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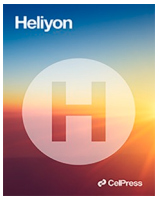

Review article

Application of LRG mechanism in normal pressure hydrocephalus

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ABSTRACT

Normal pressure hydrocephalus (NPH) is a prevalent type of hydrocephalus, including secondary normal pressure hydrocephalus (SNPH) and idiopathic normal pressure hydrocephalus (INPH). However, its clinical diagnosis and pathological mechanism are still unclear. Leucine-rich α-2 glycoprotein (LRG) is involved in various human diseases, including cancer, diabetes, cardiovascular disease, and nervous system diseases. Now the physiological mechanism of LRG is still being explored. According to the current research results on LRG, we found that the agency of LRG has much to do with the known pathological process of NPH. This review focuses on analyzing the LRG signaling pathways and the pathological mechanism of NPH. According to the collected literature evidence, we speculated that LRG probably be involved in the pathological process of NPH. Finally, based on the mechanism of LRG and NPH, we also summarized the evidence of molecular targeted therapies for future research and clinical application.

1. Introduction

Normal pressure hydrocephalus (NPH) is a communicating hydrocephalus syndrome with enlarged ventricles and normal cerebrospinal fluid (CSF) pressure [1]. The classic NPH triad is dementia, dyskinesia, and urinary incontinence [2]; whether the etiology is transparent can be divided into secondary normal pressure hydrocephalus (SNPH) and idiopathic normal pressure hydrocephalus (INPH) [3]. Recent epidemiological studies show the prevalence of INPH is 10–20 per 100,000 people, with 2.1 % of those aged≥65 and 8.9 % of those aged≥80 [4,5]. The prevalence of SNPH is related to the underlying disease, with a majority of 51%–89 % after intraventricular hemorrhage (IVH) [6–8], 15%–37 % for subarachnoid hemorrhage (SAH) [9], 0.7%–29 % for traumatic brain injury (TBI) [10–12] and about 60 % for Postinfectious hydrocephalus (PIH) [13].

Although the role of arachnoid fibrosis, pathological angiogenesis, and neuroinflammation in the pathological process of NPH has been widely promoted in recent years [14,15], the exact etiology and specific pathogenesis of NPH have yet to be definitively studied. Many references indicate that INPH and SNPH share apparent similarities in pathological processes and biomarkers [16–18]. The etiology and pathogenesis of INPH are still unclear, making its prevention and treatment extremely difficult. Although the primary etiology of SNPH is known, its pathogenesis is still a mystery; once the prodromal disease has developed, it is no longer possible to prevent the development of SNPH. The absence of clear diagnostic criteria hampers clinical work on NPH.

The diagnostic criteria of NPH are not uniform, and there are no clear indicators. In 2005, Professor Marmarou published the first international guidelines for diagnosing and treating NPH [19,20], pointing out that the diagnosis of NPH needs to combine comprehensive evidence such as the medical history, physical examination, and imaging examination results of patients [20]. With the

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in-depth research, Professor Nakajima released the latest INPH management guidelines in 2021, dividing the diagnosis of INPH into three stages: “possible”, “probable”, and “definite” [21]. The possible diagnosis is mainly based on the classic NPH triad; the probable diagnosis is mainly based on the lumbar puncture test (TT) and computed tomography (CT) or magnetic resonance imaging (MRI) findings; and the definite diagnosis is based on the apparent improvement of symptoms after shunt surgery [21].

The diagnostic methods have caused many difficulties in clinical work because a definite diagnosis can only be set after surgery [21], making the diagnosis very passive, which is not conducive to early treatment. CSF shunt surgery has successfully relieved symptoms in only 60%–80 % of patients [14], making NPH patients with unresolved symptoms challenging to definite diagnose. The classic NPH triad may not all be present in NPH patients, or the clinical manifestations may not be obvious; these symptoms can also occur in other diseases [22,23] and can be easily overlooked or misdiagnosed. Therefore, it is urgent to find sensitive and precise biomarkers to diagnose NPH, which also facilitates clarification of the underlying pathomechanism of NPH and further research into the treatment.

Leucine-rich α-2 glycoprotein (LRG) was first identified as a trace protein in human serum in 1977 [24]; this consensus sequence of 24 amino acids is called leucine-rich repeat (LRR) and has been found in many types of proteins [25]. More and more literature show that LRG is a common pathogenic factor, widely expressed in multiple human body tissues, and participates in various disease pathways [26–28]. LRG is almost exclusively produced by the liver and granulocytes [29], distributed throughout the brain, and predominantly expressed by astrocytes [30]; the expression increases with age [30]. In recent years, much literature has shown that LRG levels in the CSFof NPH patients are significantly elevated [30–32], supporting the idea that LRG may be an important biomarker in the pathological process of NPH [33]. Furthermore, Nakajima et al. demonstrated that when LRG levels ≥67 ng/ml, combined with TT and tau protein content, they can effectively predict the shunt response of INPH patients [34]. However, a study by Vanninen et al. refuted this conclusion [31]. The opposite conclusion may be related to the unclear diagnosis of INPH due to “variable diagnostic criteria” before shunt surgery; they result in selection bias. So, this phenomenon further reflects the importance of finding accurate biomarkers.

In this review, we first gather evidence for the roles of LRG, then explore the relationship of these pleiotropic effects of LRG to the pathological mechanism of NPH, and finally look for targeted Intervention drugs.

2. LRG pathogenic mechanism

LRG is widely involved in growth and metabolism in vivo. We mainly study its three regulatory roles in pathological processes such as pro-fibrosis, angiogenesis, and neuroinflammation [35–39] (Fig. 1). LRG primarily affects the metabolism of cells and tissues by regulating the TGF-β signaling pathways, and LRG can regulate these pathways by modulating type TGF-β receptors (TβR) stoichiometry. Injecting the human recombinant TGF-β into the head of mice induces communicating hydrocephalus [40], so the LRG-TGF-β axis is meaningful in the pathological process of the NPH.

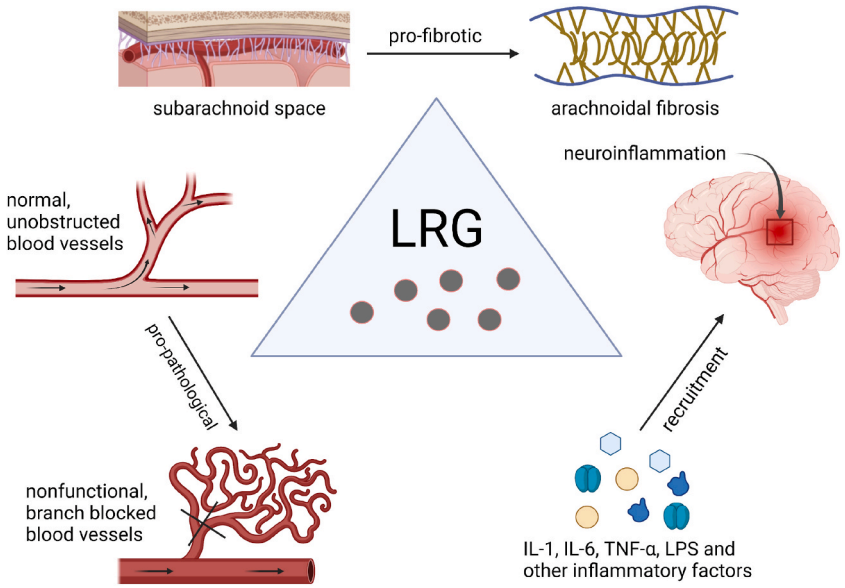

Fig. 1. The main pathological processes of LRG. LRG can promote subarachnoid and meningeal fibrosis, affecting the flow and outflow of CSF. LRG regulates vascular maturation and functional stability by affecting ECs and pericytes, transforming unobstructed vessels into abnormal vessels with disorganized and nonfunctional branches. LRG can stimulate immune cells to produce and recruit inflammatory factors to induce neuroinflammation.

2.1. Pro-fibrotic role of LRG

Fibrosis is scarring and tissue hardening due to myofibroblasts' excessive extracellular matrix (ECM) deposition in response to chronic inflammation [41,42]. Various noxious stimuli, such as toxins, pathogens, autoimmune reactions, and mechanical stress, both of these stimuli and biomarkers, can induce and aggregate fibrotic cellular responses that have irreversible and deleterious effects on tissue or organ function [43–45]. A growing body of literature suggests that extensive fibrosis in the subarachnoid space may be strongly associated with NPH [46,47].

The traditional cerebrospinal fluid dynamics holds that CSF is produced primarily in the choroid plexus (CP), flows from the ventricle into the subarachnoid space, and is reabsorbed primarily via arachnoid granules (AGs) [48,49]. Fibrosis of the meninges and AGs can reduce CSF circulation and inhibit CSF flow from AGs to the sinuses (Fig. 1), leading to the development of hydrocephalus [47, 50].

Although the mechanism of meningeal and arachnoid fibrosis is still unclear, studies have shown that TGF-β is an influential fibroblast factor in the pathogenesis of fibrosis [51,52] and plays an essential role in cell proliferation, differentiation, apoptosis, stimulating cell synthesis of extracellular matrix and so on [53]. TGF-β is expressed by endothelial, hematopoietic, and connective tissue cells in response to tissue injury, promoting wound healing and fibrosis [54]. However, astrocytes [55] and platelets [56] released it into the CSF after intracerebral hemorrhage (ICH); as a result, the levels of TGF-β in the CSF increased significantly within a short period. Connective tissue growth factor (CTGF) is a downstream mediator of TGF-β-Smad signaling in chronic fibrosis and an essential enhancer of fibroblasts [57]. CTGF is activated by TGF-β, which induces the transformation of fibroblasts into collagen-depositing myofibroblasts [58]. The pro-fibrotic effect of TGF-β occurs through the TGF-β-Smad-CTGF signaling pathway, which is involved in the pathogenesis of various fibrotic diseases [59]. TGF-β binds to type 1 and type 2 TGF-β receptors (TβRI and TβRII) on the cell surface, and TβRI acts upstream of TβRII [60,61], TβRI includes activin receptor-like kinase 1 (ALK-1) and ALK-5 [62]; ALK-5 induces Smad2/3 phosphorylation and exerts a pro-fibrotic effect [63], the role of ALK-1 is detailed below. Studies have shown that LRG can promote fibrosis in various organs and tissues, such as the lung, heart, and skin [64–66], and fibroblasts exhibit enhanced Smad2/3 signaling when LRG exists [64].

LRG recruits ALK-5 receptors through TβRII, stimulates the formation of the ALK-5/TβRII signaling complex, enhances the phosphorylation of Smad2/3, then CTGF is activated, and finally promotes fibrosis [35] (Fig. 2). We can infer that an LRG might regulated signaling pathway might be involved in fibrosis: LRG-TGF-β-ALK-5-TβRII-Smad2/3-CTGF (Fig. 2). Interestingly, our

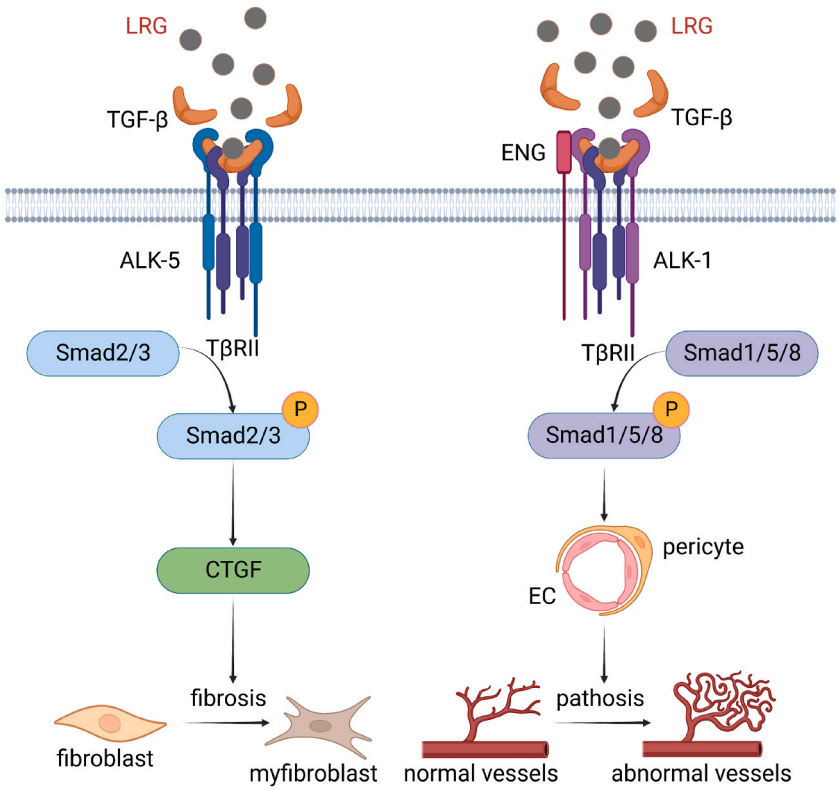

Fig. 2. LRG signaling pathways. Both pathways depicted in the figure are completed by LRG through the regulation of TGF-β signaling. During pathological angiogenesis (right), LRG binds to ENG, leading to ECs degeneration and reduced pericyte coverage through the ALK-1-Smad/1/5/8 pathway, converting normal vessels to dysfunctional ones. During promoting fibrosis (left), LRG promotes fibroblast differentiation into myofibroblasts in an ENG-independent manner through the ALK-5-Smad2/3-CTGF pathway.

previous study found that the levels of LRG, TGF-βI, and TGF-βII in the CSF of INPH patients were specifically increased [67], which is consistent with the mechanism of meningeal and arachnoid fibrosis causing NPH. While developing SNPH, especially in patients with post-hemorrhagic hydrocephalus (PHH), TGF-β has two peaks [68]. The first one is exogenous and comes from excessive TGF-β storage in platelets, plasma, and macrophages, then TGF-β enters CSF with blood after ICH. The second one is endogenous, and TGF-β in CSF acts as a chemoattractant for inflammatory cells and platelets; it can also interact with other cytokines to further promote TGF-β production [68,69]. Furthermore, the second peak also applies to the increase of TGF-β in the CSF of INPH patients [16].

The above evidence indicates TGF-β is specifically elevated in the CSF of NPH patients; LRG regulates the TGF-β based fibrotic pathway, so LRG might play an essential role in mediating meningeal and arachnoid fibrosis.

2.2. Pro-pathological angiogenesis role of LRG

The brain is the organ with the most active energy metabolism in the human body. It requires much blood and oxygen, so it mainly depends on the cerebrovascular system to provide a sufficient supply [70]. The arteries originate at the base of the brain, and the large arteries run along grooves in the subarachnoid space. They continue to divide and form smaller, interconnected arteries in complex networks [71]. In the correct location, these small arterial streams plunge headlong into the cerebral cortex. The arteries that pass through the brain parenchyma continue to fork and narrow, forming a dense network of capillaries called the capillary bed. Oxygen and nutrients in arterial blood flow primarily to neurons in the brain [72].

The characteristics of mature and functional vessels are extensive pericytes coverage on the outer wall and tight junctions formed by adjacent endothelial cells (ECs) on the inner wall to maintain barrier function [73]. The circulation of blood substances in blood vessels and the exchange of substances between the blood and interstitial fluid are very active processes. The fluid environment inside and outside the blood vessel and the stimulation of various biomarkers will affect ECs and pericytes. The interaction between the two is crucial for vascular homeostasis [74]. Disruption of these two barriers can impair the physiological function of blood vessels and even lead to abnormal growth of blood vessels, which is related to the pathogenesis of various diseases [75]. Recent studies have shown that regional cerebral blood flow (CBF) is reduced in NPH patients compared with healthy controls (HCs) [76–78]. Furthermore, several studies have also shown that the most reliable risk factors for INPH are hypertension and type II diabetes [79], both characterized by minor vessel damage. The evidence suggests that vascular destruction and dysplasia are present in NPH patients, and vascular insufficiency is significantly associated with NPH.

Compared with normal blood vessels, the characteristics of pathological ones are reduced pericyte coverage, increased tortuosity, increased permeability, poor perfusion, and often dysfunction [80]. The promotion of pathological angiogenesis has long been the subject of extensive research, especially in oncology [81]. Vascular endothelial growth factor (VEGF) is essential in promoting increased vascular permeability, angiogenesis, and neovascularization. Long-term stimulation of this growth factor accelerates the formation of new abnormal capillaries [82]. Lee et al. showed that VEGF is also highly expressed in the CSF of patients with various forms of hydrocephalus [16]. Thus, this supports VEGF as a target of excessive angiogenesis leading to hydrocephalus and again demonstrates the importance of vasculopathy in the pathological process of hydrocephalus. However, no clinical trials have used *anti*-VEGF monoclonal antibodies to alleviate hydrocephalus until now. While further exploring the relationship between VEGF-target therapy and hydrocephalus, it is also imperative to identify new biological targets of different signaling pathways to elucidate the development of vascular hydrocephalus.

Another LRG-TGF-β signaling pathway mentioned above is involved in pathological angiogenesis (Fig. 1). Currently, accumulating evidence indicates that LRG is a novel pro-angiogenic factor [38,61], and LRG has been shown to modulate TGF-β signaling in ECs, converting them from a quiescent to an active pathological angiogenic state [35]. Overexpression of LRG increases ECs proliferation and promotes pathological angiogenesis [83], while the underexpression of LRG decreases ECs proliferation, and polyclonal *anti*-LRG antibodies inhibit ECs migration [35,84]. Excessive secretion of TGF-β can lead to degeneration of vascular ECs [83], such as over-expression of TGF-β signaling in B. Marfan syndrome [85]. TGF-β secretion increases with vascular aging and vascular injury [86].

Endoglin (ENG) is a TβRII coreceptor, and hypoxia activates the production of ENG [85], which promotes angiogenesis to transport blood and oxygen, and ENG is required for TGF-β-induced vasodilation [87]. LRG binds to TGF-β through the mediation of ENG, which can assist in the activation of ALK-1 and promotes phosphorylation of Smad1/5/8, leading to a pro-angiogenic state [61,88,89] (Fig. 2). From this, we could deduce a second signaling pathway might controlled by LRG that promotes pathological angiogenesis: LRG-TGF-β-ALK-1-ENG/TβRII-Smad1/5/8 (Fig. 2). In addition, there is a competitive relationship between the two receptors, ENG and ALK-5, and ENG wins the competition. However, in the absence of ENG, the binding of TGF-β-ALK-1 and TGF-β-ALK-5 do not interact; but in the presence of ENG, the binding of the former is enhanced, and the latter is inhibited [35].

LRG also directly affects pericytes, regulating the vascular coverage of pericytes and further destabilizing blood vessels. Unstable blood vessels grow tiny branch vessels, often resulting in reduced blood flow to specific locations and dysfunction [60].

In conclusion, LRG affects vascular stability by activating ECs to promote pathological angiogenesis and reduces pericyte coverage of the vessel's outer wall. Thus, these pieces of evidence suggest that LRG is a critical biomarker in inducing vascular dysfunction.

2.3. Immunomodulatory effects of LRG

Neuroinflammation is an immune response activated by resident cells (microglia and astrocytes) in the central nervous system (CNS) [90,91]. It is usually caused by various stimuli related to central nervous system injury or infection [90]. Microglia, as macrophages in the CNS, are essential to the onset and resolution of neuroinflammation [92]; astrocytes are the most prevalent and numerous glial cell types in the mammalian brain. They are vital in maintaining homeostasis and participating in CSF circulation [93].

Both are the central cells responsible for CNS injury, participating in neuroinflammatory responses by releasing various pro-inflammatory cytokines and chemokines [94]. Studies have shown that widespread gliosis in NPH is associated with the pro-inflammatory effect of microglia and astrocytes [95,96], so neuroinflammation may be an important predisposing factor for the formation of NPH.

With the development of advanced proteomics technology [97], LRG expression has been confirmed in various inflammatory diseases, such as psoriasis [98,99], lupus nephritis [29], rheumatoid arthritis [100], vasculitis [101], and neuroinflammation [102] (Fig. 1). Both PHH and PIH detect markers of inflammation mediated by up-regulated toll-like receptor 4 (TLR4) [103]; TLR4 can recognize blood components after ICH and lipopolysaccharide (LPS) are released by Gram-negative bacterial infection [104–106]. Then it mediates microglia, and astrocytes release inflammatory factors such as LRG, interleukin-1 (IL-1), IL-6, nuclear factor kappa-B (NF-κB) and tumor necrosis factor-α (TNF-α) [103,107,108]. Several studies have shown that the contents of IL-6, IL-1, TNF-α, TGF-β and other biomarkers in the CSF and peripheral blood of patients after ICH or brain infection positively correlate with the possibility of PHH or PIH and the severity of the disease [109–112].

Among the cytokines that trigger the inflammatory response, the best known are IL-6 and TNF-α [113–115]. Signal transducer and activator of transcription 3 (STAT3) and NF-κB are major promoter elements of LRG [116]. IL-6 induces phosphorylation of STAT3, thereby activating LRG transcription [83], IL-6 inhibition results in decreased LRG production, but LRG deficiency also downregulates the IL-6 receptor (IL-6R) [117,118], thereby reducing the expression of the IL-6-STAT3 response. In vitro, LRG increased the expression of IL-6R in naive T cells through the TGF-β-ALK-5-TβRII-Smad2/3 pathway and promoted the differentiation of naive T cells into Th17 cells [117]. This evidence suggests that LRG may be a downstream regulator of the IL-6-STAT3-LRG signaling (Fig. 3). Moreover, this pathway also positively regulates neutrophil chemotaxis [119]. NF-κB signals through serine-threonine kinase (SPAK), resulting in phosphorylation and translocation of the sodium chloride-potassium transporter (NKCC1) to the choroidal apex, and the increased activity of NKCC1 promotes the massive secretion of CSF [120]. TNF-α and IL-1 can up-regulate LRG expression by activating NF-κB [116,121], while siRNA-LRG also can up-regulate the expression of NF-κB [122]; in other words, the reduction of LRG can also promote the expression of NF-κB. Like the IL-6-STAT3-LRG pathway, LRG can also regulate the expression of NF-κB downstream of the TNF-α/IL-1-NF-κB-LRG pathway (Fig. 3). A novel FOS-like 1 (FOSL1) transcription factor was discovered using transcriptome sequencing (RNA-seq) technology, which is induced early by LPS and promotes LRG expression in mouse lung endothelial cells [123] (Fig. 3). Interestingly, combined stimulation of different cytokines has a synergistic effect on LRG promoter activity, and these pathways work together to promote LRG production [114] (Fig. 3).

Glial fibrillary acidic protein (GFAP) has been detected in brain tissue and CSF samples from patients with INPH [124–126], which

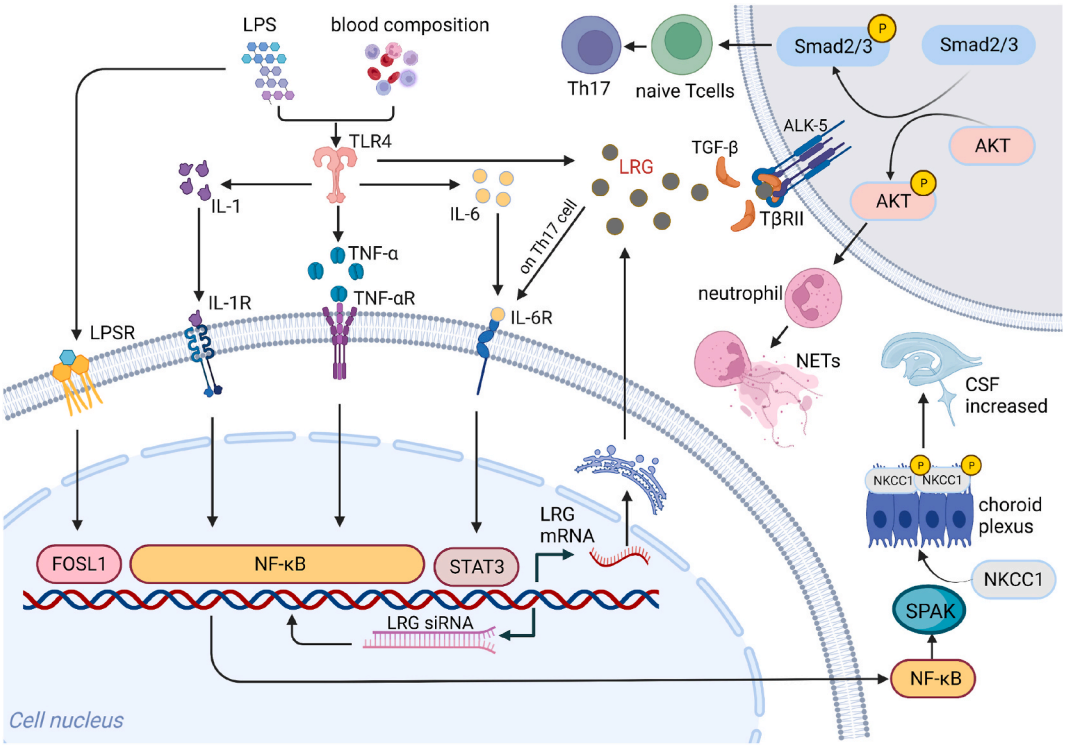

Fig. 3. LRG signaling pathways and its regulation expression. TLR4 and several TLR4-mediated inflammatory factors and the LPS released by Gram-negative bacteria can drive the expression of LRG by activating different transcription factors. Moreover, the combined stimulation of different cytokines has a synergistic effect on LRG promoter activity. LRG can promote the expression of inflammatory cells through TGF-β signaling and can also directly promote CSF accumulation through the NF-κB-SPAK pathway.

strongly supports the presence of astrogliosis in INPH [124]. Lee et al. proved that TNF-α levels were significantly elevated in the CSF of INPH patients [16], which are positively associated with cognitive decline [18], and this index is fully reversible after CSF shunt surgery [18]. Nevertheless, more literature reported that TNF-α levels were mostly normal in INPH [127–129], and there are reduction cases [130]. The increase of TNF-α levels is probably in some phase of INPH, for example, the progressive stage of cognitive impairment [131]. The relationship between TNF-α and NPH is an exciting research topic, and it may provide the theoretical basis for treatable dementia. Interestingly, neuroinflammation also increases with age [32]; this is an essential idiopathic factor that corresponds to the relationship between LRG and age. Together, these all prove that INPH is also involved in the mechanism of neuroinflammation.

In addition, LRG can also protect inflammatory cells and help eliminate pathogens [132]. Cytochrome *c* (Cyt *c*), located in the inner mitochondrial membrane, is released into the cytoplasm after mitochondrial damage and triggers apoptosis [133]. Intracellularly, LRG binds tightly to Cyt *c* [133–135], which can protect lymphocytes from the pro-apoptotic effect of exogenous Cyt *c* [132]. The release of reticulated DNA structure of neutrophil extracellular traps (NETs) is an essential mechanism for neutrophils to prevent the spread of pathogens or respond to more significant microorganisms [136]; LRG promotes the formation and function of NETs through the TGF-β-ALK-5-TβRII-protein kinase B (AKT) pathway [137].

During the neuroinflammatory process that promotes NPH, both idiopathic and secondary factors can directly lead to elevated LRG levels. LRG can also regulate inflammatory pathways and protect against inflammatory factors. Studying the inflammatory mechanism of LRG would be significant and valuable.

3. The relationship between the signaling pathways might be participated and regulated by LRG and the pathological mechanisms of NPH

NPH is a widespread form of hydrocephalus in adults and a reversible central nervous system disorder. As NPH is the only treatable form of dementia [32], detailed studies of the etiology of NPH are invaluable. We have discussed the signaling pathways might be participated and regulated by LRG in the formation of fibrosis, diseased vessels, and inflammation. Next, we discuss how LRG affects the pathologic mechanisms of NPH through these pathways.

3.1. Effects of the pro-fibrotic pathway might be participated and regulated by LRG on CSF pulsation and drainage

It can trace the dynamics of CSF circulation back to 1943 when O'Connei first suggested that CSF circulation is related to arterial pulsation [138]. Elevated CSF pulsatility is a striking finding of abnormal CSF dynamics [139–141]. Luetmer et al. demonstrated that elevated CSF pulsatility is helpful for the diagnosis of INPH and for distinguishing it from other types of dementia [142]. Abnormal CSF dynamics is the leading cause of INPH [143] and is considered the initial factor leading to ventricular dilation in INPH [3,144]. Other parameters related to CSF dynamics, such as CSF flow velocity and direction, are also significantly elevated in INPH patients; these all indicate a high level of CSF pulsatility [141,143,145,146].

Ependymal cilia on the surface of the ventricles is a key factor in CSF pulsatility [147–149]. Ciliary oscillations generate the directional flow of CSF [150], whereas ciliary dysfunction can make the flow disordered, significantly increasing CSF pulsatility [151]. Cao et al. speculated that ependymal fibrosis would impair cilia function [152], but no studies have fully confirmed this process, which may be a meaningful research direction.

It is known from some literature that increased CSF pulsatility also may be associated with decreased intracranial compliance and decreased arterial pulsatility [153–155]. The degree of fibrosis is inversely proportional to compliance [156,157]. Based on the above evidence, we boldly infer that arachnoid and meningeal fibrosis driven by the LRG-TGF-β-ALK-5-TβRII-Smad2/3-CTGF pathway probably participated in the process of reducing intracranial compliance, which in turn makes the CSF circulation channels more rigid, this mechanism plays an essential role in the development of INPH [158]. Interestingly, with increasing age, intracranial compliance gradually decreases [146]. In contrast, the expression of LRG gradually increases [30], which is entirely consistent with the epidemiological feature that the incidence of INPH increases with age [159].

LRG has also been considered a new serum biomarker for heart failure (HF), which is more effective and accurate than B-type natriuretic peptide (BNP) [160]. After HF, the heart pumps less, resulting in a significant decrease in arterial pulsation, which can cause CSF pulsatility to increase. In addition, central venous pressure (CVP) increases after HF, and CVP also decreases intracranial compliance [161]. LRG can also directly contribute to arterial fibrosis [162], with weakened arterial wall elasticity and reduced pulsatility, eventually leading to increased CSF pulsatility.

After AGs fibrosis, it will affect the drainage and discharge of CSF to the venous sinus, leading to increased accumulation of CSF in the ventricles. The combined effect of increased fluid volume and CSF pulsatility ultimately results in ventricular dilation, which is the primary anatomical feature of NPH [141,163]. Since the pathological processes of INPH and SNPH are similar and based on the literature, we deduce that these mechanisms also exist in the formation of SNPH [164,165] but that SNPH has more direct drivers than INPH. When the underlying disease occurs, factors such as blood and inflammation trigger the release of various biomarkers into the LRG signaling pathway, resulting in a more substantial fibrotic effect. Furthermore, a more immediate cause of NPH is that these substances can also directly block AGs, further affecting the outflow of CSF [166] and ultimately causing ventricular dilation.

3.2. Effects of the pro-pathological angiogenesis pathway might be participated and regulated by LRG on the white matter

High levels of LRG in CSF could activate the LRG-TGF-β-ALK-1-ENG/TβRII-Smad1/5/8 signaling pathway, promoting pathological

angiogenesis. They reduce CBF in corresponding areas and affect the metabolism of corresponding region brain tissues and destroy white matter [167,168]. Deep white matter lesions are hallmarks of small vessel disease, which is almost universal in the brains of NPH patients [169]. Since NPH patients are likely to be complicated with vascular injury factors such as hypertension and diabetes, NPH may represent a vascular disease [170–172]. More importantly, the awareness of CBF has increased in recent years, and it has been reported that the improvement of clinical symptoms in NPH patients after CSF shunt surgery is closely related to the improvement of white matter CBF in the brain [173–175].

According to the degree of depression of CBF in the corresponding functional areas of the cerebral cortex, NPH patients exhibit corresponding clinical symptoms: low CBF in frontoparietal white matter is associated with cognitive impairment [176,177]; left internal capsule anterior limb, corpus callosum and left Low CBF below the lateral supplementary motor area is associated with gait impairment [177,178]; low CBF in the frontal lobe or basal ganglia is associated with bladder dysfunction [177,179]. With improved white matter CBF after CSF shunt surgery, symptoms may resolve unless infarction has already occurred.

Dietmann et al. showed that serum ENG levels are significantly higher in patients with SAH than HCs [180]. This conclusion is consistent with the finding that the typical triad is more pronounced in SNPH patients after SAH [181].

Akiba et al. have conducted an experiment on mice with LRG gene overexpression in the brain (LRG-tg), proving the overexpression of LRG in the hippocampus can lead to memory impairment and neurodegeneration, and the memory impairment is related to synaptic dysfunction; the neurodegeneration is related to neuroinflammation (see details in 3.3) [182]. These findings may also be potential LRG action mechanisms in NPH [182].

3.3. *Effects of the neuroinflammation pathway might be participated and regulated by LRG promoting NPH formation*

NPH caused by neuroinflammation mainly reflects in the two inducing factors of hemorrhage and infection in SNPH. It is reported that PHH and PIH are the two most common forms of hydrocephalus worldwide [183,184], and they share considerable similarities, especially concerning neuroinflammation [120]. Pathological examination of the brain tissue of fetuses and infants with PHH and PIH revealed neuroinflammation [185], such as microglia secreting pro-inflammatory factors to activate astrocytes [186], causing astrogliosis and releasing a large number of inflammation factors [120]. Inflammatory factors can stimulate liver cells to produce more LRG into the blood [116], and Talukder et al. showed that LRG levels in CSF were significantly increased after meningitis [187].

The blood-brain barrier (BBB) is mainly composed of astrocytes and pericytes [188]; under normal circumstances, the BBB protects brain tissue from pollutants [189]. Various inflammatory factors constantly stimulate these barrier cells, disrupting the tissue's barrier function. It has been shown that degeneration of pericytes leads to increased permeability of the BBB [190], and BBB leakage is also associated with the degree of astrogliosis [191]. Eide et al. proved that evidence of BBB leakage also exists in INPH [192]. Circulating inflammatory factors can cross the impaired BBB to enter the CNS [193]. We speculate these inflammatory factors might stimulate the inflammatory pathway of LRG (Fig. 3); and excess LRG can enhance its pro-fibrotic and pro-pathological angiogenesis effects. Therefore, LRG might be an intermediate regulator in inflammation promoting fibrosis.

LRG, regulated by various inflammatory factors, is a promising novel biomarker [194]. Moreover, LRG can also regulate downstream inflammatory pathways, similar to a positive feedback mechanism, to further promote its production of inflammatory factors. LRG can also protect against inflammatory factors and help the body eliminate irritants. As mentioned above, neurodegeneration is

Table 1
Treatments using drugs and biological agents for hydrocephalus.

Treatment	Target	Obstructed signaling pathways	BBB permeability	Reference
Decorin	TGF-β and TβR	LRG-TGF-β-ALK-5-TβRII-smad2/3-CTGF	High	Botfield et al.
LSKL peptides	TGF-β and TβR	LRG-TGF-β-ALK-5-TβRII-smad2/3-CTGF	High	Liao et al.
SB-431542	ALK-5 and Smad3	LRG-TGF-β-ALK-5-TβRII-smad2/3-CTGF	Unknown	Li et al.
SD208	ALK-5	LRG-TGF-β-ALK-5-TβRII-smad2/3-CTGF	High	Manaenko et al.
Magacizumab	LRG	LRG-TGF-β-ALK-1-ENG/TβRII-Smad1/5/8	Unknown	Javaid et al.
MagaFab	LRG	LRG-TGF-β-ALK-1-ENG/TβRII-Smad1/5/8	Unknown	Kallenberg et al.
Tocilizumab	IL-6	IL-6-STAT3-LRG (occurs in the lungs)	Unknown	Mariette et al.
Minocycline	microglia	Multiple inflammatory pathways	High	Garrido-Mesa et al.
Heparin/its derivatives	NF-κB	TLR4-TNF-α/IL-1-NF-κB-LRG	Low	Ho Lee et al.
PDTC	NF-κB or TLR4	TLR4-TNF-α–NF–κB and TLR4-IL-1-NF-κB	High	Karimy et al.
Closantel	SPAK	NF-κB-SPAK-NKCC1	Middling	Kikuchi et al.
Bumetanide	NKCC1	NF-κB-SPAK-NKCC1	Low	Römermann et al.
Dasatinib	TLR4	Mechanism of action is unknown	High	Ryu et al.
Dehydroabietic Acid	TLR4	Mechanism of action is unknown	High	Kim et al.
5z-7-oxozeanenol	TLR4	Mechanism of action is unknown	Unknown	Chen et al.
TAK-242	NF-κB or TLR4	TLR4-TNF-α–NF–κB and TLR4-IL-1-NF-κB	High	Karimy et al.
Resveratrol	TLR4	Interferes with TLR4 dimerization	High	Sun et al.
Curcumin	TLR4	Interferes with TLR4 dimerization	High	Zhu et al.
Infliximab	TNF-α	TLR4-TNF-α–NF–κB-LRG	Unable	Zhu et al.
Canakinumab	IL-1	TLR4-IL-1-NF-κB-LRG	Unable	Zhu et al.
Levofloxacin	TLR4	Interferes with TLR4 dimerization	High	Zusso et al.
Hexadecadrol	Unknown	Mechanism of action is unknown	High	Thwaites et al.
Statins	Unknown	Mechanism of action is unknown	High and low	Ma et al.

related to neuroinflammation [182]; we can infer that LRG might cause neurodegeneration in NPH by regulating neuroinflammation. To sum up, LRG may be involved in the inflammatory process of NPH. This finding provides a new idea for further research on NPH, which can be considered a preventable and treatable neuroinflammatory disease [120].

4. Targeted therapy on the LRG signaling pathway in NPH

CSF shunt surgery is currently considered the most effective standard of care for NPH [195], but postoperative infection is a significant complication of shunt surgery [196]. According to a recent meta-analysis, 9%–38 % of patients undergoing shunt surgery develop a postoperative infection and undergo additional surgery [196]. Suppose the non-surgical treatment can treat NPH or alleviate the symptoms of NPH patients; it will bring great convenience to NPH patients and the clinical management of NPH and reduce the need for permanent shunting. Furthermore, sensitive biomarkers can also contribute to the diagnosis of NPH. However, the research on non-surgical treatment has been disappointing [197], and no FDA-approved drugs for treating NPH exist. There is an urgent need to discover sensitive biomarkers and develop targeted drugs.

Through the above discussion, we found that LRG is a promising candidate involved in multiple signaling pathways of the formation of NPH. Crucially, LRG-deficient mice usually develop without overtly abnormal phenotypes [64,65,117], suggesting that LRG is not required for growth, development, or functional homeostasis and that blockade of LRG has minimal health effects. Miyajima et al. showed that LRG levels were positively correlated with the degree of cognitive impairment [32]. In addition, LRG levels are also elevated in patients with Parkinson's disease (PDD) and Alzheimer's disease (AD), which are common cognitive impairments [32]; this phenomenon suggests that although LRG is not a specific marker of NPH [198], it may be highly sensitive [31].

Regarding LRG signaling pathways, we found evidence for non-surgical treatment, such as using small molecule inhibitors, monoclonal antibodies, heparin, polyphenols, antibiotics, hormones, and statins to prevent NPH (Table 1).

Multiple studies have shown that Decorin and LSKL peptides can inhibit fibrosis in various tissues and organs, including attenuating fibrosis in the CNS, and can effectively slow the development of NPH [69,199–203]. As natural antagonists of TGF-β, Decorin and LSKL peptides inhibit its function by forming a complex with TGF-β. Both can also inhibit the activation of TβR, thereby inhibiting the fibrosis pathway [203–205]. SB-431542 has been shown to block the phosphorylation of ALK-5 and Smad2/3, thereby inhibiting the expression of CTGF [206]. Manaenko et al. showed that the selective ALK-5 inhibitor SD208 can also inhibit the LRG pro-fibrotic pathway [207]. These inhibitors have significant anti-fibrotic effects and potentially inhibit NPH formation by interfering with the LRG-TGF-β-ALK-5-TβRII-Smad2/3-CTGF pathway.

Magacizumab is a humanized function-blocking antibody with a strong affinity for human LRG and has anti-angiogenic and anti-vascular leaky effects [208]. Giulia et al. improved this antibody and developed a better Fab fragment called MagaFab, with lower molecular weight and low pro-inflammatory probability [209]. In addition, a meta-analysis on the treatment of critically ill patients with COVID-19 revealed that IL-6 could promote the production of LRG in the lungs, leading to pulmonary vascular disease. Moreover, blocking IL-6 signaling in pulmonary microvascular endothelial cells with tocilizumab will Cause a decrease in LRG levels, thereby weakening the production of vascular pathological factors [210,211].

Minocycline is a neuroprotective agent [212] that inhibits astrogliosis and ventricular dilatation in the NPH rat model by regulating the expression of inflammatory factors in microglia [213–215]. In many in vitro models of chronic inflammatory diseases, heparin or its derivatives have successfully inhibited the TLR4-NF-κB signaling pathway [216] and the production of TNF-α, IL-1, and IL-6, thus blocking the inflammatory pathway.

Furthermore, applying the NF-κB inhibitor, pyrrolidine dithiocarbamate (PDTC), decreased the levels of SPAK and NKCC1 [217]. Closantel directly inhibits the SPAK kinase activity [218], restoring CSF secretion rates to baseline levels and normalizing ventricular size. The NKCC1 blocker bumetanide can reduce the levels of CSF secretion [219], but its effectiveness requires further study due to its low BBB permeability [219]. Some small molecule inhibitors of TLR4, such as Dasatinib [220], dehydroabietic acid [221], 5z-7-oxo-zeatenol [222], and resatorvid (TAK-242) [217], can block the production of TNF-α and IL-1, thereby, inhibiting the excessive secretion of CSF. Polyphenols, such as resveratrol [223] and curcumin [224], interfere with TLR4 signaling by directly interfering with TLR4 oligomerization. Monoclonal antibody drugs such as infliximab and canakinumab can target TNF-α and IL-1, respectively [224].

Zusso et al. showed that Quinolones such as levofloxacin may inhibit TLR4-mediated inflammation [225], and dexamethasone may also reduce the probability of PIH and PHH [226,227]. However, the side effects of antibiotics and hormones suppress the systemic immune system, leading to higher infection rates [228]. Chen et al. reported that statins can prevent hydrocephalus [229], which can also reduce serum inflammatory markers and provide potent anti-inflammatory effects [230].

These findings provide theoretical support for the application of drugs to block the LRG signaling pathways to treat NPH. However, the current research data on these treatments are preliminary, and more in-depth research and comprehensive clinical trials are needed to apply them to the treatment of patients better.

5. Conclusion

Currently, the diagnostic criteria and pathogenesis of NPH are still a mystery. This review overviews the LRG signaling pathways in forming fibrosis, pathological angiogenesis, and neuroinflammation. Also, it focuses on the role of abnormal CSF dynamics, reduction of CBF in brain tissue, and inflammatory injury in the pathological mechanism of NPH. Combining these molecular mechanisms, we find that LRG is closely related to the formation of NPH, and LRG might be one of the main biomarkers in the pathological process of NPH. This review also discusses the preventive and therapeutic effects of the current target intervention of the LRG signaling pathways on NPH, paving the way for the future diagnosis and non-surgical treatment of NPH. With further research, developing specific drugs

for treating INPH and preventing SNPH may be possible.

Data availability statement

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Ethics declarations

Review and/or approval by an ethics committee was not needed for this study because this article is not applicable. Informed consent was not required for this study because this article is not applicable.

CRediT authorship contribution statement

Luyao Ma: Conceptualization, Writing – original draft. **Wencai Wang:** Investigation, Methodology. **Yongqiang Zhao:** Formal analysis. **Menghao Liu:** Resources, Software. **Wei Ye:** Resources, Validation. **Xianfeng Li:** Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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