Congenital Lung Malformations

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Congenital lung malformations arise during development and include numerous anatomical anomalies of the lung and respiratory tree. They are usually detected prenatally by ultrasonography and comprise congenital pulmonary airway malformation (CPAM), bronchopulmonary sequestration (BPS), bronchogenic cysts (BC), and more rarely bronchial atresia, congenital lobar emphysema (CLE), and congenital tracheal obstruction. This entry focuses on the molecular and genetic determinants of the most frequent anomalies: CPAM, BPS, and BC. Congenital diaphragmatic hernia (CDH) is not usually included in this group; however, since the lung is also highly affected in this condition, we have also incorporated evidence related to lung hypoplasia.

Keywords: congenital malformations ; congenital pulmonary airway malformation (CPAM) ; bronchopulmonary sequestration (BPS) ; bronchogenic cyst (BC) ; congenital diaphragmatic hernia (CDH)

1. Congenital Pulmonary Airway Malformation

Congenital Pulmonary Airway Malformation (CPAM), previously known as Congenital Cystic Adenomatoid Malformation (CCAM), is a rare but clinically significant developmental disorder. CPAMs are the most common congenital lung abnormalities, with an estimated incidence between 1 in 25,000–35,000 live births [1]. However, recent data and reports from the European Surveillance of Congenital Anomalies (EUROCAT) suggest a much higher prevalence of this disorder [2][3]. CPAMs are associated with significant infant morbidity and mortality due to associated complications such as lung hypoplasia, respiratory distress, and fetal hydrops [4][5].

CPAM is characterized by dilation of the airways and consequent cystic lesions within the lung parenchyma; it displays a disorganized spatial arrangement of tissues where multicystic masses replace the normal lung and are connected to the tracheal-bronchial system. Most of the cases involve a single pulmonary lobe, and bilateral lesions are uncommon. Stocker's classification subdivide CPAM into five types based on clinical, macroscopic, and microscopic criteria [6][7]. CPAM type 1 is the more frequent cystic lesion (~60% frequency) and comprises multiple large cysts (2–10 cm) or a single dominant cyst. In this case, cysts are lined by ciliated pseudostratified columnar epithelium, and the walls are composed of fibromuscular connective tissue with cartilage presence, in some cases. CPAM type 2 lesion (~20% frequency) consists of smaller cysts (0.5–2 cm) with a sponge-like appearance. Cystic structures are lined by ciliated cuboidal or columnar epithelium, and walls are formed by a small portion of fibromuscular connective tissue. CPAM type 3 (~10% frequency) is characterized by multiple microscopic cysts (0.5 cm) with an adenomatoid appearance, resembling a bronchiolar structure. The more recently added subtypes are CPAM type 0 and type 4. CPAM type 0 (~2% frequency), also known as acinar dysplasia, consists of solid lesions with tracheal or bronchial-like structures composed of cartilage and smooth muscle. Lastly, CPAM type 4 (~10% frequency) or distal acinar-alveolar malformation consists of varying-sized cysts lined by type 1 and type 2 alveolar cells. All five CPAM subtypes originate from different locations of the pulmonary airway structure, from proximal tracheobronchial (type 0) to bronchial/bronchiolar/alveolar (type 1, 2, 3), to distal acinar (type 4) [5][6][8].

To perform an antenatal practical evaluation of CPAMs, Adzick's classification system based on gross anatomy and sonographic appearance is widely accepted. This classification has a relevant degree of prognosis and distinguishes between microcystic and macrocystic lesions [9]. Macrocystic lesions are composed of a single or several large cysts (≥0.5 cm) and appear as fluid-filled structures in the ultrasound. On the other hand, microcystic lesions are smaller (≤0.5 cm), solid, and bulky. While microcystic lesions are associated with a poor prognosis due to associations with hydrops, macrocystic lesions usually have a more favorable prognosis [9]. Nonetheless, several other classification systems have been proposed throughout the years [10].

The pathogenesis of CPAM remains uncertain, although it is believed that defective airway proximo-distal patterning and abnormal lung branching are associated with pulmonary cysts formation [4][10]. Some authors consider CPAM a hamartomatous abnormality, while others hypothesize that CPAM is caused by a focal arrest of lung development during

different stages of branching morphogenesis. Numerous molecular mechanisms have been explored as potential contributors to CPAM etiology [8][10][11]. For instance, altered cellular processes such as increased cell proliferation and decreased apoptosis are typically associated with CPAM lesions [12]. The protein levels of cell adhesion molecules such as Integrin and E-cadherin are altered in CPAMs, suggesting uncharacteristic cytoplasmic signaling [13]. Platelet-derived growth factor (PDGF-BB) has maximal activity in the canalicular phase, stimulating lung growth by increasing proliferation but later, in the saccular stage, PDGF-BB action decreases. In utero resected CPAM lesions with rapid growth and associated hydrops show high PDGF-BB mRNA and protein expression levels. Moreover, PDGF-BB has a high and specific expression in the mesenchymal compartment of epithelial-lined cysts [14]. Glial Cell-Derived Neurotrophic Factor (GDNF) is expressed in the epithelial and endothelial compartments during lung organogenesis but is absent postnatally. Conversely, in postnatal resected CPAMs, GDNF is highly expressed in the epithelium suggesting a dysregulation of the GDNF signaling pathway [15]. Decreased mRNA and protein levels of Fatty Acid-binding Protein-7 (FABP-7) are observed in CPAM specimens compared to normal fetal lungs, suggesting a potential decrease in glucocorticoid response in CPAM lesions [16]. In addition, Clara Cell marker 10 (CC10) overexpression is observed in CPAM cysts [11]. Also, KRAS signaling and PI3K-AKT-mTOR pathway may play a role in the pathogenesis of CPAM lesions [17]. Increased protein expression of Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) is observed in postnatal CPAM, compared to normal lung, pointing to a role for the VEGF system in these congenital lesions [18].

An imbalance of early developmental markers is also observed in CPAMs. HOXB5 transcription factor is highly expressed during the pseudoglandular period. Nonetheless, the protein expression levels decrease in the canalicular phase and, in the alveolar phase, expression is negligible [19][20]. In CPAM lesions, HOXB5 protein expression levels are increased and present in the mesenchyme adjacent to abnormal branched airways, resembling a phenotype of earlier developmental stages [21]. Likewise, TTF1 is also crucial in regulating early lung development. In CPAM lesions, TTF1 presents differential expression patterns. In CPAM types 1 and 2 TTF1 expression pattern resembles typical pseudoglandular stage lungs. On the other hand, CPAM type 4 lesion presents TTF1 spatial distribution comparable to the canalicular stage [22]. Another study detected increased *hoxb5*, *ttf1*, and *fgf9* and decreased *fgf7* expression levels in fetal CPAM lesions, but no differences were noticed for *fgf10* and *fgfr2* in both fetal and postnatal CPAM lesions [23].

FGF10 is a mesenchymal growth factor critical for the epithelial-mesenchymal interactions that occur during lung branching. Rat fetal lung localized overexpression of *fgf10* at distinct developmental stages induces CPAM-like lesions. Depending on the localization/stage, *fgf10* overexpression induces macrocystic and microcystic malformations highly similar to those observed in humans [24]. Heterotopic overexpression of *fgf7* and *fgf10* and orthotopic expression of *fgf9* in transgenic mice disrupted pulmonary morphogenesis, pointing towards a role in cysts formation [25][26][27]. Moreover, mesenchyme-free epithelial explant cultures with FGF7 supplementation promoted epithelial proliferation, leading to the formation of cyst-like structures [28]. In addition, mouse microRNA-processing enzyme DICER mutant lungs result in upregulation of mesenchymal *fgf10* expression and, consequently, lung branching arrest and large epithelial pouches (cystic-like) [29]. This mechanism may involve intermediary *shh* downregulation [30][31]. Yin Yang 1 (YY1) transcription factor lung epithelial mutations cause abrogated mouse lung branching and airway dilation comparable to human CPAMs. This phenotype can be justified by reduced *shh* expression and subsequent upregulation of mesenchymal *fgf10* in an YY1-SHH-FGF10 molecular axis [30][31]. Epithelial cell-specific deletion of small GTPase *cdc42* in fetal mice disrupts epithelial cell polarity, proliferation, and mitotic spindle orientation, resulting in dilated respiratory tubules. This phenotype was accompanied by broader *fgf10* mesenchymal expression and decreased *shh* and *ptc1* (Cell Surface Transmembrane PATCHED 1) [32]. Combined deletion of *foxa1* and *foxa2* transcription factors disrupts pulmonary branching after E12.5 and result in the formation of large cysts at E15.5 and afterward. This morphological phenotype was associated with decreased *shh* expression [33]. Loss of WNT signaling receptor Frizzled 2 (*fzd2*) in the mouse lung epithelium causes large cysts formation in the distal region of the lung. Moreover, cysts formation was associated with decreased epithelial RhoA (Transforming Protein RhoA) signaling and no impact on WNT/β-Catenin signaling. Though, increased *fgf10* expression and decreased *fgfr2* and *shh* were observed [34]. Combined mutations of Histone Deacetylases *hdac1* and *hdac2* in the developing lung epithelium resulted in defects in branching morphogenesis and cysts formation in mouse E12.5 lungs [35]. E18.5 mouse lungs with epithelial *bmpr1a* (Bone Morphogenetic Protein Receptor Type 1A) deletion develop dramatic defects, with lungs containing large-fluid spaces [36]. Similar phenotypes occur under mouse conditional deletion of the proto-oncogene *mycn* [37]. Conditional mutation of the HIPPO pathway effector *yap* also results in dilated cyst-like structures [38]. *sox2* gene has a critical role during lung branching morphogenesis. *sox2* is expressed in non-branching regions and absent from branching sites. Overexpression of SOX2 in mouse lung epithelium disrupts branching morphogenesis and results in cystic-like structures. This data suggests that forced proximal epithelial differentiation leads to the CPAM phenotype [39]. Modulating the timing of ectopic *sox2* expression of branching regions results in cystic lesions that resemble the spectrum of human CPAMs [40]. Embryonic airway epithelial markers SOX2 and TTF1 are also present in adult human CPAMs, resembling the epithelial

expression of the developing lung. Additionally, the Retinoic Acid signaling component Retinal Dehydrogenase 1 (RALDH1) shows weak expression in adult CPAM lesions [41]. In mouse epithelial-specific studies, both gain and loss of function of *sox9* gene resulted in cystic-like structures at distal epithelial branch tips [42]. Transgenic Notch signaling misexpression in lung mice prevents the differentiation of alveolar cell types and results in distal abnormal cysts, which express typical proximal markers. Such data suggests defective proximal-distal patterning [43]. While many studies focus on the epithelial compartment, recent data revealed that CPAM lesions also impact the adjacent mesenchymal tissues with alterations in airway smooth muscle cells and extracellular protein products such as elastin [44]. Although significant advances have been made in understanding the molecular basis of CPAM, the pathogenesis of this congenital defect remains quite unknown. Still, CPAM is considered a unique model to study the molecular pathogenesis of isolated structural birth defects [17].

Considerable progress has been made in the diagnosis and treatment of CPAM lesions. However, the management of CPAM is still a matter of debate. Prenatal diagnosis of CPAM is crucial for the supervision of patients in the prenatal and postnatal periods. Most abnormal lung lesions are detected as early as the 20th week of gestation. Fetal ultrasonography is usually used to detect lesions' growth and potential complications and allows the calculation of the CPAM volume ratio (CVR), a value used to predict the prenatal course. When ultrasound is unreliable or inconclusive, evaluation is performed by Magnetic Resonance Imaging (MRI). Frequently, CPAMs tend to increase in size until the 28th gestational week, reach a plateau, and then start to regress. Fetal intervention is necessary when there is a persistent mediastinal shift and/or hydrops develops. CPAM prenatal interventions include systemic corticosteroid therapy, thoracoamniotic shunts or single-needle thoracentesis, and fetal lobectomy by minimally invasive procedures or open surgery [4][10][45][46]. Most babies require respiratory support at birth, and postnatal examinations combine several imaging methods such as Computed Tomography (CT) and X-ray. The exact optimal time for surgery is still inconclusive, but early interventions are recommended in symptomatic offspring. Neonatal resection is recommended for symptomatic patients, while asymptomatic resection remains controversial. There are three general indications to operate in asymptomatic cases: risk of malignancy, risk of complications (such as the risk of infection and pneumothorax), and potential for compensatory lung growth with earlier resection. The optimal operative management methods use minimally invasive approaches, with thoracoscopic techniques adopted over traditional thoracotomy [4][45][46][47]. According to the existing data, no apparent decrease in lung function is observed after surgery in the short term. As for the long term, children who undergo surgery display normal exercise tolerance and similar quality of life compared to otherwise healthy children [4].

2. Bronchopulmonary Sequestration

Bronchopulmonary sequestration (BPS) is a rare congenital malformation of the lower respiratory tract characterized by a non-functioning mass of lung tissue with an anomalous arterial supply from systemic circulation (usually the aorta) not involved in lung oxygenation [48]. In this disorder, embryonic pulmonary tissue detaches from the tracheobronchial tree and then degenerates into a cyst alongside the normal developing lung. Concurrently, an abnormal connection between this cystic structure and systemic circulation occurs [49]. BPS is classified as intralobar (ILS) or extralobar (ELS), depending on their location in the lung [50]. ILS is located inside a normal pulmonary lobe and shares a common pleura. In opposition, ELS is separated by the visceral pleura and forms a separate lobe [51]. Moreover, ELS is often linked with other congenital malformations, including congenital diaphragmatic hernia (CDH), congenital bronchopulmonary foregut malformations, CPAM, congenital heart disease, pulmonary hypoplasia, vertebral anomalies, and colonic duplication [50].

Bronchopulmonary sequestration accounts for 1.1% to 1.8% of all congenital bronchopulmonary anomalies. Intralobar cysts are more common, predominantly on the left lower lobe, and are frequently diagnosed in adolescent or adult patients; failure of earlier diagnosis can lead to repeated pneumonia and hemoptysis [52][53][54][55]. Conversely, ELS is a disease confined to neonates because of the high frequency of concomitant congenital abnormalities [56][57]. Pulmonary sequestration is not believed to be familial; however, some rare cases point to the possibility of a genetic predisposition for this condition [58][59].

Human studies have established that both types of BPS are commonly associated with CPAM [60][61][62][63]. The aberrant features of BPS and CPAM lesions are thought to be due to alterations in cell adhesion mechanisms that lead to atypical cell migration and proliferation during early lung branching morphogenesis. In fact, altered α2β1-integrin signaling triggers alterations in cell-cell adhesion and, consequently, changes in epithelial cell migration and cell proliferation [13]. In addition, β1-integrin signaling is essential for the migration of epithelial cells during lung development [64]. It has been demonstrated that abnormal Hoxb5 regulation triggers alterations in branching, such as the formation and persistence of immature and dysfunctional tissue, and is associated with BPS [21][65]. Additionally, in BPS, there is a decrease in α2-integrin protein levels, which is consistent with HOXB5 downregulation and its well-known role as a regulator of integrins and E-cadherins [66].

In the past, BPS malformations were thought to be rare and were mainly seen in autopsy cases, associated with other developmental abnormalities such as CDH, hydrops, and polyhydramnios. Nowadays, BPS is identified on prenatal ultrasound, and fetus outcome depends on the location of the lesion. Lesions located below the diaphragm usually have a more favorable prognosis, while intrathoracic lesions are commonly correlated with poor prognostic due to associations to hydrothorax, which can lead to fetal hydrops, polyhydramnios, and fetal death. In this case, a thoracoamniotic shunting may be required [67]. Postnatal complications, such as respiratory distress, infection, intrathoracic bleeding, hemoptysis, cardiac failure, and the potential risk of malignancy require early surgical excision.

3. Bronchogenic Cyst

Bronchogenic cyst (BC) is a developmental anomaly that results from abnormal budding of the primitive foregut. BCs are isolated choristomas characterized by closed respiratory epithelium-lined sacs with walls composed of cartilage. Other bronchial structures can also be found in BCs, such as smooth muscle and mucous glands. BC lesions are typically unilocular and fluid or mucus-filled. Though they can locate anywhere along the foregut, they are frequently localized in the mediastinum, adjacent to the carina region. BCs can also arise in the lung parenchyma, but no communication occurs with the airways [5][45][68].

The molecular mechanisms underlying BCs are still unknown. However, it is believed that abnormal growth of the upper gastrointestinal and respiratory tracts contributes to this condition. Moreover, BCs are not typically associated with genetic or chromosomal differences [69].

Bronchogenic cysts rarely require prenatal intervention. However, occasionally, they become large and cause complications, such as external compression and resulting hydrops. Prenatal interventions to remove BC lesions include thoracentesis or thoracoamniotic shunts to relieve fluid accumulation; resection is only necessary for rare complications. Nonetheless, removing BCs in the postnatal period is preferred considering the high risk of infection associated with prenatal procedures. Still, BCs always need to be removed due to the risk of becoming malignant [5][45][68].

When asymptomatic and not detected by prenatal ultrasound, BC lesions are only detected postnatally due to an infection or mass-related symptoms (congenital lobar overinflation, dysphagia, hemothorax, respiratory distress, dyspnea, recurrent pneumonia, or hemorrhage). Correct diagnosis using X-ray, CT, and MRI and subsequent management are crucial since BCs can become malignant. Postnatal treatment consists of surgical enucleation or resection by lobectomy using Video-Assisted Thoracoscopic Surgery (VATS) whenever possible. Definite diagnosis is determined by histopathology, and recurrence is improbable after complete resection [5][45][68][70]. Children with bronchogenic cysts have normal lung function after lesions removal [69].

4. Congenital Diaphragmatic Hernia

Congenital Diaphragmatic Hernia (CDH) is a congenital condition, with a prevalence rate between 1 in 2500–3000 live births [71]. CDH is characterized by a defect in the diaphragm that leads to the protrusion of the abdominal content into the thoracic cavity, impacting lung growth and development [72]. Human diaphragm development starts approximately at the fourth week of gestation, and by week 12, it is already fully formed. Closure of the diaphragm occurs typically around the eighth week of gestation, and sealing of the left side occurs one week later than the right side [73][74]. Based on the anatomical position of the defect, CDH can be classified into the posterolateral (Bochdalek hernia), anterior (Morgagni hernia), and central hernia [74][75]. In CDH, abnormal pulmonary development is characterized by decreased terminal branching leading to hypoplasia, reduced gas exchange area, thickened alveolar walls, and increased interstitial tissue. Concurrently, the pulmonary circulation is also profoundly affected, triggering persistent pulmonary hypertension, contributing to higher mortality and morbidity [76]. Consequently, babies with CDH often suffer from cardiorespiratory failure at birth [77].

The pathogenesis of CDH is still not fully understood. Chromosomal anomalies such as aneuploidies, structural rearrangements, copy number variants, single-gene mutations, and monogenic syndromes contribute to the heterogenic etiology of CDH [78][79]. Nonetheless, only 30% of the CDH cases have been associated with genetic factors and, for this reason, several animal models have been used to study this condition. Teratogenic and genetic rodent models have contributed to disentangling CDH pathophysiology and unravelling the molecular mechanisms underlying lung underdevelopment and diaphragmatic defect. On the other hand, large experimental animal models (sheep and rabbit) have been valuable to improve surgical approaches and prenatal therapies [76][80][81].

One of the most used teratogenic models is the mouse/rat nitrofen model. Nitrofen is an herbicide (considered a 2B class carcinogen) that disrupts critical pathways for diaphragm development, lung branching morphogenesis, and alveolar differentiation, mimicking human CDH defects [80][81]. Data obtained from the nitrofen model revealed that pulmonary hypoplasia could be settled without the diaphragmatic defect. These findings lead to the proposal of the *dual-hit hypothesis*, which explains lung hypoplasia in CDH as the result of two independent developmental insults: an early insult that occurs before diaphragmatic closure and a late insult that follows the appearance of the diaphragmatic defect and, consequently, herniation of abdominal organs into the thoracic cavity [82][83].

The molecular characterization of the nitrofen model revealed that nitrofen targets several steps/components of RA signaling. For instance, it inhibits retinal dehydrogenase 2 activity (RALDH2), a key enzyme in the RA synthetic pathway, and downregulates the retinol storage enzyme, lecithin:retinol acyltransferase (LRAT), and the RA-degrading enzyme CYP26. At the genomic level, it causes mutations in the STRA6 membrane receptor for serum retinol and deletions on the 15q chromosome, which contains the encoding gene for a cellular retinoic acid-binding protein (CRABP1). Conversely, antenatal administration of RA to the nitrofen model clearly reduced CDH incidence [84][85]. Furthermore, human studies detected low retinol levels in infants diagnosed with CDH compared to non-CDH babies [86][87]. In summary, it seems that a disruption in the RA pathway could be responsible for the morphological changes seen in CDH [76][81][88][89][90].

Lung development requires a synchronized pool of several growth factors/signaling pathways to give rise to a fully functional organ. Alongside RA, other signaling pathways underlying early and late pulmonary epithelial differentiation and mesenchymal development, such as FGF, BMP, WNT, are downregulated in the nitrofen-induced CDH model, thus contributing to lung hypoplasia [88]. In some cases, these findings have been corroborated with human data from amniotic fluid [91] or lung tissue [92][93]. Additionally, transcription factors and ECM components also contribute to the etiology of diaphragmatic defects and associated lung abnormalities. For instance, GATA4, a retinoic acid-inducible transcription factor, is essential for diaphragm and lung organogenesis. Hence, the lack of GATA4 during mouse development causes CDH [94][95]. Concurrently, knockout mice for NR2F2 (formerly called COUP-TFII) and ZFPM2 (also known as FOG2), both modulators of RA transcriptional activity, exhibit diaphragmatic hernia and lung hypoplasia [96][97]. Ablation of several other RA-dependent transcription factors such as WT1, SOX7, GATA6, and MYRF leads to CDH development, causing different types of herniation and pulmonary underdevelopment [98][99][100][101]. GLI, KIF7, and PBX1 knockout mice have revealed a role for SHH signaling in CDH [102][103][104]. Knockout mice for SLIT3, ROBO1, GPC3, NDST1, FREM1, FRAS1, and FREM2 uncovered their function in different aspects of normal diaphragm development [76][81][105].

More recently, epigenetic alterations, particularly microRNAs, have been associated with CDH pathophysiology. Several miRNAs have been associated with different lung developmental stages [106]. In the CDH context, miR-200b is upregulated in both human and animal samples. Moreover, tracheal fluid from CDH survivor babies that underwent FETO (fetoscopic endoluminal tracheal occlusion) exhibited elevated levels of miR-200b when compared to non-survivors [107][108]. Furthermore, the same group demonstrated that miR-200b prenatal treatment reduces the incidence of CDH defects in the nitrofen model [109]. The authors suggest that this upsurge in miR-200b levels may result from compensatory mechanisms to promote lung maturation [110].

Despite the relatively low prevalence rate of this congenital condition, the mortality rate is considerably high. Long-term outcomes depend on the characteristics of the diaphragmatic defect [72][111], and CDH survivors have a high risk of long-term morbidities and a lower quality of life. CDH lesions can be identified by ultrasonography around the 22–24th week of gestation; prenatal MRI can also be performed to predict prenatal course [73]. Fetal interventions, such as FETO, have been associated with increased survival among some CDH-infants; however, studies are still ongoing to further determine patient risk/benefit [111][112]. Postnatal surgical intervention to repair the diaphragmatic effect is required, and the surgical approach depends on the size/type of defect. However, babies born with CDH exhibit life-threatening pulmonary hypertension that needs to be resolved before surgery. Lung-protective ventilator strategies or “gentle ventilation”, extracorporeal membrane oxygenation (ECMO), and cardiopulmonary pre-operative stabilization are strategies currently used to tackle hypertension and improve patient outcomes [113][114][115].

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