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Airway tissue engineering for congenital laryngotracheal disease

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ABSTRACT

Regenerative medicine offers hope of a sustainable solution for severe airway disease by the creation of functional, immunocompatible organ replacements. When considering fetuses and newborns, there is a specific spectrum of airway pathologies that could benefit from cell therapy and tissue engineering applications. While hypoplastic lungs associated with congenital diaphragmatic hernia (CDH) could benefit from cellular based treatments aimed at ameliorating lung function, patients with upper airway obstruction could take advantage from a de novo tissue engineering approach. Moreover, the international acceptance of the EXIT procedure as a means of securing the precarious neonatal airway, together with the advent of fetal surgery as a method of heading off postnatal co-morbidities, offers the revolutionary possibility of extending the clinical indication for tissue-engineered airway transplantation to infants affected by diverse severe congenital laryngotracheal malformations. This article outlines the necessary basic components for regenerative medicine solutions in this potential clinical niche.

Clinical background

Tracheal failure is devastating in any patient group but is particularly emotive within the neonatal population. Structural congenital anomalies (Table) are the most common cause of airway obstruction and insufficiency in this period,[1] with malformations forming a spectrum of severity affecting any portion of the upper respiratory tract from face to bronchi.[2] Although complete congenital laryngotracheobronchial obstruction is rare—the European Organization for Rare Diseases reports the prevalence of tracheal agenesis to be around 1 in 100,000 births—these anomalies are universally lethal without intervention.

Presentation and diagnosis of extreme laryngotracheal birth defects usually occurs following routine prenatal ultrasound scanning with confirmation by in utero MRI,[3] but can present later with immediate respiratory distress at birth. Without immediate surgical intervention, the lack of a patent proximal airway is unsurvivable unless a bypassing pathway exists for intubation of the bronchi via associated broncho-esophageal fistulae. Fortunately, rates of prenatal diagnosis are improving allowing planned delivery via the EXIT procedure, where a precarious neonatal airway may be salvaged or established de novo via anesthetic techniques or tracheostomy prior to cutting the umbilical cord.[4] An increasing number of children are being born alive with previously “unsurvivable” airway defects, with the clinical team's intention to treat by subsequent airway reconstructive procedures (Figure 1).

Anatomical malformations of the fetal trachea may occur in association with a constellation of other mediastinal abnormalities; cardiac, vascular, and esophageal malformations are particularly common. Definitive surgical correction of the trachea requires careful timing and coordination between otolaryngology, cardiothoracics, obstetrics, pediatric surgery, and neonatal intensive care for maximal chances of survival.[5] In some cases, babies with proximal airway anomalies are also found to have an underlying chromosomal abnormality.[6–8] The argument for pre- and

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Table
Examples of congenital anomalies leading to severe pediatric airway insufficiency.

Anomaly	Examples of conditions
Congenital high airway obstruction syndrome (CHAOS)	Laryngeal or tracheal agenesis Laryngeal webs or cysts Congenital neck masses, for example, cystic hygromas, teratomas
Abnormal aerodigestive tract connections	Type IV laryngeal clefts Tracheo-oesophageal fistulae
Extrinsic mediastinal compression	Vascular ring or sling
Stenosis of the trachea and/or bronchi	Complete tracheal rings
Poor tracheal quality	Tracheomalacia (in isolation or downstream of airway stenosis)

perinatal treatment of these children is even more nebulous given the potential presence of other underlying unsurvivable co-morbidities, and for this reason chromosomal and genetic testing via amniocentesis provides vital information for counseling parents on treatment options.

Despite perinatal intervention, death is sadly inevitable for many of these babies for two main reasons. The first of these is the in utero development of secondary severe congenital lung disease. Without a patent connection between mouth and lungs to provide a route of escape, the constant production of lung fluid over-distends the lungs throughout gestation, leading to congestive heart failure in the fetus (hydrops).[9] In cases of extensive tracheo-esophageal connections or CDH, the opposite problem where babies are born with hypoplastic lungs may also occur because the fetus has been unable to generate intra-pulmonary negative pressure in utero.[10] Fetal surgical techniques have gained acceptance in a variety of conditions including CDH,[11,12] and fetal tracheostomy is gaining momentum as a viable treatment option to relieve tracheal obstruction in some fetal surgical centers.[13]

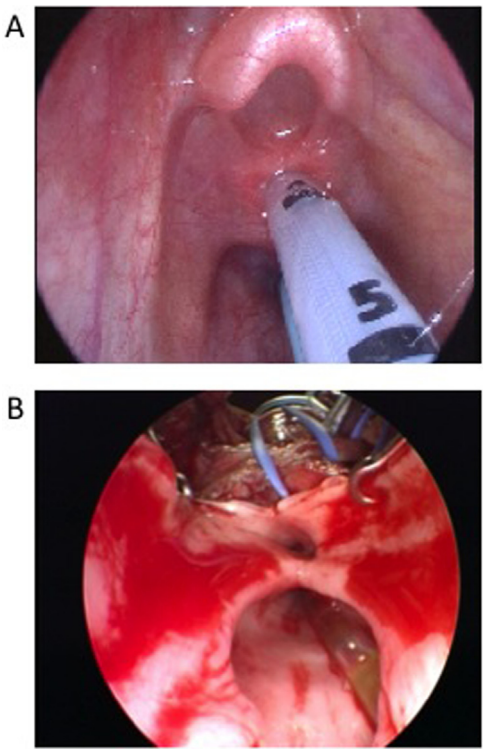

Fig. 1. Severe congenital airway defects; (A) laryngeal agenesis viewed at bronchoscopy. (B) Type IV laryngeal cleft viewed at open repair surgery.

The second, as-yet insurmountable, obstacle to survival occurs if insufficient salvageable trachea exists to reconstruct a functional airway. Anterior augmentation surgery, for example using tracheal donor allografts,[14] has been largely superseded by the highly successful slide tracheoplasty technique,[15,16] but resections are still limited to 30% of the total tracheal length.[17] Stents may be of help in cases of malacia and recurrent stenosis, but carry a large inherent morbidity.[18] Nevertheless, existing treatments fail or are insufficient in a small proportion of babies who therefore require whole-scale tracheal replacement. Tracheal replacement by conventional organ transplantation has generally not been possible in the neonatal setting, due to the paucity of appropriate-sized donor organs and the generally poor condition of donor tracheae following prolonged end-of-life intubation and ventilation.[14] The decision to subject a child to the accompanying lifelong immunosuppression with its multiple risks and co-morbidities would also not be taken lightly.

Concept of tissue engineering

Tissue engineering unites the fields of cell biology, materials science and engineering toward a common goal of creating substitutes to repair, replace or regenerate tissues and organs.[19] The basic principle is to create a biocompatible scaffold in which growth of the patient's cells can be encouraged, either by seeding prior to implantation or by subsequent recruitment into the scaffold in its in vivo position. The prerequisite for the graft to be free from immunogenicity is another key objective of tissue engineering as a personalized therapy and distinguishes the field from conventional transplantation where immunosuppression is required to prevent rejection.

Tissue-engineered trachea could be of particular value in the context of a prenatal tracheal diagnosis because an organ replacement could be built to individual fetal dimensions during gestation, ready for use in the perinatal or immediate postnatal period (Figure 2).

The trachea was initially considered, perhaps naively, to be a convenient “starter organ” on which to concentrate tissue engineering efforts, due to its relatively simple anatomy as a hollow air-conduction organ with no moving parts.[20] However, early attempts in animals to replace the trachea with simple silicon, Dacron or metal[21,22] tubes proved disastrous, as the trachea occupies a frontline immunological position with the body's external environment. The pseudostratified ciliated epithelium of the proximal airways is highly specialized to trap and remove inhaled pathogens and debris, and lack of a functional mucociliary escalator post-transplantation is therefore highly problematic. Establishment of a blood supply is essential for epithelialization of any graft, but with a finely segmental native blood supply in place of a vascular pedicle amenable to anastomosis, bioengineered tracheal grafts are relatively slow to establish connections capable of supporting cell growth and integration with host tissues. Notwithstanding these issues, tracheal tissue engineering raises fewer potential ethical objections as an experimental therapy than in other clinical niches, given the total lack of alternative treatment options, and the greater intrinsic regenerative potential of pediatric patients compared to adults increases the likelihood of success. As such, regenerative approaches in the trachea have outstripped other organs in terms of high profile clinical compassionate cases both in adults,[23] and in children.[24,25]

Organ scaffolds

Scaffold design, to create a framework on which cells can engraft and differentiate, is a core component of tissue