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Low-dose naltrexone (LDN): A promising treatment in immune-related diseases and cancer therapy

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ABSTRACT

Naltrexone, a non-selective antagonist of opioid receptors, is mainly used as rehabilitation therapy for discharged opiate addicts to eliminate addiction in order to maintain a normal life and prevent or reduce relapse. In recent years, there have been some novel and significant findings on the off-label usage of naltrexone. Within a specific dosage window, LDN can act as an immunomodulator in multiple autoimmune diseases and malignant tumors as well as alleviate the symptoms of some mental disorders. The results of increasing studies indicate that LDN exerts its immunoregulatory activity by binding to opioid receptors in or on immune cells and tumor cells. These new discoveries indicate that LDN may become a promising immunomodulatory agent in the therapy for cancer and many immune-related diseases. In this article, we review the pharmacological functions and mechanisms of LDN as well as its clinical therapeutic potential as revealed by our team and other researchers.

1. Introduction

Opioid receptors are groups of receptors (μ-, κ-, δ- and ζ-opioid receptors) that are widely distributed in nerve cells of the brain, the spinal cord and the digestive tract. The main function of ζ-receptors is related to growth and development. Thus, the ζ-receptor is also called the opioid growth factor receptor (OGFr). OGFr also expresses in or on the immune cells, which indicates that agonists and antagonists of OGFr can play immunoregulatory roles.

Naltrexone is a type of general antagonist of opioid receptors [1]. It has a strong blocking effect on OGFr [2]. It can be used for drug withdrawal and prevention of relapse at the label dosage of 50 mg/day. Currently, naltrexone has been used to treat chronic pain syndrome and autoimmune diseases at a dose of 5 mg/day, which commonly is referred to as LDN [3].

Many studies mainly focused on the traditional pharmacological effects of LDN on substance abuse and addiction disorder which achieved some success. LDN could relieve the symptoms of physical dependence [4–10], reduce withdrawal symptoms [11,12], and prevent drug-addict relapse after detoxification [13,14] as well as provide supportive therapy for heavy alcohol and tobacco dependence [15–17]. However, the immunoregulatory activity of LDN should not be neglected. In 1983, an article in *Science* first reported [18] that LDN intermittently blocked OGFr and significantly inhibited the growth of neuroblastoma in tumor-bearing mice. In the past three decades, the immunoregulatory actions of LDN have attracted more attention, and increasing trials and experiments are still ongoing.

Previous articles published by our research team indicate that LDN could modulate the function of immune cells such as bone marrow dendritic cells (BMDCs) and macrophages [19,20]. On the basis of its immunomodulatory and anticancer properties, our team has already applied the combination of LDN and methionine enkephalin (MENK, also called OGF) as a novel antitumor agent [21]. In this article, we summarize the work of our laboratory, other researchers and physicians. Our work intends to provide a comprehensive summary of LDN's pharmacological functions, especially in anti-inflammation and immunoregulation, and its potential for immune-related disease and cancer therapy.

Abbreviations: LDN, low dose naltrexone; OGFr, opioid growth factor receptor; OGF, opioid growth factor; FDA, Food and Drug Administration; HDN, high dose naltrexone; TLR-4, Toll like Receptor 4; BMDCs, bone marrow dendritic cells; MENK, methionine enkephalin; MS, multiple sclerosis; EAE, experimental autoimmune encephalomyelitis; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; CD, Crohn's disease; AIDS, acquired immune deficiency syndrome; CNS, central nervous system; SCCHN, squamous cell carcinoma of the head and neck

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2. Pharmacological functions and potential mechanisms

2.1. OGF-OGFr axis

In 1987, Zagon and MeLaughlin [22] found that the OGF-OGFr axis is made up of OGF and its specific receptor in the developing rat brain and a neuroblastoma cell line. In physiological conditions such as developing brain and cerebellum [23] and in the cornea [24], the binding of OGF-OGFr has been recorded by immunoelectron microscopy and confocal microscopy, which plays an important role in supporting growth and development of tissues and organs. OGF and naltrexone can promote cell proliferation and wound healing.

However, many physical diseases, including multiple sclerosis, Crohn's disease, diabetes, and cancer, as well as mental disorders are related to OGF-OGFr axis dysregulation. For instance, the existence of the OGF-OGFr axis has been confirmed in many malignant tumor cells [25,26]. In vitro studies, OGF could significantly inhibit cell replication of squamous cell carcinoma of the head and neck (SCCHN) via the mechanism of receptor mediation [27]. As an antagonist of OGFr, LDN has been found that could regulate tumor cell proliferation through the OGF-OGFr axis in recent studies [2,28].

Evidence suggested that the effect on cell growth is mediated by OGFr and is seem to be associated with dose but actually related to duration of action [29]. It is observed that LDN lead to inhibitory growth of tumor growth, while HDN lead to accelerated tumor growth and somatic cell development. As shown in Fig. 1, continuous blockage by label-usage naltrexone can promote cell proliferation, while intermittent blockage by LDN can inhibit cell proliferation, which plays a therapeutic role in cancers and autoimmune diseases. During the window period of intermittent blockage caused by LDN, endogenous opioids and their receptors were compensatory up-regulated. Therefore, the availability of receptors can be enhanced after the blocking of the intermittent antagonist, and the receptor availability was inhibited after continued blockage. Treatment with LDN upregulates the expression of OGF and OGFr in SKOV-3 cells [30], LDN can reverse the altered homeostasis by exerting a partial inverse agonist effect. Moreover, LDN or OGF treatment cannot produce inhibition of cell proliferation in OGFr-knockdown SKOV-3 cells [31]. The effects of LDN on cell proliferation and synthesis of DNA may relate to the p16 and/or the p21 cell cycle-dependent inhibitory protein kinase [26,30,32].

2.2. Directly as an immunomodulating agent

Naltrexone, as a non-selective opioid receptor antagonist, can block the binding of endogenous opioids and opioid receptors. The mechanistic pathways of LDN are still unclear. Some studies indicate that LDN works as an immunomodulating agent by directly bind on the OGFr within immune cells [33,34]. Additionally, evidences suggest that naltrexone acts on the body through at least two different receptor mechanisms. Microglia are considered as resident macrophage of the CNS, which are activated by various triggers. In addition to the antagonism of mu-opioids and other opioid receptors, naltrexone simultaneously blocked non-opioid receptors such as TLR-4 in macrophages and microglia [35–37]. LDN is thought to exert its anti-inflammatory effects through non-opioid antagonist pathways.

2.3. Elevate endogenous opioids and inhibit proliferation of T and B lymphocytes

Zagon and colleagues found that LDN short-term effects could produce upregulation of opioid receptors. By increasing the production of endogenous opioids, LDN could inhibit the proliferation of B lymphocytes [38], T lymphocytes [39] and the corresponding immune responses. Bihari and colleagues [40] first used LDN to treat acquired immune deficiency syndrome (AIDS) patients in 1995. The number of T cells in people with AIDS did not decrease after using LDN, and their pathologically elevated level of acid-labile alpha interferon was reduced. LDN can increase the level of β-endorphin in vivo and stabilize the number of T cells in HIV-infected individuals [41]. The results indicated that LDN could reduce opportunistic infections and increase the survival rate of AIDS patients. OGF and LDN had no significant effect on the number of central nervous system (CNS) mononuclear infiltrates in the established experimental autoimmune encephalomyelitis (EAE) model [42], but both could limit the number of $CD3^+/CD4^+$ T cells in the lumbar spinal cord. Another study reported that LDN reduced the proliferation rate of activated T cells in EAE mouse models [43].

2.4. Influence cytokine production

The results of a study from our laboratory [20] revealed that LDN could enhance the phagocytic ability of macrophages by influencing surface marker expression and secretion of various cytokines. In addition, our laboratory explored the effect of LDN on BMDC maturation, which revealed that LDN increased the concentration of interleukin (IL)-2 and induced the secretion of tumor necrosis factor (TNF)-α [19]. At the same time, LDN could improve the expression of MHCII, CD40, CD83, CD80 and CD86 molecules on the surface of BMDCs.

2.5. Other potential mechanisms

The mechanism of LDN is not fully understood. Because opioid receptors are widely distributed in many kinds of immune cells, research on the effects of different concentrations of naltrexone on immune cells is necessary. Recent studies have shown that 10^{-4} mol/L naltrexone has a suppressing effect on the proliferation of lymphocytes by blocking μ-opioid receptors and increasing the expression level of TLR-4 [44]. Additionally, increasing studies suggested that LDN may work not only through the OGF-OGFr axis [26,32,38,42,45] or through immune-related signaling such as the Toll-like receptor 4 (TLR-4) pathway [36,44,46]. LDN can also downregulate the expression of pro-apoptotic proteins by activating apoptotic pathways [47]. It relieves the neurotoxicity of glutamate on nerve cells by inhibiting inducible nitric oxide

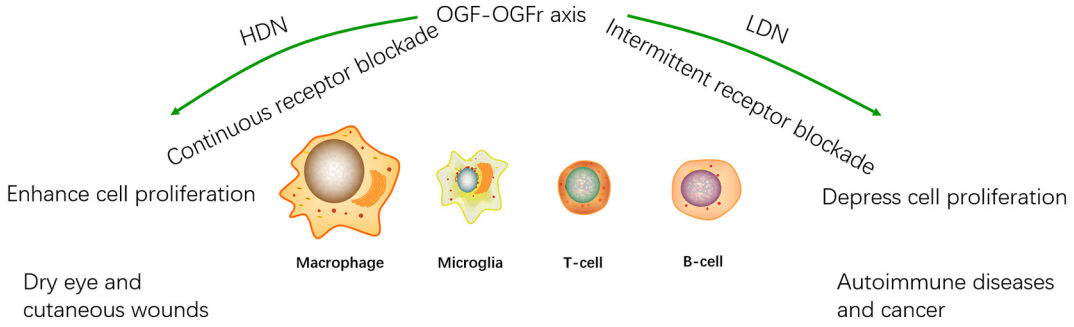

Fig. 1. The effect of HDN and LDN on OGF-OGFr axis.

synthase (iNOS) activity [48] and reducing inflammation [49].

3. LDN and autoimmune-related disease

In the 1980s, LDN was found to have immunomodulatory and therapeutic effects. Recent studies confirmed previous reports and suggested that LDN played a significant role in the treatment and control of a variety of autoimmune diseases.

3.1. LDN and multiple sclerosis

Ten years ago, LDN was first used spontaneously by MS patients worldwide, with substantial results before medical institutions conducted rigorous clinical trials [49]. LDN can not only prevent the recurrence of MS but also reduce the progression of the disease [50]. A series of trials [51–54] of patients diagnosed with MS (relapsing-remitting and secondary progressive MS, primary progressive MS) have shown that LDN is well tolerated and does not cause adverse reactions while significantly improving the patient's quality of life and mental health. Similar results had been acquired in the animal model of EAE [55,56] and MS patients [57]. These data suggested that LDN, as a safe, non-toxic and inexpensive biotherapeutic, does not lead to further deterioration of the disease symptoms [58].

3.2. LDN and inflammatory bowel disorders

An open-label prospective trial conducted by Zagon and colleagues [59] first investigated the safety and efficacy of LDN in patients with active Crohn's disease (CD). The CD activity index scores were significantly decreased, and quality of life surveys were improved after LDN treatment. A series of studies [60,61] found that LDN was well tolerated and might reduce disease activity. In addition, LDN was able to treat CD and mesentery panniculitis with little or no adverse reactions [62,63].

LDN could regulate inflammatory cytokine production by influencing the level of endogenous opioid peptides in the body [64]. Treatment with sulfasalazine, LDN or a combination significantly improved the measured parameters, including serum levels of TNF-α and C-reactive protein, disease activity index and macroscopic and microscopic pathological scores compared with those of the enteritis group. Ploesser and colleagues [65] reviewed the therapeutic effects and side effects of LDN therapy in 206 patients with a variety of gastrointestinal disorders, including either irritable bowel syndrome, chronic idiopathic constipation, or inflammatory bowel disease. The use of LDN had side effects including neurological complaints such as anxiety, drowsiness, headache, dizziness, insomnia, muscle pain, vivid dreams, mood change and trouble concentrating, gastrointestinal reactions such as nausea, abdominal pain, diarrhea and anorexia, which were tolerable in most cases. In addition, intravenous LDN administration effectively reversed chronic opioid-induced constipation and transit changes [66], which indicated that LDN was beneficial to the management of opioid-induced gut motility disorder in chronic pain patients.

3.3. LDN and fibromyalgia

In single-blind crossover experiments on several female fibromyalgia patients, LDN was found to significantly relieve pain in more than half of the patients [67,68]. Some scholars [69] have suggested that, if fibromyalgia is an endocrine deficiency disease, LDN may be an effective drug for the treatment of the disease. Subsequent studies found that LDN had a glial cell modulator effect and thereby improved the patient's fibromyalgia symptoms [35]. In addition, some scholars proposed that the dynamic prediction model should be used to formulate the optimal dose curve for patients with chronic fibromyalgia through the engineering control to achieve personalized treatment of patients with LDN, reduce costs and improve efficacy [70].

LDN was found to improve fibromyalgia and prolong pain tolerance [71], which was thought to work through modulation of inflammatory mediator concentrations in plasma [72]. Although increasing numbers of fibromyalgia patients have used off-label LDN as a potentially useful drug, resulting in a rebound of endorphin function to attenuate the pain of the disease, further controlled trials are needed to verify this observation before LDN is recommended as first-line therapy [73,74].

3.4. LDN and type I diabetes

Insulin-dependent diabetes mellitus (IDDM) (also called type 1 diabetes) is an autoimmune disease characterized by inflammation of pancreatic islets and destruction of β cells by the immune system, in which patients have an absolute lack of insulin and a variety of complications such as dry eye and corneal disease. LDN could maintain a short period of tear secretion in dry-eye rats and could restore a loss of corneal sensory sensitivity to normalization [75], in addition to promoting growth of corneal granulation tissue and angiogenesis [76,77]. LDN was found to accelerate the healing of damaged corneal lesions in rats [78]. In addition, LDN also has a certain effect on refractory painful diabetic neuropathy [79].

3.5. LDN and pruritus

Systemic sclerosis is an autoimmune disease that causes skin, lung and gastrointestinal fibrosis and vascular lesions, and pruritus as a common symptom. LDN treatment has achieved initial results for pruritus and pain of other inflammatory bowel diseases. Three series of cases reports [80] suggested that LDN was an effective, highly tolerated and inexpensive treatment for pruritus symptoms of systemic sclerosis.

3.6. LDN and AIDS

LDN can induce the production of two endorphins (β-endorphin and enkephalin) in vivo. Serum β-endorphin levels in AIDS patients are one-third the levels of people without AIDS. Taking 3 mg/day of LDN can increase levels of endorphins without blocking them. Further studies showed that there was a significant difference in the incidence of opportunistic infections with long-term use of LDN and a decrease in the number of $CD4^+$ T cells; some patients took LDN for up to 7 or 8 years, with no disease progression or $CD4^+$ T-cell decline [40]. LDN, as an immune-stabilizing agent for the treatment of AIDS, is effective. In Nigeria, LDN has been approved for the treatment of AIDS [20].

4. LDN and cancer

LDN has an antitumor effect. It could modulate the tumor response in neuroblastoma mice by delaying the onset and reducing the incidence rate of tumors [18]. In ovarian tumor-bearing mice, LDN caused intermittent opioid receptor blockade and upregulated the expression of OGF and OGFr [32], inhibiting tumor progression in a cytotoxic manner by reducing DNA synthesis and angiogenesis rather than altering cell survival. When the tumor cells were given intermittent LDN for a short period of time (4–6 h) followed by immediate LDN clearance, there was a window of 18 to 20 h during which time the tumor cell growth was significantly inhibited [28]. During this window, the numbers of endogenous OGF and intracellular OGFr in tumor cells were detected to increase, and the mechanism of intermittent naltrexone-administered antitumor effect and the mechanism of exogenous OGF antitumor effect were both associated with the OGF-OGFr axis effect [1,81].

Tissue culture and nude mouse transplantation experiments with human ovarian cancer cells (SKOV-3) [31] both confirmed that LDN could significantly inhibit the DNA synthesis of SKOV-3 cells, significantly reduce the number of tumor cells and inhibit angiogenesis. The therapeutic approach to the OGF-OGFr axis not only inhibits the

growth of breast cancer cell lines and their DNA synthesis but also alleviates the adverse effects of conventional chemotherapy, protecting non-tumor cells from death caused by paclitaxel [26].

In squamous cell carcinoma of the head and neck (SCCHN), OGF can reduce the size of the tumor via the OGF-OGFr axis and delay the tumor appearance [82]. LDN can intermittently block the opioid receptor-mediated OGF-OGFr axis indirectly, which plays a role in inhibiting tumor growth, extending the tumor's incubation period up to 1.6 times. LDN treatment significantly reduced tumor volume and weight and reduced DNA synthesis in the tumor. As the number of weekly LDN administrations increased, the effect of inhibiting tumor growth was enhanced [45]. The weight of the mouse spleen and the volume of the tumor gradually decreased.

Berkson and colleagues reported that, after treatment with the combination of LDN and α-lipoic acid (ALA/N) [83,84], patients with metastatic or non-metastatic pancreatic cancer achieved long-term survival without any adverse effects. Tumor marker levels decreased, symptoms and physical examinations improved and clinical manifestations disappeared. They also found a patient with B-cell lymphoma [85] whose signs and symptoms attenuated after use of LDN alone. These cases not only prompted the potential role of LDN in cancer therapy but also emphasized good compliance with this therapeutic agent.

Two children, one having a congenital hepatoblastoma and the other having polycystic kidney disease with predictive chemotherapy-sensitive congenital hepatoblastoma, had disease-free survival rates of 10 years and 5 years after OGF/LDN treatment. These two cases suggested that LDN might be a less toxic alternative to conventional chemotherapy when traditional chemotherapy for hepatoblastoma was impractical [86].

Clinical trials [87] of 10 patients with chemoresistant advanced metastatic cancer and 1 with hormone-refractory advanced prostate cancer were followed up. It was found that the use of hydroxycitric acid (HCA) + α-lipoic acid (α-LA) + LDN was safe and effective for the treatment of refractory end-stage cancers and was capable of modulating the metabolism of various cancers.

LDN reduces tumor growth by interfering with cell signaling and by regulating immune system function. LDN selectively affects the genes involved in cell cycle regulation and immune regulation [88]. In addition, cells pretreated with LDN are more sensitive to the cytotoxic effects of common chemotherapeutic drugs. LDN not only functions as a monotherapy for cancer but is also effective in combination with other agents such as aged garlic extract [89], vitamin D [90] and panobinostat [26] to inhibit tumor growth.

Our team has already used the combination of low-dose naltrexone and MENK (also called OGF) as an anti-cancer treatment that can inhibit DNA replication of pancreatic tumor cells as well as stimulate activation and proliferation of immune cells and promote the body to heal itself [21]. LDN and OGF bind to opioid receptors on the cell surface of the body's immune system, thereby stimulating the activation and proliferation of immune cells and improving immune function.

5. LDN and inflammatory diseases

Autism is considered a hyperopioidergic disorder caused by endogenous opioid hormone system disorders [71]. In addition, CNS demyelination can be observed in the brain of patients with autism, accompanied by increased NO levels in vivo [91]. LDN can reduce the in vivo activity of inducible nitric oxide synthase in patients and reduce inflammation. Oral administration of 0.5 mg/kg of LDN daily improved clinical symptoms in children with autism, resulting in significantly increased plasma β-endorphin and normalized serotonin levels [92]. With the anti-inflammation effect, LDN could be applied in the treatment of autism [48]. Additionally, the use of LDN for complex post-traumatic dissociative disorders [93], short-term memory impairment caused by acute stress [94], self-biting behavior [95] and depressive disorder [96] showed some benefit, and larger studies are needed for further confirmation.

Complex Regional Pain Syndrome (CRPS) is a neuropathic pain syndrome involved in glial activation and central sensitization in the CNS, which is associated with local or systemic inflammation. The mechanism by which LDN is used to treat chronic pain is not fully understood. In addition to increasing endogenous opioid levels by blocking opioid receptors [97], LDN binds to receptors on the surface of immune-related cells (microglia) while reducing proinflammatory cytokine release and inflammation [98]. LDN can be used as a central nervous system anti-inflammatory and glial cell modulator for the treatment of chronic pain syndromes.

LDN can enhance the effect of acupuncture analgesia [99]. Acupuncture affects the opioid and the cannabinoid system by releasing endogenous receptor ligands, and LDN also acts on both systems and upregulates opioid and cannabinoid receptors. Physical and pharmacological treatments have a synergistic effect, relieving chronic pain syndrome.

Although no large randomized controlled trials have been conducted, the results of two case reports in 2013 [36] and 2016 [100] indicate that when conventional CRPS medications failed to suppress their refractory CRPS symptoms, LDN was utilized in these patients by antagonizing the TLR-4 pathway, attenuating glial activation and central sensitization [37] and inducing the production of anti-inflammatory endorphins. Another case of refractory chronic low back pain [101] treated with LDN received satisfactory treatment. Additionally, a case was firstly reported in 2016 that LDN was effective for an old man with a 30-year diabetes history and 7-year-long diabetic neuropathic symptoms which was refractory to other available treatments [79].

In 2017, two case studies [102,103] simultaneously reported that patients with familial benign pemphigus (Hailey-Hailey disease) achieved satisfying clinical symptom resolution by treatment with LDN. LDN might be developed into a novel therapeutic agent for this disease. In addition to influencing the OGF-OGFr axis or the TLR signaling pathway, the possible mechanism may involve improving keratinocyte differentiation and wound healing.

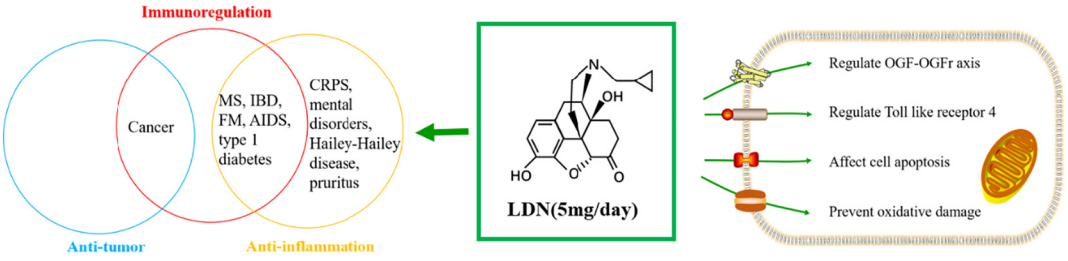

Fig. 2. The immune-related pharmacological functions and potential mechanisms of LDN.

6. Prospects

Until now, no review specific focused on the immunoregulatory functions of LDN has been reported. In this article, we provide a comprehensive summary of the immune-related pharmacological functions and potential mechanisms of LDN, which have been displayed in Fig. 2.

To our knowledge, LDN could modulate the immune system function of the body to resist an abnormal immune response, and it has been widely accepted [104] by patients with MS, IBD such as CD and many types of malignant tumors. Successful reports of patients with fibromyalgia, ALS and type 1 diabetes treated with LDN are increasing. Future studies and clinical work are warranted to confirm the role of LDN in the treatment of immune-related diseases. LDN may be considered as a novel immunomodulator and tumor biotherapy agent, which is routinely recommended for people with autoimmune diseases and cancer. At the same time, researchers also found that LDN could control appetite and the intake of high-sugar and high-fat foods [105–107] and that the effect and mechanism of LDN on body weight control were of great value. Moreover, it is believed that LDN will have more novel dosage forms, such as passive transdermal delivery [108], liquid nasal spray and sustained-release preparations [109], in the near future.

Although there are many advantages of LDN therapy, such as low cost, low adverse reaction, high safety, easy availability and better compliance, some issues are still worth noting. Since LDN is thought to play a role in the regulation of inflammatory mediators and the upregulation of endogenous opioid receptors, physicians should be alert to patients who have prior chronic use of LDN in pain management when using exogenous opioids in order to prevent hypersensitivity to exogenous opioids [110]. Additionally, patient-funded research on LDN for the treatment of multiple sclerosis is good news for both doctors and patients, but attention should be paid to issues such as program reviews and conflicts of interest [111].

Declarations of interest

Noreen Griffin is a Founder, CEO and a member of the Board of Directors for Immune Therapeutics Inc., Fengping Shan is the Chief Scientific Officer for Immune Therapeutics Inc. and has patents on naltrexone that have been licensed to Immune Therapeutics Inc. The authors have no additional competing financial interests.

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