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Molecular Mechanisms Driving Alveolarization and Their Clinical Implications: A Literature Review

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Abstract

Introduction: The highly coordinated process of lung organogenesis is essential for healthy respiratory function. This review aims to unveil the molecular pathways underlying alveolar development, a critical component of lung maturation.

Methods: A comprehensive literature analysis was conducted, focusing on significant signalling pathways, transcription factors, and regulatory components involved in each stage of alveolar development. This approach was taken to understand the molecular intricacies of both prenatal and postnatal lung development.

Results: Lung development progresses through five stages: embryonic, pseudoglandular, canalicular, saccular, and alveolar. Each stage involves distinct morphological changes, alongside specific molecular interactions that regulate alveolar cell differentiation and maturation. FGF signalling is crucial during the pseudoglandular and canalicular stages, while Wnt and TGF-β signalling are particularly active in late-stage alveolarization, facilitating alveolar septation and surfactant production. Transcription factors like Nkx2.1, Foxa2, and Sox2 orchestrate the development of epithelial cell populations that give rise to alveoli. Disruptions in these molecular processes can result in impaired lung function and conditions such as ARDS and BPD.

Discussion: The intricate crosstalk between signalling pathways, transcription factors, and the extracellular matrix is critical for proper alveolar development. The complex interplay of genetic, environmental, and mechanical factors can significantly impact alveolar development, leading to severe respiratory conditions. While current research provides valuable insights, in vivo studies are needed to elucidate the dynamics of crucial signalling pathways during lung development. Furthermore, the long-term effects of early-life environmental exposures on alveolarization and lung function need to be explored.

Conclusion: Alveolarization is vital for lung development and respiratory function. This review highlights the importance of signalling pathways and cellular interactions in this process.

Keywords: lung development; alveolarization; signaling pathways; transcription factors, bronchopulmonary dysplasia (BPD); acute respiratory distress syndrome (ARDS); extracellular matrix (ECM); growth factors

Introduction

Human lung formation is essential to the proper function of the respiratory system. This process is divided into five stages: the embryonic, pseudoglandular, canalicular, saccular, and alveolar stages [1]. Every stage is distinguished by specific morphological and molecular alterations that set the stage for later development and result in the production of the alveoli, which are the primary sites for gas exchange in the lungs. Comprehending these phases is essential for clarifying the processes that underpin typical lung growth and the root cause of diverse pulmonary illnesses like ARDS and BPD. This review summarizes the molecular mechanisms regulating lung development, specifically alveolarization, and the pathologies resulting from perturbations in the signalling pathways necessary for proper pulmonary development.

Methods

A thorough literature search was conducted on the molecular pathways and mechanisms underlying alveolar formation and alveolarization. The search included PubMed, Toronto Metropolitan University libraries, and Google Scholar databases. The following keywords and combinations were used: "alveolar development," "alveolarization," "molecular pathways," "mechanisms," "lung development," "alveolar epithelial cells," "growth factors," and "signalling pathways." A total of 153 papers were initially identified through this search. Only peer-reviewed articles published after the year 2000 that concentrated on the molecular processes or pathways essential to alveolar formation, like WNT, TGF-β, FGF, BMP, and Notch pathways were used. This includes reviews, meta-analyses, and experimental research; which are free to download and offered in English. Studies that mainly addressed non-lung organogenesis or general

epithelial development without a focus on alveolarization were excluded. 45 papers were ultimately shortlisted following the initial round of exclusions. Studies that did not provide original research data or a thorough understanding of molecular pathways were further eliminated following a thorough examination. Ultimately 27, publications made up the final review.

Results

The lower respiratory tract develops in five phases, with the first stage starting on day 22 of gestation. Maturation is completed at the age of eight [2].

5 Stages of Lung Development

Embryonic Stage (weeks 3-6)

Lung development begins at the embryonic stage when the two primordial right and left buds emerge from the foregut's ventral wall during the fourth week of gestation. These then divide into the primary bronchial buds on the left and right, giving rise to the secondary and tertiary bronchi [3]. Branching morphogenesis starts with the development of the primary bronchial buds. Future lung lobes are formed in the fifth week when the primary bronchial buds divide asymmetrically to generate secondary bronchial buds. In the sixth week, the last wave of branching divides secondary buds into tertiary buds, forming adult lung bronchopulmonary segments [2]. At this point, the bronchial trees' basic structure is established [3]. The larynx, trachea, lung primordia, lobe, and bronchopulmonary segments have formed by the conclusion of the embryonic stage [2].

Pseudoglandular Stage (weeks 5-17)

During the pseudoglandular stage, the branching morphogenesis of the bronchial tree continues, forming the airways. By week 16, the tertiary bronchial buds undergo considerable branching morphogenesis, forming the first 20 generations of the human respiratory tree [1]. By the time this stage ends, the respiratory tree has grown to the point of the terminal bronchioles, where smooth muscle, cartilage, and an arterial system have all formed. Due to the lack of development in the respiratory bronchioles, babies born at this stage cannot facilitate gas exchange and will, therefore, not survive [2]. Pulmonary fibroblasts are the main cell type that produces extracellular matrix (ECM) proteins. At the epithelial-mesenchymal interface, the ECM consists of collagens I, III, and VI, decorin, lumican, biglycan, and proteoglycans (PGs), which form a sleeve around the bronchiolar ducts. Heparin sulphates, a sulphated proteoglycan found in the ECM, can regulate growth factor binding, signalling, and airway branching [4].

Canalicular Stage (weeks 16-25)

The differentiation of the airway epithelium and the onset of vascularization are features of the canalicular stage [5]. In the respiratory tree, this level denotes the separation of the conducting and respiratory units [2]. During this phase, the terminal bronchioles develop, and each one gives rise to alveolar ducts and respiratory bronchioles. Numerous cell types, such as ciliated and secretory cells, also differentiate, preparing the groundwork for developing gas exchange units [5]. Three to six alveolar ducts are produced by the acinus. This is formed by the extension and development of terminal bronchioles. The thick capillary network formed by angiogenesis in the mesodermal tissue surrounding the acinus forms the blood-air barrier. In week 20, lamellar structures in cuboidal type II pneumocytes' cytoplasm appear, releasing pulmonary surfactant into the alveoli [6]. Since this part of the lungs exchanges gasses, infants delivered at this stage can survive with intensive care, but the limited surface area and type II pneumocytes' inability to generate pulmonary surfactant often lead to death [1].

Saccular Stage (weeks 24-birth)

The development of primitive alveoli, or terminal sacs, occurs during the saccular stage. The lungs' gas-exchange surface area grows during this phase, forming terminal sacs, or "saccules." A thick primary septa featuring a twofold capillary network and a central layer of connective tissue divide these saccules apart [2]. Type II alveolar cells differentiate into flattened, squamous type I cells. These produce surfactants which lower surface tension in alveoli and prevent lung collapse. The sites where the capillary endothelium and AT1s come into close contact will eventually create the air-blood barrier [1]. The blood-air barrier is made up of type I pneumocytes, the capillaries' thin basement membrane, and endothelium. This is formed when capillaries infiltrate the sacculi's thin walls and creates an essential surface for effective gas exchange. The creation of pulmonary surfactant starts at 24 weeks, but it does not reach sufficient levels to stop atelectasis until 32 weeks. Consequently, babies born beyond 32 weeks have a significantly higher probability of surviving [2].

Final stage: Alveolarization (weeks 36-8 years)

The alveolar stage lasts from late fetal to early childhood and up to around eight years after birth. This stage is characterized by extensive alveolarization, which increases the surface area accessible for gas exchange significantly by causing terminal air sacs to septate into mature alveoli [7]. This stage involves the intricate remodelling of distal lung airspaces into millions of tiny alveoli, enhancing gas exchange efficiency and increasing lung surface area. [1].

Immature alveoli develop as bulges from the sacculi that infiltrate the major septa before birth. The protrusions in the primary septa enlarge as the sacculi continue to grow; these new, longer, thinner septations are called secondary septa, and they oversee the respiratory tree of sacculi's final division into alveoli. Septation happens in the interstitium at locations where there is an increase in fibroblast activity, as well as collagen and elastin fibre secretion [2]. The key

ECM component influencing the alveolar walls' flexibility is elastin, a structural protein whose deposition is greatest around the locations of potential secondary crests [4]. Alveolar division is a process that lasts until the child is three years old, with most divisions happening in the first six months to make the diffusion barrier thinner. As maturity advances, the double-layer capillary networks merge into a single-layered network, each closely linked to two alveoli. Lung enlargement occurs from alveolar growth until the third year of life and continues until mature lungs form at age eight [2].

Type I and type II alveolar epithelial cells develop from the undifferentiated, glycogen-rich cuboidal epithelial cells of the future alveolar ducts. The majority of the inner surface area of the sacculi and alveolar ducts is covered in thin, sheet-like extensions made up of type I cells.

The type II cells are situated in the space between type I cells, frequently near the points where three alveolar septa converge. The future air-blood barrier forms at these sites where the capillary endothelium and type I alveolar epithelial cells come into close contact [1].

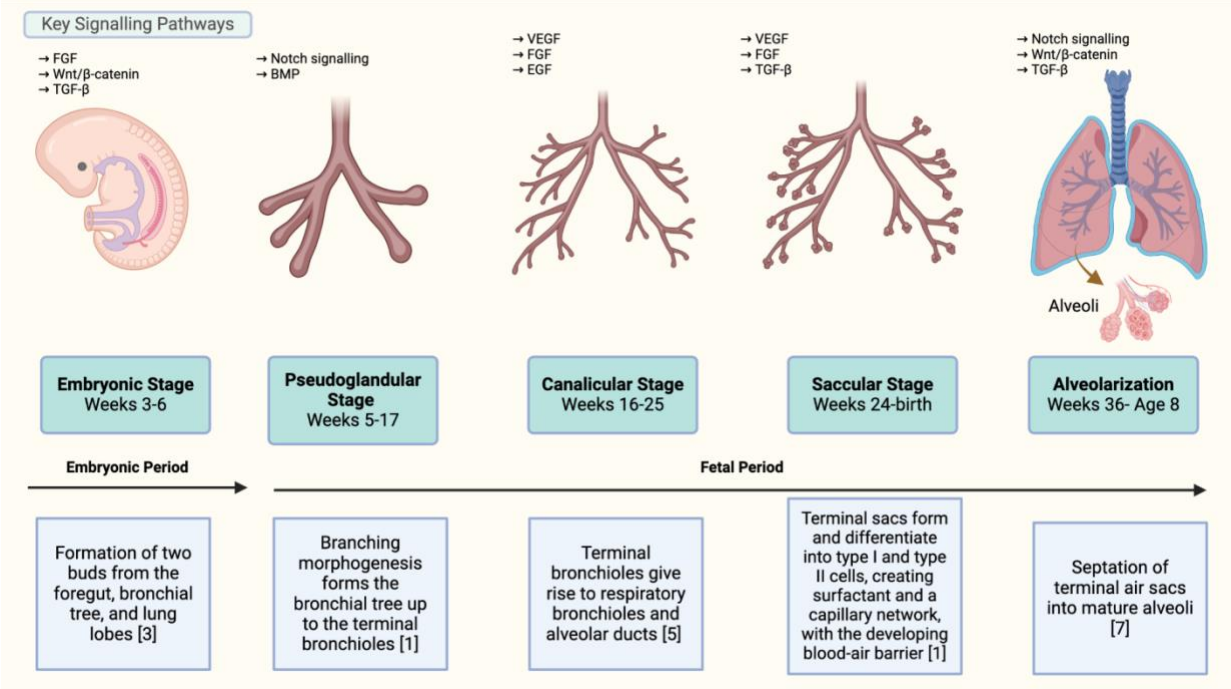

Figure 1. The Five Stages of Lung Development and the Key Signalling Pathways (Created in BioRender.com).

Cellular/Molecular Mechanisms (Growth Factors/Signalling Pathways)

Lung branching morphogenesis and alveolar formation are primarily driven by epithelial-mesenchymal interactions facilitated by fibroblast growth factors (FGFs), particularly FGF10 [8]. Alveolar septation relies on the balance between the synthesis and breakdown of the extracellular matrix, regulated by transforming growth factor-beta (TGF-β) signalling [9].

Transcriptional networks distinct to different lineages coordinately regulate cell growth in lung formation. Before reaching the pseudoglandular stage, multipotent endodermal progenitor cells develop into Sox2+ proximal or Id2+/Sox9+ distal endodermal progenitors. During the pseudoglandular stage, Sox9+ distal lung progenitor cells develop early alveolar type 1 (AT1) and AT2 expression characteristics. The primitive pulmonary terminal sac arises during the canalicular stage. Differentiating fibroblasts release Wnt, which can encourage the terminal sac epithelium to differentiate into AT1 and AT2 cells. During the saccular stage, the terminal sac epithelium starts separating and is encircled by capillaries. Squamous AT1 cells cover the gas exchange-related surface area in adult alveoli and are near the capillary endothelial cells. On the other hand, surfactants are mostly produced by AT2 cells and are stored in lamellar bodies. By secreting factors (i.e. surfactant protein, cytokines, chemokines, etc.) that prevent bacterial growth and stimulate alveolar macrophages (AMs) to fight infections, AT2 cells actively participate in innate immunity. A subgroup of AT2 cells with strong regenerative ability enables rapid expansion and regeneration of alveolar epithelium, responding specifically to viral or bacterial infections, cigarette smoke exposure, and other stimuli. Quiescence, proliferation, and differentiation of AT2 cells are all controlled by an intricate web of signalling pathways that span from lung development to maintaining homeostasis in adults. These pathways include cytokines (IL-1β, IL-4, IL-13, and IL-6),

growth factors (e.g., TGF-β, FGFs, PDGF, EGF, and VEGF), Wnt, Notch, Hippo/Yap, and bone morphogenetic protein [10]. TGF-β, which AT2 cells release, is a key mediator in converting fibroblasts to myofibroblasts and induces a phenotype that preserves the matrix. It is also linked to the secretion of ECM proteins and tissue inhibitors of metalloproteinases (TIMPs). TGF-β-mediated fibroblast activation in fibrotic tissues may also be responsible for the proliferation of myofibroblasts in circulating progenitors, endothelial cells, pericytes, and epithelial cells. By encouraging the release of fibrogenic cytokines, growth factors, and matricellular proteins by macrophages, vascular cells, and epithelial cells, TGF-β may also indirectly activate fibroblasts [11].

Lung development is governed by various chemical signals, including retinoic acid, BMP, EGF, FGF, Hedgehog, TGF-β, and WNT families [2]. Early lung development depends on transcription factors such as Nkx2.1, Foxa2, and Sox2, which regulate gene expression necessary for lung tissue formation and differentiation. Growth factors like VEGFs, TGF-β and FGFs, especially FGF10, drive epithelial-mesenchymal interactions, branching morphogenesis, and the formation of alveolar structures. Vascular endothelial growth factors (VEGFs) promote the development of the capillary network and endothelial cell expansion [5]. TGF-β signalling is crucial for myofibroblast differentiation and ECM deposition. However, tight regulation is needed, as excessive TGF-β activity can lead to fibrosis, hindering alveolar formation [12].

Signaling pathways, notably Notch, Hedgehog, and Wnt, manage cell division, proliferation, and spatial organization during lung development ([5]. The transcription factor Nkx2.1, essential for lung development, is regulated by the Wnt/beta-catenin pathway in the foregut's ventral endoderm; inactivation of Wnt2a, Wnt2b, or beta-catenin leads to lung aplasia [2]. Wnt signalling controls alveolar epithelial cell growth and differentiation. Activation of the Wnt pathway increases type II cell proliferation and prevents their differentiation into type I cells, maintaining the balance of alveolar cellular composition [13]. The balance of these signals supports the differentiation of alveolar epithelial cells, the growth of the capillary network, and the deposition of ECM components, all essential for the lung's functional architecture [5].

Pathologies related to Alveolar Development

Chronic lung disease and respiratory distress are primarily caused by genetic abnormalities that impact alveolar formation, including deficiencies in surfactant protein [14]. Environmental factors like high oxygen levels and mechanical ventilation in preterm infants can exacerbate these issues [15].

Acute respiratory distress syndrome (ARDS) is characterized by low oxygenation and “stiff" lungs. ARDS leads to alveolar damage and capillary endothelial injury, resulting in pulmonary artery vasoconstriction and potential pulmonary hypertension in patients. There are not many effective treatment options for ARDS, and the syndrome has a significant death rate (9% to 20% mortality rate). Alveolarization is an important process that has a major impact on the pathophysiology of ARDS. Acute, diffuse lung parenchymal inflammation is the hallmark of ARDS, which impairs gas exchange and causes respiratory failure. This illness causes damage to the alveolar-capillary barrier, leading to increased permeability, alveolar edema, and subsequent fibrosis [16].

Patients with ARDS experience severe inflammation characterized by leukocyte infiltration, procoagulant activation, and cell damage, which leads to the breakdown of the alveolar-epithelial barrier and the formation of protein-rich edema in the alveoli. This allows fluid and big plasma proteins to enter the interstitial tissue and flood the alveolar airspaces. Alveolar epithelial damage can result from various mechanisms, including cell death, reduced tight junction (TJ)-mediated contact, ECM modifications, immune cell-epithelial communication adjustments, mechanical strain, inflammatory responses, incorrect platelet activation, and increased pro-coagulation signal production [17].

Effective ARDS treatment and management aim to prevent further lung damage and promote alveolar healing. To enhance outcomes for ARDS patients, therapies aimed at ECM remodelling, such as antifibrotic medications, are being investigated [17]. If alveolar development does not improve, infants diagnosed with ARDS are later diagnosed with BPD at 36 weeks’ gestation [18].

Bronchopulmonary dysplasia (BPD), a common chronic lung disease in preterm infants, is characterized by arrested alveolar development and abnormal vascularization [19]. One of the main characteristics of BPD is the disturbance of normal alveolar growth. Premature birth disrupts the alveolar stage, which results in alveolar simplification, a smaller surface area for gas exchange, and decreased lung function. The compromised lung function that characterizes BPD results from disruptions in alveolarization brought on by inflammation, infection, mechanical ventilation and oxygen toxicity, ECM alterations, and growth factor dysregulation [20].

Infections, such as bacterial, viral, fungal and mechanical ventilation, frequently cause prenatal and postnatal inflammation, which interferes with the signalling pathways needed for alveolarization. Alveolar epithelial and endothelial cells are susceptible to damage from pro-inflammatory cytokines like IL-1β and TGF-β and oxidative stress, which can hinder their growth and differentiation. These cytokines are elevated in BPD and promote inflammatory reactions. Both oxygen toxicity and volutrauma can result from necessary therapies for premature newborns, such as oxygen therapy and mechanical ventilation. These therapies produce reactive oxygen species (ROS), which promotes inflammation and

impairs normal lung architecture and function by causing damage to the alveoli and vasculature. Deviations from normal growth factor signalling, including decreased VEGF or modified TGF-β pathways, hinder angiogenesis and the function of epithelial cells, which are essential for alveologenesis [20].

Changes in the composition and remodelling of the ECM impact the signalling and structural integrity required for alveolarization. In BPD, fibrosis and increased ECM deposition are frequently seen. These changes include elevated elastin, increased collagen types I, III, and IV, and increased matrix deposition in the basement membrane and interstitial ECM [20].

Exogenous surfactants and corticosteroids are currently used to treat BPD in preterm newborns, but their limitations necessitate the development of better therapeutic alternatives [21]. Corticosteroids, such as hydrocortisone and dexamethasone, reduce lung inflammation in premature newborns. When given postnatally, they have been proven to reduce the incidence of BPD [21]. However, there are serious hazards connected to these treatments, including the possibility of adverse neurodevelopmental effects [22]. When systemic corticosteroids are administered within the first week of life, they may cause side effects such as cerebral palsy and developmental delays [21].

Recent research has looked at the intratracheal delivery of corticosteroids and surfactants to alleviate these side effects. This approach targets the lungs directly while limiting systemic exposure. Trials such as the PLUSS (The Preventing Lung Disease Using Surfactant + Steroid Trial) study are investigating the safety and efficacy of this strategy. The PLUSS experiment aims to assess whether intratracheal budesonide combined with surfactant increases survival without causing bronchopulmonary dysplasia (BPD) in preterm infants. According to the results of the randomized studies, intratracheal budesonide in a surfactant vehicle is a potentially effective treatment for improving survival in patients without BPD; but more research must be done [22].

In premature newborns, exogenous surfactant therapy is used to treat respiratory distress syndrome (RDS), which has been linked to the development of BPD. Surfactant therapy has been shown to be beneficial in reducing the need for mechanical ventilation and improving lung function, but by itself has not been able to significantly lower the overall incidence of BPD since it does not address the underlying injury and inflammation [23].

Better therapeutic alternatives are required to solve these issues. Novel anti-inflammatory medications, targeted therapy that reduces systemic adverse effects, and less invasive surfactant administration techniques are among potential tactics [24].

Discussion

The intricate process of lung development, particularly alveolarization, ensures effective respiratory function. Understanding these mechanisms is essential for comprehending lung development and identifying the causes of pulmonary diseases, such as BPD and ARDS. The disruption of alveolar development due to genetic, environmental, and mechanical factors can lead to significant respiratory complications. Treatments for diseases like BPD and ARDS have been greatly impacted by our growing understanding of alveolar formation leading to various clinical implications. In order to reduce lung damage in preterm infants with BPD who have decreased alveolar growth as a result of oxygen therapy and mechanical ventilation, physicians are using gentler techniques like continuous positive airway pressure (CPAP) and non-invasive ventilation [25]. With regard to ARDS, knowledge of alveolar repair has resulted in lung-protective ventilation techniques that lessen the strain on damaged alveoli [26]. The goal of cutting-edge therapies like extracorporeal membrane oxygenation (ECMO) and other strategies like stem cell therapy is to encourage alveolar repair [27].

Ongoing research into signalling pathways and ECM remodelling offers promising avenues for developing targeted therapies to mitigate these conditions and improve respiratory outcomes.

However, the current literature has some limitations. More detailed in vivo studies are needed to better understand the temporal and spatial dynamics of key signalling pathways during lung development. Additionally, there needs to be more research on the long-term impacts of early-life environmental exposures, such as pollutants and infections, on alveolarization and lung function in adulthood. Future studies should focus on how these early environmental influences affect the development of alveoli and signalling pathways over time. Comprehending these pathways can aid in the formulation of preventive and therapeutic approaches aimed at reducing long-term detrimental impacts on lung function. By filling in these gaps, we can improve our understanding of lung development and associated illnesses, leading to the development of new treatments for patients with disorders like ARDS and BPD.

Conclusion

In summary, alveolarization is a vital process in lung development that underpins effective respiratory function throughout life. This review has highlighted the stages of lung development, from the embryonic phase to alveolarization, emphasizing the molecular mechanisms and cellular interactions that drive these processes. Future studies focusing on the intricate balance of growth factors, signalling pathways, and ECM components will be crucial in advancing our knowledge and treatment of lung development disorders.

List of Abbreviations
AMs: alveolar macrophages
ARDS: acute respiratory distress syndrome
AT1: alveolar type 1
AT2: alveolar type 2
BMP: bone morphogenetic proteins
BPD: bronchopulmonary dysplasia
CPAP: continuous positive airway pressure
ECM: extracellular matrix
ECMO: extracorporeal membrane oxygenation
EGF: epidermal growth factor
Fbs: fibroblasts
FGF: fibroblast growth factors
Foxa2: forkhead box protein A2
HS: heparin sulphates
Id2+: inhibitor of DNA binding 2
IL-13: interleukin 13
IL-1β: interleukin-1 beta
IL-4: interleukin 4
IL-6: interleukin 6
Nkx2.1: NK2 homeobox 1
PDGF: platelet-derived growth factor
PGs: proteoglycans
PLUSS: preventing lung disease using surfactant + steroid trial
RDS: respiratory distress syndrome
ROS: reactive oxygen species
Sox2: SRY-box transcription factor 2
Sox9+: SRY-box transcription factor 9
TGF-B: transforming growth factor-beta
TIMPs: tissue inhibitors of metalloproteinases
TJ: tight junction
VEGF: vascular endothelial growth factor
Wnt: wingless-related integration site
Yap: yes-associated protein

Conflicts of Interest
The author declares that they have no conflicts of interest.

Ethics Approval and/or Participant Consent
This review paper presents and evaluates already published research; thus, no ethics approval nor participant agreement are needed. The study did not acquire any new data from participants who were humans or animals, nor did it involve any confidential information that would require ethical review.

Authors' Contributions
RS: Contributed to all aspects of the manuscript, including conceptualization, literature review, drafting, revisions, and final approval of published manuscript.

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