Insulin-like growth factor-1: A potential target for bronchopulmonary dysplasia treatment (Review)

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Abstract. Bronchopulmonary dysplasia (BPD) is a common respiratory disorder among preterm infants, particularly low-birth-weight infants (LBWIs) and very-low-birth-weight infants (VLBWIs). Although BPD was first reported 50 years ago, no specific drugs or efficient measures are yet available for prevention or treatment. Insulin-like growth factor-1 (IGF-1) belongs to the insulin family. It promotes mitosis and stimulates cell proliferation and DNA synthesis, the primary factors involved in pulmonary development during the fetal and postnatal periods. Several studies have reported that IGF-1 exerts certain effects on BPD genesis and progression by regulating BPD-related biological processes. In addition, exogenous addition of IGF-1 can alleviate lung inflammation, cell apoptosis and eliminate alveolar development disorders in children with BPD. These findings suggest that IGF-1 could be a new target for treating BPD. Here, we summarize and analyze the definition, pathogenesis, and research status of BPD, as well as the pathogenesis of IGF-1 in BPD and the latest findings in related biological processes.

Contents

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1. Introduction

With the rapid advancements in neonatal care, the survival rates of very-low-birth-weight infants (VLBWIs) and critical preterm infants have significantly improved. However, bronchopulmonary dysplasia (BPD) is still associated with high annual morbidity among preterm infants (1,2). Northway *et al* first described BPD in 1967 (3). It is a common respiratory system disease in premature infants whose birth weight is less than 1,000 g. It is characterized by high fatality rates, and the surviving premature infants have a high possibility of other sequelae (4-6). Due to different diagnostic methods and medical levels, the prevalence rate of BPD varies greatly between 11 and 50% in different countries (7). The USA witnesses an annual of over 10,000 births with BPD (8). In preterm infants born before the 32nd gestational week, BPD is associated with an incidence of 12 to 32% (9). The incidence of BPD in infants with birth weight less than 1,000 g is 30 to 50% (10). The causes of death in children include recurrent respiratory tract infections (RTIs), pulmonary heart diseases, and persistent pulmonary hypertension (PH). For those who survive, the readmission rate is as high as 50% in the first year of survival (11,12). The main cause of readmission is recurrent lower RTI. The effect of lung tissue damage in children can persist from the neonatal period to adulthood (13-15). Currently, the drugs used to treat BPD have several side effects and poor efficacy (16-20). Therefore, finding new therapeutic targets and drugs is a great challenge faced by researchers and pediatricians.

Insulin-like growth factor-1 (IGF-1), which belongs to the insulin family, plays a key role in body development, vascular differentiation, and metabolism (21). IGF-1 plays a pivotal function in treating chronic obstructive pulmonary disease (COPD), asthma, idiopathic fibrosis, and acute respiratory distress syndrome (ARDS) (22). Recently, studies have shown a close association between IGF-1 and the occurrence and development of BPD in preterm infants. Immunohistochemistry of the lung tissues of children with BPD has revealed increased IGF-1 staining in alveolar epithelium, airway, and mesenchymal cells (23). Hyperoxia can interfere with the binding of IGF-1 and its receptor, IGF-1R, affect the development of lung tissues, and subsequently hamper the normal alveolar and microvascular development, causing pathological changes similar to those seen in BPD (22,24). In addition, studies have

shown that the serum levels of IGF-1 are associated with the risk of developing BPD (25,26). These studies have highlighted that IGF-1 could be used as a novel anti-BPD therapeutic target. The present review is a PubMed (https://pubmed.ncbi.nlm.nih.gov/)-based literature review, starting from several key words in different combinations as mentioned in the specific 'Key words' section. Case reports, case series and literature review-type articles were included in the present research. A total number of 91 references are included from 2003 to 2021. Inclusion criteria included English language and full-length articles that were recently published with the majority of the articles published within the last five years.

2. Definition and naming of BPD

'Classic' BPD, also called 'old' BPD, refers to 32 cases of BPD initially described by Northway *et al* in 1967 (3). 'Old' BPD was associated with a higher fatality rate. The average gestational age of children was 34 weeks. Children with old BPD developed severe respiratory distress syndrome (RDS) after birth accompanied by respiratory failure; therefore, mechanical ventilation with high airway pressure was required for more than 28 days. The pathological characteristics of 'old' BPD include chronic inflammation of lung parenchyma, localized emphysema, and alveolar septal fibrosis. With the continuous evolution of neonatal intensive care and perinatal medical management, coupled with the prenatal preventive use of glucocorticoids, the application of exogenous pulmonary surfactants, and the implementation of protective ventilation techniques (27), the incidence of 'classic' BPD has been greatly reduced. Now, a more common form, called 'light' or 'new' BPD is used (28,29). The pathology of 'new' BPD is characterized by a simplified alveolar structure, increased alveolar volume, reduced numbers, and abnormal pulmonary vascular morphology. 'New' BPD usually occurs in VLBWIs born before the 26th gestational week or infants with birth weight <1,000 g. For nearly half a century, there existed no agreement in the naming and definition of BPD (30,31). In the 1990s, most of the experts believed that BPD with abnormal chest X-ray changes was collectively referred to as chronic lung disease (CLD), which required continuous oxygen consumption after 36 weeks of gestational age, or oxygen or mechanical ventilation at 28 days after birth (32). At a workshop organized by the National Heart, Lung and Blood Disorders Office (NHLBI) and the National Institute of Child Health and Human Development (NICHD) in 2000, BPD was redefined as: newborns who are oxygen dependent (>21%) for more than 28 days (33). According to the new definition, there are three types of BPD: mild, no oxygen required; moderate, FiO2 less than 30%; severe, FiO2 greater than or equal to 30% or requiring mechanical ventilation (33,34).

3. Pathogenesis and current situation of BPD

The factors that contribute to the development of BPD are numerous, and the mechanisms are complex (35). It is now generally accepted that BPD is based on genetic susceptibility and adverse factors such as infection, mechanical ventilation and hyperoxia, damage to the developing lung, and abnormal repair after injury (Fig. 1).

High oxygen concentrations and prolonged mechanical ventilation therapy are the main reasons for the development of 'classical' BPD (36). Premature infants of gestational age <28 weeks are at the advanced lung development stage, which is caused by premature pulmonary development, high oxygen level exposure after birth, or damage to the airway, lung vessels, and parenchyma aggravated by mechanical ventilation, ultimately resulting in BPD. In animal experiments, newborn rats were placed in a hyperoxic environment to investigate morphological changes in their lung tissue from 0 to 28 days. They showed simple alveolar structures, fibrosis at the alveolar septum, and reduced pulmonary microvasculature with prolonged oxygen exposure (37,38). In addition, preterm infants have weak resistance to oxidative stress. Under hyperoxic conditions, the production of large amounts of reactive oxygen species (ROS) exceeds the body's antioxidant capacity causing oxidative stress damage and inhibiting the growth and differentiation of the alveolar epithelium, hindering the development of lung septa and alveolar formation after birth and eventually developing BPD (39). Furthermore, hyperoxia can induce lung injury through the cyclooxygenase-2 (Cox-2) and endoplasmic reticulum stress pathways, leading to impaired alveolarization of lung tissue (40). Teng *et al* demonstrated that hyperoxia increased the expression of endoplasmic reticulum stress pathways and downstream markers (41), whereas endoplasmic reticulum stress led to impaired vascular endothelialization through oxidative stress mechanisms and p38MAPK (42). These animal studies established that significant lung injury occurs in preterm infants even when ventilated at very low ventilator pressures because the lungs of preterm infants are immature, and the collagen in the alveoli and interstitium does not limit the expansion of the lungs leading to hyperinflation. Overall, hyperoxia and mechanical ventilation play an important role in the development of BPD.

Inflammatory response or intrauterine infection is an important cause of 'mild' BPD development (43-45). Over 90% of premature infants born before the 28th gestational week have an intrauterine infection, whereas co-morbid BPD shows a higher prevalence (46). Intrauterine infections cause the inflammatory cells to be accumulated within the fetal lungs, resulting in the release of abundant pro-inflammatory cells, which can impair fetal lung development and lead to preterm delivery (47). Postnatal high levels of oxygen therapy, mechanical ventilation, and certain infections may cause a pulmonary inflammatory response (48,49). When the alveolar-capillary barrier becomes impaired, the injured alveolar tissue promptly releases inflammatory factors resulting in the dysregulated levels of pro- and anti-inflammatory factors, increased apoptosis, and decreased proliferation of lung epithelial cells, thereby affecting the differentiation of endothelial cells, lung epithelial cells, and mesenchymal cells and further hindering the alveolar development. Kumar *et al*, in their study on bronchoalveolar development in children with BPD, found that interleukin (IL)-1β, IL-6, IL-8, IL-10, and tumor necrosis factor (TNF)-α expression was significantly increased by lavage tests (50). In addition, blood and urine tests on children with BPD can also reveal the above biomarkers (51,52). The above results suggest that an

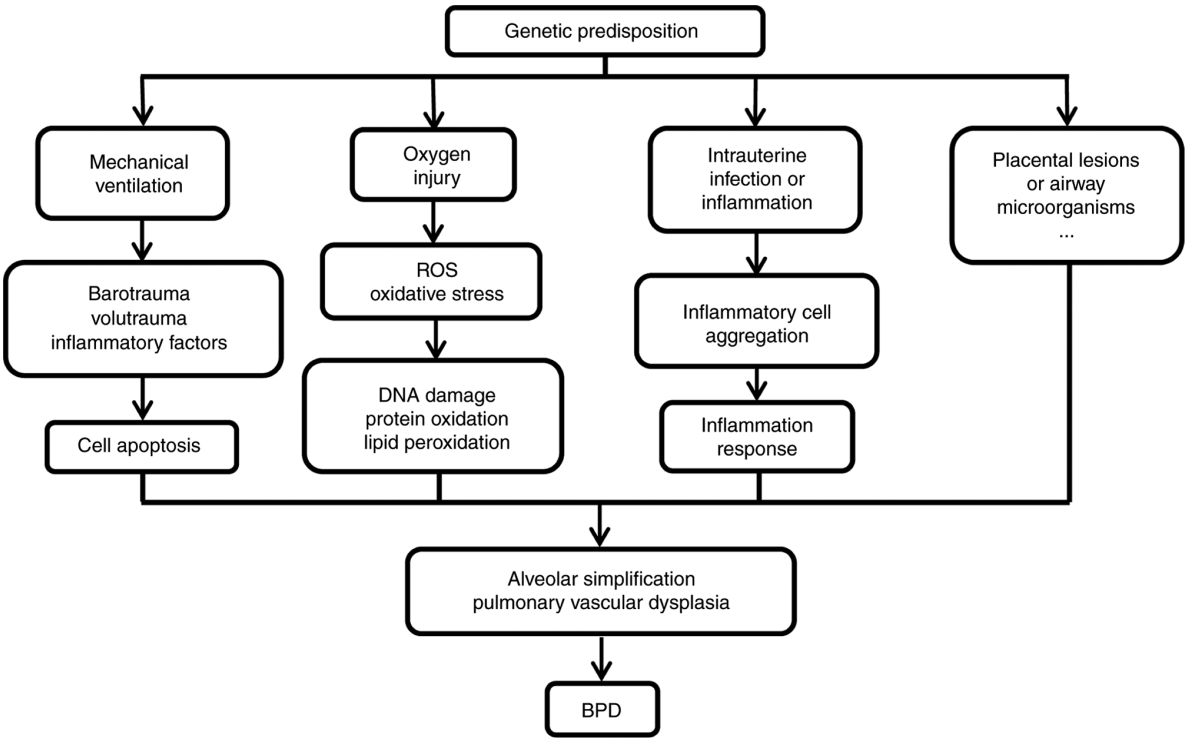

Figure 1. Pathogenesis of bronchopulmonary dysplasia (BPD).

intrauterine or postnatal inflammatory response is involved in the development of BPD in infants.

Several recent studies have hypothesized that placental lesions have an important function in BPD etiology, which is related to moderate-to-severe BPD among the VLBWIs (53,54). In addition, the association between microorganisms in the airway and BPD has drawn researchers' attention, with studies evidencing astounding differences in airway microorganisms between children with BPD, preterm infants, and full-term infants (55). Airway microorganisms among premature infants who require mechanical ventilation are potentially related to BPD severity (56).

Surviving children with BPD develop proliferation of airway smooth muscle cells and epithelial cells, airway remodeling, and combined inflammatory infiltration of the lungs, resulting in airway hyperresponsiveness, impaired lung function, and increased chances of respiratory viral infections in the first year of life (38,57). Based on the follow-up of children with BPD, this impairment of lung function lasts until adolescence or even an adult stage and may be accompanied by long-range respiratory disorders such as chronic obstructive pulmonary disease (COPD) or asthma (58,59). Saarenpää *et al*, in their age-matched study on 29 adults (age group, 18-27 years) with a previous diagnosis of BPD with age-matched healthy adults, documented that first-second exertional expiratory volume and first-second exertional expiratory volume/exertional lung capacity were significantly lower than those in healthy adults (60). According to Kotecha *et al* (61), a 20% decrease in first and/or second exhalation exertion among BPD cases in comparison with controls suggested that the adulthood COPD risk elevated among BPD children. This was related to the simplification of alveolar structure and increased and decreased alveolar volumes and numbers in patients with BPD.

4. Biological characteristics and activity of IGF-1

IGF-1 belongs to a class of polypeptides of the insulin family (tyrosine kinase) and was discovered by Salmanh and Daughudy in 1957 (62). Somatic growth hormone is mediated by a substance in serum that exerts a growth-promoting effect and is termed sulfation-activated factor (SFA) because it acts through sulfation. Later, Dulak and Temin discovered (63) that certain cells secrete a substance that promotes cell growth; hence the name multiplication-stimulating activity (MSA) was coined. Until 1978, these two substances were successfully isolated from the plasma and named insulin-like growth factor because of their structural and functional similarity to insulin (64). To date, only two members, IGF-1 and IGF-2, have been identified. IGF-1 is a 7.5 kDa polypeptide formed by 70 amino acids, four domains, and three pairs of disulfide bonds, which is highly homologous (about 49%) to insulin (65). The biological effects of IGF-1 are predominantly 2-fold (66). First, it stimulates the synthesis of DNA and RNA, mediates cell proliferation and differentiation, and helps in promoting mitosis. Second, it promotes fat and protein synthesis, regulates glycolysis and glucose isogenesis, and has insulin-like metabolic effects. Several tissues supply IGF-1 to cells through autocrine or paracrine forms/modes; however, in the circulation, IGF-1 is mostly produced from the liver under the regulation of growth hormone, which acts on target tissues through endocrine, autocrine, or paracrine manner, exerts biological effects, and plays a vital function in regulating different cell growth and differentiation processes (21) (Fig. 2).

5. IGF-1 in lung development

IGF-1 is required for lung development processes. IGF-1 is widely distributed in the lungs of newborn rodents (67), and

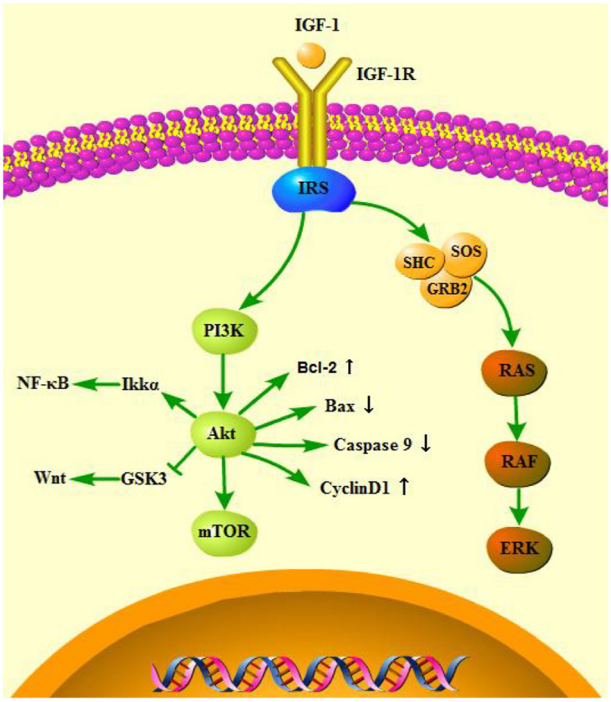

Figure 2. Underlying mechanism of insulin-like growth factor-1 (IGF-1). IGF-1R, IGF-1 receptor; SHC, SHC adaptor protein 1; SOS, son of sevenless; GRB2, growth factor receptor bound protein 2; PI3K, phosphatidylinositol-3-kinase; Akt, protein kinase B; GSK2, glycogen synthase kinase 3; mTOR, mammalian target of rapamycin; ERK, extracellular regulated protein kinases.

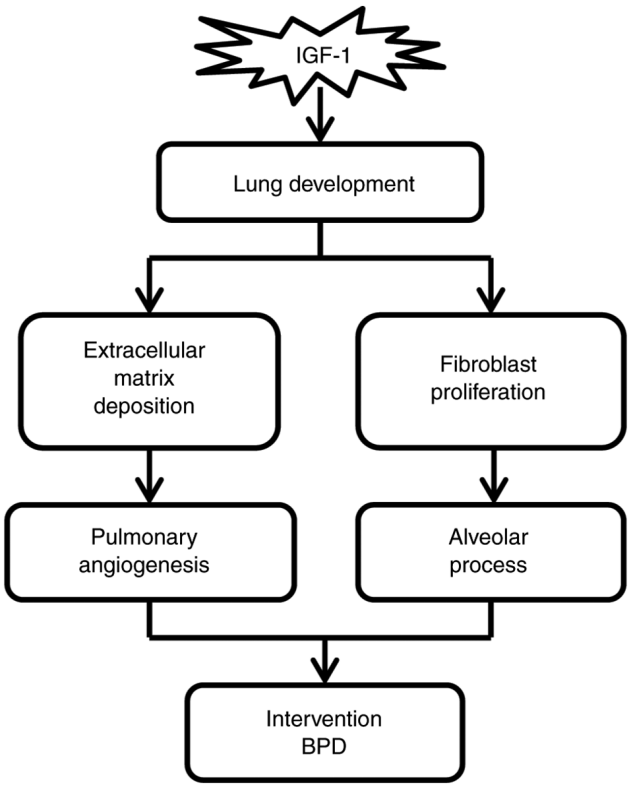

Figure 3. Possible mechanisms of insulin-like growth factor-1 (IGF-1) for the treatment of bronchopulmonary dysplasia (BPD).

IGF-1 deletion is suggested to greatly affect the development of the lungs. The concentration of IGF-1 in the cord blood of newborns is associated with the development of the fetal lung. ATII cells play a pivotal role in lung tissue development. When ATII cells are transformed to type I alveolar (ATI) cells, the expression of IGF-1 is significantly increased (68). The exogenous application of recombinant IGF-1 promoted the conversion of ATII to ATI. However, the addition of the IGF-1 antibody inhibited the proliferation and differentiation of ATII (69). Moreover, ATII cells showed a high percentage in IGF-1-deficient mice (70), indicating that the IGF-1 deficiency affected the differentiation of ATII cells. In addition, IGF-1 promotes lung tissue development by modulating alveolar epithelial and airway basal cells. The mechanism has not yet been elucidated but could be related to the interaction between IGF-1 and its downstream factors, or maybe via a paracrine or autocrine manner. A similar finding was observed in certain *in vivo* and *in vitro* studies. IGF-1$^{-/-}$ mutant mice are born with poor lung development, which is characterized by thickening of the alveolar interstitium, thinning of smooth muscles, dilatation of blood vessels, diffuse deposition of the extracellular matrix (ECM), delayed long-term lung development, susceptibility to respiratory distress syndrome, and elevated mortality (71).

6. IGF-1 and lung injury

When lung injury response occurs, lung epithelial cells, type II alveolar (ATII) cells, and inflammatory cells activate and release IGF-1 (72), which is involved in the proliferation and migration of lung tissue fibroblasts and stimulates collagen production, ultimately causing ECM remodeling and aggregation. IGF-1 modulates epithelial-mesenchymal transition (EMT) in ATII cells during lung damage (73), greatly affecting ECM production. The airway basal cells play a vital function in the injury to the airway as well as its repair, and IGF-1 may regulate basal cell differentiation and proliferation through FOXO-mediated p63 (74). Thus, IGF-1 may be an important factor in lung injury repair.

7. Possible underlying mechanisms of IGF-1 in BPD development

The level of IGF-1 was found to be markedly elevated in myofibroblasts, alveolar epithelial cells, and mesenchymal cells when the lungs of patients who died from BPD were studied (23). Significantly increased levels of IGF-1 were found in bronchoalveolar lavage fluid (BALF) obtained from BPD premature infants (28). In animal studies, IGF-1 expression was significantly elevated in the lungs during hyperoxia exposure and recovery (69). These studies indicate the involvement of IGF-1 in BPD development (Fig. 3).

In IGF-1-knockout mice, lung development is characterized by severe lung dysplasia with increased apoptosis, decreased airway volume, and collapsed alveoli (70), which is similar to the pathology of BPD. According to a study (75), the ventilation and breathing patterns of IGF-1R$^{neo/-}$ mice were significantly better than those of IGF-1R$^{+/+}$ mice under hyperoxic conditions, and they could better survive under hyperoxic conditions. IGF-1R$^{+/+}$ group mice were more likely to present with abnormal breathing patterns due to hyperoxia and increased probability of respiratory failure. In addition,

the lung tissues in IGF-1R$^{+/+}$ mice showed significant pulmonary edema, intra-alveolar hemorrhage along the formation of the hyaline membrane relative to those observed in IGF-1R$^{neo/-}$ mice. This indicates that interference or destruction of the IGF-1 signaling pathway plays an important role in hyperoxia-induced BPD.

Stagnation of lung development, decreased alveolus number and elevated size, and reduced pulmonary vascular production are some of the characteristics of BPD. Echocardiography during pregnancy found that fetal pulmonary vascular disease is closely related to the occurrence of BPD at 36 weeks of corrected gestational age (76). The mechanisms affecting alveolar development and angiogenic alveolar development during this process have not been elucidated. In the fetus, alveolarization is initiated at about the 36th gestational week, and most children who develop BPD are born before 32 weeks of gestation and have not yet developed alveoli at birth (24). Studies conducted in animal models have shown that alveoli are initially formed by inward growth of secondary cristae and septum, a process regulated by multiple cytokines. IGF-1 regulates the generation of secondary cristae during alveolar formation. Studies have shown that loss of IGF-1 reduced the synthesis of elastin fibers, type I pre-collagen, and secondary cristae cell DNA, severely affecting alveolar development and even causing lethal respiratory distress (77). Findings from several studies have revealed that hyperoxia affects the affinity of IGF-1 and its receptors, interfers with the formation of secondary cristae, and hinders the formation of alveoli (24). Most organs, including the vascular system, depend on IGF-1 for their growth and differentiation (21,78). In the vascular and alveolar epithelial development process, IGF-1 and leukemia inhibitory factor (LIF) exert synergistic effects (70). LIF and IGF-1 double knockout mice exhibit severe alveolar collapse and pulmonary vascular malformations. Previous studies have shown that vascular endothelial growth factor (VEGF) plays an essential function during lung vascular development. VEGF signals can hinder the alveolarization process and participate in the occurrence and development of BPD (79). It has been shown that IGF-1 can activate VEGF signaling through the MAPK and Akt pathways and can play a protective role in angiogenesis, endothelial differentiation, and regeneration (80). In addition, IGF-1 may upregulate VEGF protein expression by increasing the rate of transcription of the *VEGF* gene (81). In a recent study, intraperitoneal injection of rhIGF-1/BP3 promoted the formation of alveoli and microvessels, thereby improving lung function (82). Alveolar development and angiogenesis are important processes in lung development. IGF-1 treatment may affect alveolar development and angiogenesis, and thus restores lung injury in children with BPD.

The aggregation of inflammatory cells, such as neutrophils, greatly affects lung damage among BPD cases (45). IGF-1 participates in the regulation of T-helper cell subset 1/2 (Th-1)/Th-2 balance in the body (83). Clinical studies (84) indicate that when serum IGF-1 is <20 mg/l, symptoms of infection occurred nine times (out of a total of 16) higher, suggesting the involvement of IGF-1 in the inflammatory response of lung tissues. These studies indicate that lower levels of IGF-1 in the circulation and the destruction of the IGF-1 signaling pathway may be related to the pathogenesis of BPD.

8. IGF-1 as a new option for BPD treatment

Experiments concerning IGF-1 have been carried out. Several *in vitro* and *in vivo* studies suggest the vital role of IGF-1 in BPD genesis and development. As demonstrated in animal research (85), exposure to hyperoxia for a long time induced alveolar cell apoptosis and suppressed Clara cell secretory protein (CCSP) expression. Intraperitoneal injection of IGF-1 was found to increase the secretion of CCSP, reduce the inflammatory response in the lung, and inhibit the apoptosis of lung tissue cells. In addition, CC10 is the main secreted protein of Clara cells and plays a protective role in lung injury due to its anti-inflammatory properties. Previous studies have shown that the lower the expression of CC10, the higher the risk of BPD development. In an animal model of BPD (86), exogenous injection of recombinant IGF-1 was found to increase the number of Clara cells, which indirectly acted as an anti-inflammatory agent and reduced the risk of BPD. In clinical studies, IGF-1 in fetal serum was found to be elevated in mid and late gestational periods. The levels of IGF-1 in preterm infants are significantly lower than intrauterine levels at the same gestational age. The lack of IGF-1 in the serum of preterm infants in the early postnatal period suggests an increased risk of developing BPD. Recombinant rhIGF-1/IGFBP-3 is currently in clinical trials as a therapy for preterm infants. A phase I and II Randomized Controlled Trial (RCT) on the pharmacokinetics and safety of rhIGF-1/IGFBP-3 did not reveal any significant adverse effects at this time, and the safety variables were within normal limits (87-89). In addition, in a study of rhIGF-1/IGFBP-3 for the prevention of retinopathy of prematurity (ROP), secondary findings found a significant reduction in the incidence of severe BPD in the full analysis set group (53%) (90). A recent study found that rhIGF-1/IGFBP-3 treatment improved lung function in 2 prenatal BPD models of intrauterine infection and pre-eclampsia, as well as in a hyperoxia-induced postpartum BPD model (82). An RCT (Identifier: NCT03253263) containing the clinical efficacy of rhIGF-1/IGFBP-3 in the treatment of BPD in very preterm infants is underway, and it is believed that the results of this study will provide strong evidence for the future clinical treatment of BPD with IGF-1.

9. Challenges and prospects of IGF-1

To the best of our knowledge, IGF-1 is involved in both BPD induced by prolonged hyperoxia exposure and BPD mediated by inflammation of intrauterine infection. In addition, the exogenous supplementation of IGF-1 can reduce BPD symptoms. Although extensive research has been conducted on IGF-1, there are still numerous issues that require elucidation. First, there are contradictory reports on the expression of IGF-1, which may be related to its biological characteristics. Further studies are required to explore the ability of IGF-1 to promote both proliferation and differentiation, as well as insulin-like metabolism. In addition, most of the current data are derived from animal models, and adequate clinical data are lacking. Thus, results from a large number of multicenter randomized controlled trials are still required to support this hypothesis. Further studies can incorporate the knowledge and findings of the present review to integrate basic experimental

and clinical studies for the early use of IGF-1 to prevent and treat BPD among premature infants.

10. Conclusion

The current review discusses the association between IGF-1 and BPD. IGF-1 is an important chemical in the human body that is associated with over 100 diseases and even the early onset of aging. We believe this review will enlighten the community and prove helpful in reducing morbidity and mortality in preterm and postnatal children affected with BPD. However, more clinical trials are warranted to establish conclusive and convincing associations in humans.

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Authors' contributions

SZ contributed to the investigation and wrote the original draft of the manuscript. XL and SZ performed the relevant literature research and revised the manuscript. HL and XL contributed to the literature search and processing of the findings. ZJ contributed to the conceptualization of the review. Data authentication is not applicable. All authors read and approved the final manuscript for publication.

Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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