To cite this article: Kumbasar U, Dikmen E, Uysal S. Tissue engineering in the treatment of congenital diaphragmatic hernia. Turk Clin Lab 2017; 8(3): 124-129.

Review

Tissue engineering in the treatment of congenital diaphragmatic hernia

Konjenital diyafragma herni tedavisinde doku mühendisliği

Ulaş KUMBASAR[1], Erkan DİKMEN[1], Serkan UYSAL[2*]

[1]Department of Thoracic Surgery, Hacettepe University, Faculty of Medicine, Ankara,
[2]Department of Thoracic Surgery, Bülent Ecevit University, Faculty of Medicine, Zonguldak, TURKEY

ABSTRACT

Congenital diaphragmatic hernia (CDH) is one of the most common major congenital anomalies and is described as the presence of a diaphragmatic defect that leads the herniation of abdominal organs into the chest. Although advanced treatment strategies are introduced over the recent years, they have not really improved the survival rate which stayed at around 70%. Major determinants of poor outcome in CHD are pulmonary hypoplasia and pulmonary hypertension. Various surgical interventions and novel medical therapies are attempted to improve lung function and survival but remains less than desired. Repair of the diaphragmatic defect with prosthetic materials was found to be associated with high rates of complications and recurrences during follow-up. Therefore, regenerative medicine should be considered as an alternative treatment strategy in CDH both by inducing cellular function in the hypoplastic lungs (stem cell therapy) and by developing a functional myogenic patch (tissue engineering). Nearly 30% of infants who have CDH born with severe pulmonary hypoplasia and hypertension which may lead to respiratory failure and prompt mechanical support, since the survival of these newborns relate to the degree of pulmonary hypoplasia, accurate prenatal evaluation of this degree is of paramount importance. The two main diagnostic tools which could be used for this purpose are prenatal ultrasound (US) and magnetic resonance imaging (MRI). Various prenatal treatment strategies have been tried to cure pulmonary hypoplasia and hypertension in CDH. Vitamin A, corticosteroids, antioxidants such as vitamin C, E, N-acetylcystein, phosphodiesterase inhibitors, glucagon-like peptide 1 agonists and tyrosine kinase inhibitors have all been analyzed in animal studies and demonstrated variable results. Since there are very few human studies, further researches should be performed in humans confirming the clinical benefit of these therapies. Due to the advancements in prenatal screening methods, we, now have the ability to detect most of the major genetic disorders in gestation and have chance to provide optimal treatment strategy in the postnatal period. Results of the animal studies regarding the application of regenerative medicine for treatment of children with CDH are encouraging. Hopefully, with the support of further studies focusing especially on safety and ethical issues, the near future will provide us the evidence necessary for their application in our clinical practice.

Keywords: congenital, diaphragmatic hernia, tissue engineering,

Corresponding Author*: Serkan UYSAL, MD. Department of Thoracic Surgery, Bülent Ecevit University, Faculty of Medicine, A Blok 2. Kat Kozlu, Zonguldak, TURKEY
Phone:0090532 408 74 81 e-mail: drsuysal@msn.com
Received 05.02.2017 accepted 14.03.2017
Doi. 10.18663/tjcl. 289871

Volume 8 Number 3 p: 124-129

ÖZ

Doğumsal diyafragmatik herni (CDH), en sık karşılaşılan konjenital anomalilerden biri olup abdominal organların göğsüne herniyasyonuna neden olan diyafram kusurunun varlığı olarak tanımlanmaktadır. Son yıllarda ileri tedavi stratejileri getirilmesine rağmen hayatta kalma oran, % 70 civarında kalmışve geliştirilememiştir. KKH'de kötü sonuçların başlıca belirleyicileri pulmoner hipoplazi ve pulmoner hipertansiyondur. Akciğer fonksiyonlarını ve sağkalımı geliştirmek için çeşitli cerrahi müdahaleler ve yeni tıbbi tedaviler denmektedir, ancak istenilen seviyeden daha az orandadır. Protez materyali ile diyafragma defektinin onarımının, takip sırasında yüksek komplikasyonlar ve rekürrens oranları ile ilişkili olduğu tespit edilmiştir. Bu nedenle, rejeneratif ilaç hem hipoplazi akciğerlerde hücresel fonksiyonu indükleyerek (kök hücre tedavisi) hem de işlevsel bir miyojenik yama (doku mühendisliği) geliştirerek, CDH'de alternatif bir tedavi stratejisi olarak düşünülmektedir.Solunum yetmezliğine sebep olan ciddi pulmoner hipoplazi ve hipertansiyon ile doğan CDH'li yenidoğanların yaklaşık % 30'unun hayatta kalması pulmoner hipoplazi derecesi ile ilişkili olduğundan, bu dereceyi prenatal olarak değerlendirmek büyük önem taşır. Prenatal ultrasonografi (US) ve manyetik rezonans görüntüleme (MRI) iki ana tanı aracıdır. CDH'de pulmoner hipoplazi ve hipertansiyonu iyileştirmek için çeşitli doğum öncesi tedavi stratejileri denendi. Vitamin A, kortikosteroidler, C vitamini, E, N-asetilsistein, fosfodiesteraz inhibitörleri, glukagon benzeri peptit 1 agonistleri ve tirozin kinaz inhibitörleri gibi antioksidanlar hayvan çalışmalarında analiz edildi ve değişken sonuçlar gösterdi. İnsanlar üzerinde çok az çalışma olduğu için, bu terapilerin klinik yararlarını teyit edebilmek için ileri aşama araştırmalar insanlar üzerinde olmalıdır. Doğumdan sonra bebeğe destekleyici tedavisinin yanı sıra solunum yetmezliği durumunda tercihen yüksek frekanslı salınımlı ventilasyon ile solunum desteği de uygulanmalıdır. Eksojen kök hücreler, özellikle AFS hücreleri akciğer gelişimini hem çeşitli pulmoner hücre tiplerine entegre ederek, hem de anti-inflamatuvar ve immünomodülatör etkiler yoluyla parakrin modele göre veya doğal progenitör hücreleri aktive ederek geliştirebilir. Ancak, akciğer hasarının altında yatan mekanizmayı ve kök hücrelerin moleküler tepkisini anlamak için, özellikle de insanlarda yapılacak daha ileri araştırmalara ihtiyaç vardır. Doğum öncesi tarama yöntemlerindeki ilerlemeler sayesinde, artık gebelikteki en büyük genetik bozuklukların çoğunu tespit etme ve postnatal dönemde optimal tedavi stratejisi sunma olanaği bulunmaktadır. CDH'li çocukların tedavisinde rejeneratif tıbbın uygulanmasına ilişkin hayvan çalışmalarının sonuçları gelecek vadetmektedir. Yakın gelecekte özellikle güvenlik ve etik konular çerçevesinde yoğunlaşan daha ileri çalışmaların desteğiyle, klinik olarak uygulanması için gerekli kanıtlar bu çalışmalar ile sağlanacaktır.

Anahtar Kelimeler: doğumsal, diyafragma hernisi, doku mühendisliği

Introduction

Although perinatal care and treatment options progress in the last decades, congenital malformations are still causing major morbidity and mortality [1]. The aim of regenerative medicine is to restore damaged organs by repairing and/or replacing involving cells and tissues. The two main approaches in regenerative medicine are; stem cell therapy, which means stimulating regeneration by injecting functional cells into the damaged site, and tissue engineering defined as formation of new tissues by using biocompatible materials [2].

Congenital diaphragmatic hernia (CDH) is one of the most common major congenital anomalies and is described as the presence of a diaphragmatic defect that leads the herniation of abdominal organs into the chest [3]. Although advanced treatment strategies are introduced over the recent years, they have not really improved the survival rate which stayed at around 70% [4, 5]. Major determinants of poor outcome in CHD are pulmonary hypoplasia and pulmonary hypertension. Various surgical interventions and novel medical therapies are attempted to improve lung function and survival but remains less than desired. In addition, repair of the diaphragmatic defect with prosthetic materials was found to be associated with high rates of complications and recurrences during follow-up [6-8]. Therefore, regenerative medicine should be considered as an alternative treatment strategy in CDH both by inducing cellular function in the hypoplastic lungs [stem cell therapy] and by developing a functional myogenic patch [tissue engineering] [9-12]. We herein review these two popular therapeutic strategies in scope of the latest developments in this topic.

Pulmonary hypoplasia

Nearly 30% of infants who have CDH born with severe pulmonary hypoplasia and hypertension which may lead to respiratory failure and prompt mechanical support [13]. Since the survival of these newborns relate to the degree of pulmonary hypoplasia, accurate prenatal evaluation of this degree is of paramount importance.

Diagnosis

The two main diagnostic tools which could be used for this purpose are prenatal ultrasound (US) and magnetic resonance imaging (MRI). Various US parameters have been identified to foresee the extent of pulmonary hypoplasia such as lung-to-head ratio, total fetal lung volume and the position of the liver and

stomach [14, 15]. Commonly used MRI measurements, that have higher sensitivity and specificity for estimating the degree of pulmonary hypoplasia, include total fetal lung volume, predicted lung volumes and liver herniation percentage [16-18].

Prenatal pharmacologic management

Various prenatal treatment strategies have been tried to cure pulmonary hypoplasia and hypertension in CDH. Vitamin A [19], corticosteroids [20, 21], antioxidants such as vitamin C, E, N-acetylcystein [22], phosphodiesterase inhibitors [23], glucagon-like peptide 1 agonists [24] and tyrosine kinase inhibitors [25] have all been analyzed in animal studies and demonstrated variable results. Since there are very few human studies, further researches should be performed in humans confirming the clinical benefit of these therapies [26, 27].

Postnatal management

Apart from the supportive therapy of the infant after birth, respiratory assistance preferably with high-frequency oscillatory ventilation, should be implemented in case of respiratory failure [3, 28]. Extra-corporeal membrane oxygenation (ECMO) can be considered as an option when the respiratory failure is severe until proper gas exchange is achieved. However, since there is poor evidence regarding the benefits of ECMO in CDH, it should mainly be used in patients for whom lung hypoplasia would cause inadequate gas exchange or severe circulatory failure [3, 29].

Surgical repair of CDH is not advised before cardio-respiratory functions become stable. The herniated abdominal organs are placed back into the abdomen and the diaphragmatic defect is closed either primarily or with a prosthetic patch via a subcostal or transverse abdominal incision [30]. Minimally invasive approaches via thoracoscopy or laparoscopy are alternative options in infants with less severe symptoms [31, 32].

Stem cell therapy

Regeneration of the hypoplastic lungs of the infants with CDH by using stem cell therapy has gained popularity in recent years. The lungs continue to develop during postnatal life and have extensive repair and regeneration capability after destruction [33]. Thus, early intervention with cellular based therapies can induce parenchymal development by increasing the number and size of bronchopulmonary segments in patients with hypoplastic lungs and may restore normal function. Lung development is stimulated by exogenous stem cells through two main mechanisms. They may integrate and differentiate, or induce resident stem cells by paracrine actions [34, 35]. Resident stem cell activation seems to be more successful in regenerating the lung tissue compared to using a single exogenous cell source [36]. Recently, De Coppi and Deprest investigated different kind of stem cells including basal cells, multipotent lung stem cells and multipotent cells which expresses tyrosine kinase c-kit, which all may have the ability to generate different niches in postnatal lung [1]. Among these, the most promising progenitor was found to be multipotent, clonogenic and self-renewing lung stem cells represented by tyrosine kinase c-kit expression as they have the ability to generate bronchiolar, alveolar and pulmonary vessel tissue when injected in mice [35, 37]. Mesenchymal stem cells [MSC] are ideal cells which could be used in pulmonary hypoplasia in CDH due to their immunomodulatory potential [38, 39]. Also, Haaften et al demonstrated in their animal model that MSCs prevent arrested alveolar and vascular growth in part through their paracrine activity [40].

MSCs can be harvested from placenta, fetal bone marrow, cord blood, adipose tissue and amniotic fluid. Amniotic fluid sampling is routinely considered to detect chromosomal and genetic defects in CDH. Thus, using amniotic fluid-based stem (AFS) cells is more ethical than the obtaining samples from other sources. In addition, harvesting stem cells from the above mentioned alternative sources is more challenging and is associated with higher morbidity [39]. Moreover, AFS cells are less immunogenic, feasible for autologous cell-based therapy and available before birth [41]. Their mechanism of action and the potential pathways which activate the hypoplastic lungs have been investigated in many animal models [42, 43]. Pederiva et al showed that lung growth, bronchial motility, and innervation increased with AFS cell exposure in rats [44]. Recently, Di Bernardo et al showed in a nitrofen model that AFS cells induce fetal rodent lung growth by their paracrine action [45].

In summary, exogenous stem cells, especially AFS cells may improve lung development both by integrating and differentiating into various pulmonary cell types and by a paracrine fashion via anti-inflammatory and immunomodulatory effects or by activating the native progenitor cells. However, further studies, especially in humans, are needed to understand the underlying mechanism of lung damage and the molecular response of stem cells.

Tissue engineering for diaphragmatic repair

Rationale of tissue engineering

Although primary closure of the diaphragmatic defects is associated with low recurrence rate, it can be performed in nearly half of the patients. Defect size is considered to be the most significant surgical predictor of morbidity and mortality in CDH and also associated with longer ventilation duration and hospital stay [46, 47]. Repair of large defects could be performed with various surgical techniques including abdominal or thoracic muscle flaps, free facia lata grafts and different kinds of prosthesis (poly-propylene, poly-tetra-fluoro-ethylene (Teflon), Dacron, and others).

However, most surgeons do not prefer muscle flaps due to the residual defects left in the muscle source, complexity of the procedure and high morbidity [48]. Use of prosthesis for

diaphragmatic repair has been related with higher infection rate, more adhesions, more small bowel obstruction rate and most importantly high recurrence rate, as high as 40-50%, than primary repair [49-51].

The underlying mechanism of hernia recurrence in prosthetic repair is probably the traction and related detachment in the rapidly growing diaphragm of the infant [49]. Therefore, a cell based engineered graft which has the ability of remodeling over time may adapt the rapid growth of the diaphragm and become an ideal alternative for hernia repair.

Cell Sources

Tissue engineering consists of cells, a supportive 3D scaffold and a bioreactor. While, scaffolds consist of bioactive natural materials which does not have mechanical strength, synthetic materials do not have bioactivity, but are mechanically stronger. These two materials can be engineered and with addition of bioactive properties cellular growth can be achieved [52].

The first diaphragmatic repair by using an engineered construct was reported by Fauza and colleagues in 2001. In that animal study they were able to show that, unlike acellular grafts, engineered cellular diaphragmatic constructs are similar to normal muscle in terms of anatomic and histologic structure [53].

Muscular or tendinous constructs can be used for diaphragmatic repairs. Kunisaki et al compared these two options in their study and showed that tendinous grafts lead to improved structural outcomes when compared to alike muscular grafts [54]. The potential reasons of the preference of tendinous constructs are: (i) the residual diaphragm muscle will continue to grow over time; (ii) normally, most of the diaphragm is tendinous and (iii) function of the muscle construct may decline over time due to lack of innervation.

Fetal cells seem to be the best option that could be used for diaphragmatic engineering. Because; fetal cells (i) multiply more rapidly than postnatal cells, (ii) are more resistant to hypoxia, (iii) survive better through the refrigeration and cryopreservation processes, (iv) have ability to grow in vivo due to their angiogenic properties [55, 56]. There are several kind of fetal cell sources such as placenta, amniotic fluid, Wharton's jelly and umbilical cord blood. Among these amniotic fluid considered to be the safest source. AFS cells can be easily obtained during amniocentesis or birth. Throughout gestation MSCs can be obtained from small amounts of amniotic fluid [57-59]. If the need for patch repair can be foreseen via prenatal US or MRI, cells which are obtained by amniocentesis could be engineered to create an autologous muscle or tendon construct and used to repair the diaphragmatic defect in the postnatal period. Recently, Turner at al provided preclinical efficacy by demonstrating in their animal study that diaphragmatic repair by using autologous tendon engineered with amniotic mesenchymal stem cells improved outcomes with no local or systemic adverse effects [60].

In summary, according to the results of various animal models so far, diaphragmatic repair with tissue engineered constructs is safe and associated with better outcomes in comparison to acellular bioprosthesis [60-62].

As a conclusion due to the advancements in prenatal screening methods, we, now have the ability to detect most of the major genetic disorders in gestation and have chance to provide optimal treatment strategy in the postnatal period. Results of the animal studies regarding the application of regenerative medicine for treatment of children with CDH are encouraging. Hopefully, with the support of further studies focusing especially on safety and ethical issues, the near future will provide us the evidence necessary for their application in our clinical practice.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

References

1. De Coppi P. Regenerative medicine for congenital malformations. J Pediatr Surg 2013;48[2]:273-280.
2. Atala A. Regenerative medicine strategies. J Pediatr Surg 2012;47[1]:17-28.
3. Tovar JA. Congenital diaphragmatic hernia. Orphanet J Rare Dis 2012;7:1.
4. Rocha GM, Bianchi RF, Severo M et al. Congenital diaphragmatic hernia. The post-neonatal period. Part ii. Eur J Pediatr Surg 2008;18[5]:307-312.
5. Jeanty C, Kunisaki SM, MacKenzie TC. Novel non-surgical prenatal approaches to treating congenital diaphragmatic hernia. Semin Fetal Neonatal Med 2014;19[6]:349-356.
6. Nobuhara KK, Lund DP, Mitchell J, Kharasch V, Wilson JM. Long-term outlook for survivors of congenital diaphragmatic hernia. Clin Perinatol 1996;23[4]:873-887.
7. Waag KL, Loff S, Zahn K et al. Congenital diaphragmatic hernia: A modern day approach. Seminars in pediatric surgery 2008;17[4]:244-254.
8. Fauza DO. Tissue engineering in congenital diaphragmatic hernia. Seminars in pediatric surgery 2014;23[3]:135-140.
9. Jesudason EC, Connell MG, Fernig DG, Lloyd DA, Losty PD. Early lung malformations in congenital diaphragmatic hernia. J Pediatr Surg 2000;35[1]:124-127; discussion 128.
10. Fuchs JR, Kaviani A, Oh JT et al. Diaphragmatic reconstruction with autologous tendon engineered from mesenchymal amniocytes. J Pediatr Surg 2004;39[6]:834-838; discussion 834-838.

11. Montedonico S, Sugimoto K, Felle P, Bannigan J, Puri P. Prenatal treatment with retinoic acid promotes pulmonary alveologenesis in the nitrofen model of congenital diaphragmatic hernia. J Pediatr Surg 2008;43[3]:500-507.
12. Conconi MT, Bellini S, Teoli D et al. In vitro and in vivo evaluation of acellular diaphragmatic matrices seeded with muscle precursors cells and coated with vegf silica gels to repair muscle defect of the diaphragm. J Biomed Mater Res A 2009;89[2]:304-316.
13. Prendergast M, Rafferty GF, Milner AD et al. Lung function at follow-up of infants with surgically correctable anomalies. Pediatr Pulmonol 2012;47[10]:973-978.
14. Kitano Y, Okuyama H, Saito M et al. Re-evaluation of stomach position as a simple prognostic factor in fetal left congenital diaphragmatic hernia: A multicenter survey in japan. Ultrasound Obstet Gynecol 2011;37[3]:277-282.
15. Ruano R, Takashi E, da Silva MM, Campos JA, Tannuri U, Zugaib M. Prediction and probability of neonatal outcome in isolated congenital diaphragmatic hernia using multiple ultrasound parameters. Ultrasound Obstet Gynecol 2012;39[1]:42-49.
16. Barnewolt CE, Kunisaki SM, Fauza DO, Nemes LP, Estroff JA, Jennings RW. Percent predicted lung volumes as measured on fetal magnetic resonance imaging: A useful biometric parameter for risk stratification in congenital diaphragmatic hernia. J Pediatr Surg 2007;42[1]:193-197.
17. Walleyo A, Debus A, Kehl S et al. Periodic mri lung volume assessment in fetuses with congenital diaphragmatic hernia: Prediction of survival, need for ecmo, and development of chronic lung disease. AJR Am J Roentgenol 2013;201[2]:419-426.
18. Bebbington M, Victoria T, Danzer E et al. Comparison of ultrasound and magnetic resonance imaging parameters in predicting survival in isolated left-sided congenital diaphragmatic hernia. Ultrasound Obstet Gynecol 2014;43[6]:670-674.
19. Thebaud B, Barlier-Mur AM, Chailley-Heu B et al. Restoring effects of vitamin a on surfactant synthesis in nitrofen-induced congenital diaphragmatic hernia in rats. Am J Respir Crit Care Med 2001;164[6]:1083-1089.
20. Okoye BO, Losty PD, Fisher MJ, Wilmott I, Lloyd DA. Effect of dexamethasone on endothelial nitric oxide synthase in experimental congenital diaphragmatic hernia. Arch Dis Child Fetal Neonatal Ed 1998;78[3]:F204-208.
21. Taira Y, Miyazaki E, Ohshiro K, Yamataka T, Puri P. Administration of antenatal glucocorticoids prevents pulmonary artery structural changes in nitrofen-induced congenital diaphragmatic hernia in rats. J Pediatr Surg 1998;33[7]:1052-1056.
22. Gonzalez-Reyes S, Martinez L, Martinez-Calonge W, Fernandez-Dumont V, Tovar JA. Effects of antioxidant vitamins on molecular regulators involved in lung hypoplasia induced by nitrofen. J Pediatr Surg 2006;41[8]:1446-1452.
23. Shue EH, Schecter SC, Gong W et al. Antenatal maternally-administered phosphodiesterase type 5 inhibitors normalize enos expression in the fetal lamb model of congenital diaphragmatic hernia. J Pediatr Surg 2014;49[1]:39-45; discussion 45.
24. Romani-Perez M, Outeirino-Iglesias V, Gil-Lozano M, Gonzalez-Matias LC, Mallo F, Vigo E. Pulmonary glp-1 receptor increases at birth and exogenous glp-1 receptor agonists augmented surfactant-protein levels in litters from normal and nitrofen-treated pregnant rats. Endocrinology 2013;154[3]:1144-1155.
25. Ghofrani HA, Morrell NW, Hoeper MM et al. Imatinib in pulmonary arterial hypertension patients with inadequate response to established therapy. Am J Respir Crit Care Med 2010;182[9]:1171-1177.
26. Lally KP, Bagolan P, Hosie S et al. Corticosteroids for fetuses with congenital diaphragmatic hernia: Can we show benefit? J Pediatr Surg 2006;41[4]:668-674; discussion 668-674.
27. Frenckner B, Broome M, Lindstrom M, Radell P. Platelet-derived growth factor inhibition--a new treatment of pulmonary hypertension in congenital diaphragmatic hernia? J Pediatr Surg 2008;43[10]:1928-1931.
28. Fujino Y, Takezawa J, Nishimura M, Imanaka H, Taenaka N, Yoshiya I. High-frequency oscillation for persistent fetal circulation after repair of congenital diaphragmatic hernia. Crit Care Med 1989;17[4]:376-377.
29. Mugford M, Elbourne D, Field D. Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants. Cochrane Database Syst Rev 2008[3]:CD001340.
30. Clark RH, Hardin WD, Jr., Hirschl RB et al. Current surgical management of congenital diaphragmatic hernia: A report from the congenital diaphragmatic hernia study group. J Pediatr Surg 1998;33[7]:1004-1009.
31. Nguyen TL, Le AD. Thoracoscopic repair for congenital diaphragmatic hernia: Lessons from 45 cases. J Pediatr Surg 2006;41[10]:1713-1715.
32. Meehan JJ, Sandler A. Robotic repair of a bochdalek congenital diaphragmatic hernia in a small neonate: Robotic advantages and limitations. J Pediatr Surg 2007;42[10]:1757-1760.
33. Fung ME, Thebaud B. Stem cell-based therapy for neonatal lung disease: It is in the juice. Pediatr Res 2014;75[1-1]:2-7.
34. Angelini A, Castellani C, Ravara B et al. Stem-cell therapy in an experimental model of pulmonary hypertension and right heart failure: Role of paracrine and neurohormonal milieu in the remodeling process. J Heart Lung Transplant 2011;30[11]:1281-1293.
35. Anversa P, Kajstura J, Leri A, Loscalzo J. Tissue-specific adult stem cells in the human lung. Nat Med 2011;17[9]:1038-1039.
36. Garcia O, Carraro G, Navarro S et al. Cell-based therapies for lung disease. British medical bulletin 2012;101:147-161.
37. Kajstura J, Rota M, Hall SR et al. Evidence for human lung stem cells. The New England journal of medicine 2011;364[19]:1795-1806.

38. Caplan AI, Dennis JE. Mesenchymal stem cells as trophic mediators. J Cell Biochem 2006;98[5]:1076-1084.
39. Pozzobon M, Ghionzoli M, De Coppi P. Es, ips, msc, and afs cells. Stem cells exploitation for pediatric surgery: Current research and perspective. Pediatr Surg Int 2010;26[1]:3-10.
40. van Haaften T, Byrne R, Bonnet S et al. Airway delivery of mesenchymal stem cells prevents arrested alveolar growth in neonatal lung injury in rats. Am J Respir Crit Care Med 2009;180[11]:1131-1142.
41. Roubelakis MG, Pappa KI, Bitsika V et al. Molecular and proteomic characterization of human mesenchymal stem cells derived from amniotic fluid: Comparison to bone marrow mesenchymal stem cells. Stem Cells Dev 2007;16[6]:931-952.
42. Iritani I. Experimental study on embryogenesis of congenital diaphragmatic hernia. Anat Embryol [Berl] 1984;169[2]:133-139.
43. Greer JJ, Cote D, Allan DW et al. Structure of the primordial diaphragm and defects associated with nitrofen-induced cdh. J Appl Physiol [1985] 2000;89[6]:2123-2129.
44. Pederiva F, Ghionzoli M, Pierro A, De Coppi P, Tovar JA. Amniotic fluid stem cells rescue both in vitro and in vivo growth, innervation, and motility in nitrofen-exposed hypoplastic rat lungs through paracrine effects. Cell Transplant 2013;22[9]:1683-1694.
45. Di Bernardo J, Maiden MM, Hershenson MB, Kunisaki SM. Amniotic fluid derived mesenchymal stromal cells augment fetal lung growth in a nitrofen explant model. J Pediatr Surg 2014;49[6]:859-864; discussion 864-855.
46. Kamata S, Usui N, Kamiyama M et al. Long-term follow-up of patients with high-risk congenital diaphragmatic hernia. J Pediatr Surg 2005;40[12]:1833-1838.
47. Congenital Diaphragmatic Hernia Study G, Lally KP, Lally PA et al. Defect size determines survival in infants with congenital diaphragmatic hernia. Pediatrics 2007;120[3]:e651-657.
48. Bianchi A, Doig CM, Cohen SJ. The reverse latissimus dorsi flap for congenital diaphragmatic hernia repair. J Pediatr Surg 1983;18[5]:560-563.
49. Lally KP, Paranka MS, Roden J et al. Congenital diaphragmatic hernia. Stabilization and repair on ecmo. Annals of surgery 1992;216[5]:569-573.
50. Moss RL, Chen CM, Harrison MR. Prosthetic patch durability in congenital diaphragmatic hernia: A long-term follow-up study. J Pediatr Surg 2001;36[1]:152-154.
51. Laituri CA, Garey CL, Valusek PA et al. Outcome of congenital diaphragmatic hernia repair depending on patch type. Eur J Pediatr Surg 2010;20[6]:363-365.
52. Orlando G, Wood KJ, Stratta RJ, Yoo JJ, Atala A, Soker S. Regenerative medicine and organ transplantation: Past, present, and future. Transplantation 2011;91[12]:1310-1317.
53. Fauza DO, Marler JJ, Koka R, Forse RA, Mayer JE, Vacanti JP. Fetal tissue engineering: Diaphragmatic replacement. J Pediatr Surg 2001;36[1]:146-151.
54. Kunisaki SM, Fuchs JR, Kaviani A et al. Diaphragmatic repair through fetal tissue engineering: A comparison between mesenchymal amniocyte- and myoblast-based constructs. J Pediatr Surg 2006;41[1]:34-39; discussion 34-39.
55. Kunisaki SM, Freedman DA, Fauza DO. Fetal tracheal reconstruction with cartilaginous grafts engineered from mesenchymal amniocytes. J Pediatr Surg 2006;41[4]:675-682; discussion 675-682.
56. Kunisaki SM, Fuchs JR, Steigman SA, Fauza DO. A comparative analysis of cartilage engineered from different perinatal mesenchymal progenitor cells. Tissue Eng 2007;13[11]:2633-2644.
57. De Coppi P, Bartsch G, Jr., Siddiqui MM et al. Isolation of amniotic stem cell lines with potential for therapy. Nat Biotechnol 2007;25[1]:100-106.
58. Deprest J, De Coppi P. Antenatal management of isolated congenital diaphragmatic hernia today and tomorrow: Ongoing collaborative research and development. Journal of pediatric surgery lecture. J Pediatr Surg 2012;47[2]:282-290.
59. Piccoli M, Franzin C, Bertin E et al. Amniotic fluid stem cells restore the muscle cell niche in a hsa-cre, smn[f7/f7] mouse model. Stem cells [Dayton, Ohio] 2012;30[8]:1675-1684.
60. Turner CG, Klein JD, Steigman SA et al. Preclinical regulatory validation of an engineered diaphragmatic tendon made with amniotic mesenchymal stem cells. J Pediatr Surg 2011;46[1]:57-61.
61. Kunisaki SM, Armant M, Kao GS, Stevenson K, Kim H, Fauza DO. Tissue engineering from human mesenchymal amniocytes: A prelude to clinical trials. J Pediatr Surg 2007;42[6]:974-979; discussion 979-980.
62. Steigman SA, Armant M, Bayer-Zwirello L et al. Preclinical regulatory validation of a 3-stage amniotic mesenchymal stem cell manufacturing protocol. J Pediatr Surg 2008;43[6]:1164-1169.