown that vitamin D can inhibit the production of inflammatory cytokines such as IL-6 and L-17 while increasing anti-inflammatory cytokines such as IL-10 [46]. This could lead to a reduction in CRP and inflammation.

Studies show that vitamin D deficiency can exacerbate RTI in vulnerable populations (elderly and those with underlying health conditions). To maintain an adequate vitamin D status and prevent mortality, supplementation is recommended to restore vitamin D levels depleted due to insufficient sunlight exposure. The clinical data on vitamin D status on COVID-19 disease is still in the initial stage. As of now, many of the papers in this field have been published without extensive peer review, retrospectively, and with only associative data [47].

7. Supplemental vitamin D acts as an anti-inflammatory agent

By regulating the production of inflammatory cytokines and inhibiting the growth of pro-inflammatory cells, vitamin D aids in modulating the immune system [48]. According to various studies assessing the association between low vitamin D levels and acute infections, vitamin D supplementation improves clinical responses to acute infections. In addition to its role in natural cellular immunity, vitamin D also plays a role in physical barriers and adaptive immunity [49]. Several studies have shown that vitamin D influences the adaptive immune response in inflammatory and autoimmune diseases [50, 51]. In addition, it may play a role in the etiology of chronic inflammatory disorders, such as asthma, atherosclerosis-associated cardiovascular disease, inflammatory bowel disease, nonalcoholic fatty liver disease, and chronic renal disease [52]. During the autumn and winter months in the UK, the National Institute for Health and Care Excellence has recommended taking vitamin D supplements to prevent bone, muscle, and immunological problems [53].

Vitamin D intake reduces the likelihood of contracting influenza, according to a study [54]. More research, however, is needed to confirm these findings. Vitamin D supplementation aids in HIV infection by blocking viral entry, regulating $CD4^+$ cell surface antigen expression, dampening viral p24 production, and reducing monocyte proliferation [55]. A deficit of vitamin D is associated with acute respiratory distress syndrome, chronic illness, and increased mortality rates in the elderly [56]. An experimental report indicates that high-dose vitamin D supplementation may be beneficial, especially for the elderly, obese, those with dark skin, those living at higher latitudes, and those living at 35° north, where sunlight intake is insufficient to maintain adequate vitamin D levels during winter. A vitamin D supplement may be beneficial to people at risk of chronic diseases such as respiratory tract infections, cardiovascular disease, cancer, diabetes, and hypertension. In the bloodstream, levels

of vitamin D above 50 ng/ml (125 nmol/l) have been linked to a lower risk of many viral infections, including COVID-19 [57, 58].

8. Conclusion

Based on recent clinical investigations, we conclude that vitamin D may have a role in lowering the complications associated with COVID-19-induced uncontrolled inflammation and cytokine storm. Additionally, researchers found a link between patients with COVID-19 and insufficiency of serum vitamin D. The widespread effects of vitamin D on various organ systems have sparked discussion regarding a possible interaction between it and the processes by which the SARS-CoV-2 virus infects humans. In COVID-19 patients, adequate vitamin D levels in serum were associated with a significantly lower frequency of disease severity, despite limited clinical data. It is expected that there will be more studies published regarding its role in upper respiratory infections such as COVID-19 in the near future. A sufficient amount of patient-level data is required to demonstrate the protective effect of vitamin D.

Author contributions

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List of abbreviations

ACE II	Angiotensin-Converting Enzyme II
APC	Antigen-Presenting Cell
ARDS	Acute Respiratory Distress Syndrome
CD-4 & 10	Cluster of Differentiation-4 & 10
COVID-19	Coronavirus disease-19
CRP	C-reactive protein

DHCR7	7-Dehydrocholesterol Reductase
HIV	Human Immunodeficiency Virus
IFN-γ	Interferon gamma
IL	Interleukin
MERS	Middle East Respiratory Syndrome
RBD	Receptor-Binding Domains
RCTs	Randomized Controlled Trials
RNA	Ribonucleic acid
RTI	Respiratory Tract Infections
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
TMPRSS2	Transmembrane Protease Serine-2
TNF-α	Tumor Necrosis Factor-alpha
UK	United Kingdom
UV-B	Ultraviolet B
VDR	Vitamin D Receptor

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