UCLA
UCLA Previously Published Works

Title
On the evolution of the pulmonary alveolar lipofibroblast

Permalink
https://escholarship.org/uc/item/8n3195s3

Journal
Experimental Cell Research, 340(2)

ISSN
0014-4827

Authors
Torday, John S
Rehan, Virender K

Publication Date
2016

DOI
10.1016/j.yexcr.2015.12.004

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

Experimental Cell Research 340 (2016) 215–219

Contents lists available at ScienceDirect

Experimental Cell Research

journal homepage: www.elsevier.com/locate/yexcr

Review article

On the evolution of the pulmonary alveolar lipofibroblast

John S. Torday*, Virender K. Rehan

Department of Pediatrics, Harbor-UCLA Medical Center, 1124 West Carson Street, Torrance, CA 90502-2006, USA

ARTICLE INFO

Article history:
Received 24 August 2015
Received in revised form
5 December 2015
Accepted 15 December 2015
Available online 17 December 2015

Keywords:
Fibroblast
Cell–Cell interactions
Neutral lipid trafficking
PTHrP
ADRP
PPARγ

ABSTRACT

The pulmonary alveolar lipofibroblast was first reported in 1970. Since then its development, structure, function and molecular characteristics have been determined. Its capacity to actively absorb, store and 'traffic' neutral lipid for protection of the alveolus against oxidant injury, and for the active supply of substrate for lung surfactant phospholipid production have offered the opportunity to identify a number of specialized functions of these strategically placed cells. Namely, Parathyroid Hormone-related Protein (PTHrP) signaling, expression of Adipocyte Differentiation Related Protein, leptin, peroxisome proliferator activator receptor gamma, and the prostaglandin E2 receptor EP2- which are all stretch-regulated, explaining how and why surfactant production is 'on-demand' in service to ventilation–perfusion matching. Because of the central role of the lipofibroblast in vertebrate lung physiologic evolution, it is a Rosetta Stone for understanding how and why the lung evolved in adaptation to terrestrial life, beginning with the duplication of the PTHrP Receptor some 300 mya. Moreover, such detailed knowledge of the workings of the lipofibroblast have provided insight to the etiology and effective treatment of Bronchopulmonary Dysplasia based on physiologic principles rather than on pharmacology.

© 2015 Elsevier Inc. All rights reserved.

Contents

1. Discovery of the pulmonary alveolar lipofibroblast

The presence of lipid droplets in pulmonary interstitial cells was first described by Hitchcock et al. in 1970 [1]. Vaccaro and Brody were the first to name the associated cell-type the lipid interstitial cell (LIC) [2]. They emphasized the abundance of lipid droplets, the high glycogen content, and localization of LICs to the central region of the alveolar septum [3]. LICs were later better characterized as differentiated mesenchymal cells, meriting their designation as Lipofibroblasts (LIFs) [4].

LIFs are evident in rat lung by gestational day 16, and the triglyceride content of whole lung tissue increases three-fold between gestational days 17 and 19 (=term) [5]. The lung triglyceride content then increases another 2.5-fold between gestational day 21 and postnatal day 1, peaking during the second postnatal week [5]. The abundance of LIFs in the lung follows the same time-course, as evidenced by the yield of LIFs isolated by centrifugal sedimentation at various postnatal ages [6]. The amount of lipid per cell appears to remain constant from postnatal day 4 through 8. The lipid droplets primarily contain neutral lipids —65% triglycerides, 14% cholesterol esters—and an additional 7% are free fatty acids and cholesterol [6]. Phospholipids comprise the

* Corresponding author.
E-mail addresses: jtorday@labiomed.org (J.S. Torday), vrehan@labiomed.org (V.K. Rehan).

http://dx.doi.org/10.1016/j.yexcr.2015.12.004
0014-4827/© 2015 Elsevier Inc. All rights reserved.

remaining 14% of the cellular lipids. The number of LIFs decreases prior to weaning and appears result from both a decrease in cellular proliferation [7], and increased apoptosis [8].

LIFs are found in the lungs of mice and hamsters at postnatal day 8, although the volume density of lipid droplets is lower than in neonatal rats [9]. When identified by their signature location in the alveolar wall, LIFs are observed in adult rats, mice, and hamsters, although they contain far less lipid than in the neonate [9]. The volume density of the lipid droplets in lung fibroblasts is higher in the adult mouse than in the adult rat or hamster [9].

Surprisingly, the functional properties of the LIF did not advance for decades, until Torday et al. performed LIF co-culture experiments with alveolar type II (ATII) cells to determine the metabolic fate of the stored triglycerides [10]. The discovery of the robust transit of radiolabeled triglyceride from LIFs to ATIIs, termed Neutral Lipid Trafficking revealed the developmental, homeostatic, and ultimately the evolutionary significance of the LIF [10,11].

2. In the process of lung evolution, homologies run deep

The LIF is like an ontogenetic–phylogenetic 'Rosetta Stone' for the evolution of the lung [12], offering the opportunity to 'reverse-engineer' the processes by which the alveolus evolved to accommodate metabolic drive. The physiologic relevance of the LIF to alveolar growth, differentiation, homeostasis and repair has revealed such deep evolutionary homologs as [1] the peroxisome, which is thought to have evolved in response to the otherwise pathologic effects of Endoplasmic Reticulum stress in unicellular organisms; [2] Neutral Lipid Trafficking, encompassing lipid uptake and storage in defense against hyperoxia mediated by Adipocyte Differentiation Related Protein (ADRP), and release under the control of Prostaglandin E_2. This mechanism refers all the way back to the advent of cholesterol [13], and the evolution of the fat cell [14], producing the hormone leptin, ultimately coopted to regulate surfactant production by the Alveolar Type II Cell (ATII), coming full circle from the antioxidant property of the LIF. For orientation to these cellular–molecular evolutionary properties of the lung, the pathways for ontogeny, phylogeny and evolution of the LIF–ATII interactions are illustrated in Figs. 1 and 2 respectively.

LIFs in the alveolar wall of rat lung were first described by Hitchcock et al. [1], and extensively documented in rodent [2,6–9], and more recently in human [15] lung. However, their functional relevance to the alveolus was not determined for two more decades, though their cytoprotective nature was suggested by comparative studies of Frank et al. [16], who described the association between the LIFs and their putative role in overall antioxidant protection. These physiologic studies were paralleled by biochemical studies of triglyceride metabolism conducted by Mostello et al. [17]. The breakthrough in understanding the functional nature of these cells in lung alveolar physiology came with the co-culture of LIFs pre-labeled with radiolabeled triglyceride and naïve ATIIs, resulting in active uptake of the triglyceride by the ATIIs, and their subsequent robust incorporation into surfactant phospholipid by these cells [10], termed Neutral Lipid Trafficking. Experimentally, it was observed that LIFs could readily take up triglyceride and store it in a stable form; furthermore, this process could be stimulated by glucocorticoids, highlighting its regulated nature. Moreover, the presence of neutral lipid droplets in the LIFs protected them against oxidant injury [18], providing a physiologic function for these cells. This property of the LIF may have evolved from the myofibroblast in response to the rise in atmospheric oxygen during the Phanerozoic Era, as shown experimentally by Csete et al. [14], who found that if myocytes were cultured in 6%

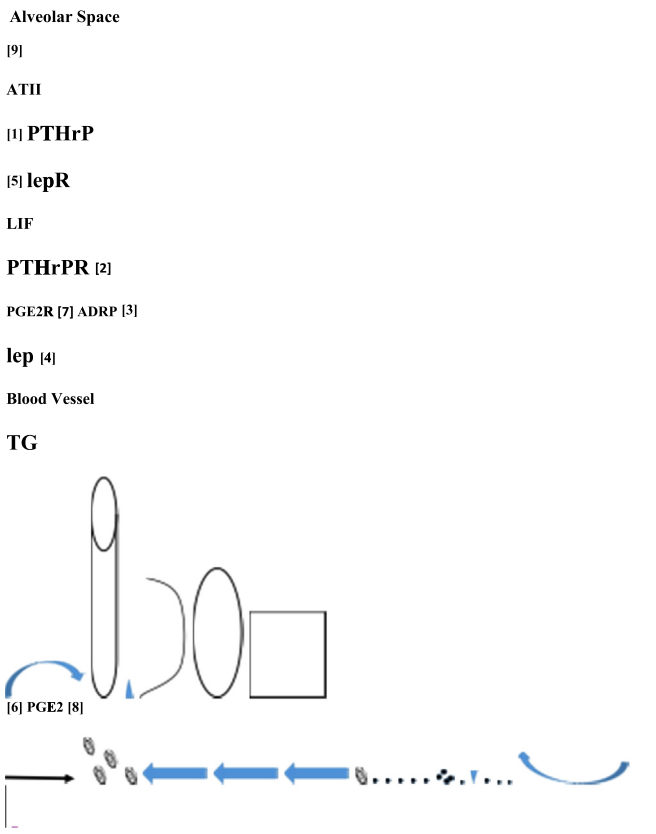

Fig. 1. Cell–cell interactions determine alveolar development. PTHrP secreted by the ATII [1] binds to its receptor on the LIF [2] initiating alternating signals between the ATII and LIF, beginning with the stimulation of ADRP [3], which is necessary for the 'trafficking' of triglyceride (TG) from the circulation to the LIF, and from the LIF to the ATII. PTHrP also stimulates leptin [4] expression by the LIF, which then binds to its receptor on the ATII [5], stimulating surfactant synthesis [8]. The ATIIs secrete surfactant into the alveolar space [9], reducing surface tension to prevent alveolar collapse.

oxygen they retained a myofibroblast phenotype, but in 21% oxygen they differentiated into adipocytes. It was subsequently determined that the uptake, storage and transfer of the neutral lipids was actively mediated by ADRP [19], a member of the PAT (Perilipin, Adipocyte Differentiation Related Protein, TIP47) family of proteins that mediate the trafficking and storage of neutral lipids throughout the body.

During the course of these studies, it was discovered empirically that isolated ATIIs could not absorb TGs, and isolated LIFs could not release them, implying the existence of active regulatory mechanisms for Neutral Lipid Trafficking. Such a mechanism had long been suspected since surfactant production is known to occur 'on demand' [20,21]. That led to the discovery that the prostaglandin PGE_2, secreted by ATIIs specifically causes PGE_2 -specific EP_2 receptor-mediated release of TGs by LIFs [22], and leptin produced by the LIFs facilitates the uptake of TGs by binding to its specific cell surface receptors on ATIIs [23].

*Please note that all but steps 1,3 and 9–11 are lipofibroblast specific genes.

3. Gene expression

The culmination of these cell–cell interactions mediating and facilitating the production of lung surfactant phospholipid production was the discovery that Neutral Lipid Trafficking is stretch-regulated, providing key insights to both the cellular–molecular basis for the mechanism of alveolar ventilation–perfusion

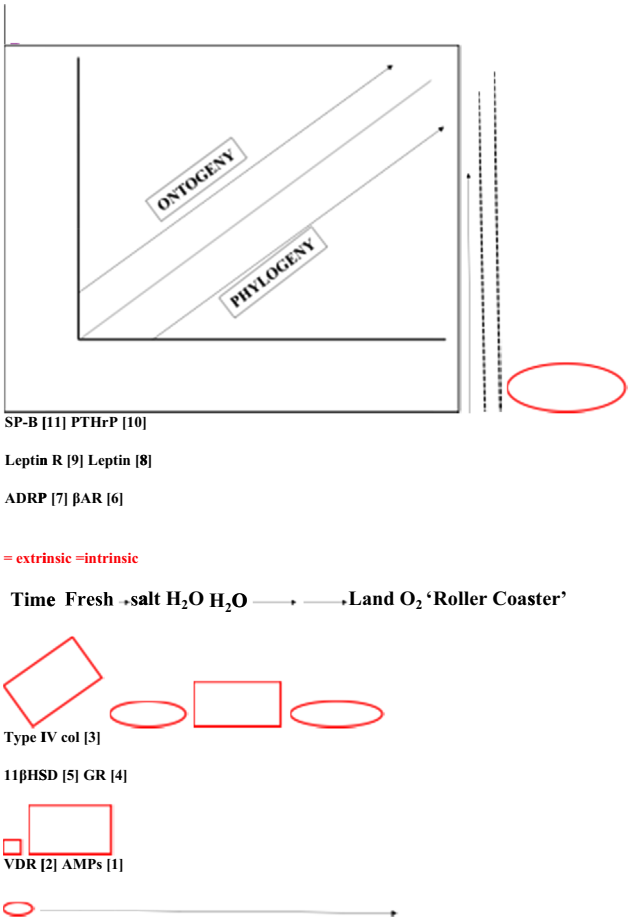

Fig. 2. Alternating extrinsic and intrinsic selection pressures for the genes of lung phylogeny and ontogeny. The effects of the extrinsic factors (salinity, land nutrients, oxygen) on genes that determine the phylogeny and ontogeny of the mammalian lung alternate sequentially with the intrinsic genetic factors, highlighted by the red circles and square. [1] AMPs=Antimicrobial Peptides; [2] VDR=Vitamin D Receptor;[3] type IV col=type IV collagen;[4] GR=Glucocorticoid Receptor; [5] 11βHSD=11beta Hydroxysteroid Dehydrogenase; [6] βAR=beta Adrenergic Receptor; [7] ADRP=Adipocyte Differentiation Related Protein; [8] Leptin=Leptin; [9] Leptin R=Leptin Receptor; [10] PTHrP=Parathyroid Hormone-related Protein; [11] Surfactant Protein-B= Surfactant Protein-B. Fresh→salt H_2O=transition from fresh to salt water; H_2O →land=water-to-land transition; Oxygen 'roller coaster'=fluctuations in atmospheric oxygen tension over the last 500 million years.

matching, and to the evolutionary history of the lung.

Initially, it was discovered that Parathyroid Hormone-related Protein (PTHrP) is necessary for the formation of alveoli during lung morphogenesis [24], and that PTHrP secreted by the ATIIs stimulates LIF development, including TG uptake and leptin secretion, providing evidence for the hypothesized paracrine epithelial signal to the mesenchyme [25] during the course of the paracrine cell–cell interactions that mediate alveolar development. That, combined with the observation that PTHrP mRNA expression by ATIIs is stretch-regulated led to the broader physiologic insight that the PTHrP Receptor, leptin, the leptin Receptor and PGE_2 are all stretch- regulated signals, coordinating the effect of physical distension of the alveolar wall for the up-regulation of surfactant production. These coordinated stretch-regulated signaling mechanisms promote lung development in utero [26], and prevent alveolar atelectasis during air breathing [27].

The elucidation of this cellular–molecular mechanism for the coordinate regulation of surfactant production by alveolar distension provides the mechanistic basis for ventilation–perfusion matching. These insights led to the realization that the endodermal and mesodermal components of the alveolar wall evolved over evolutionary time to generate their structural–functional properties through epithelial–mesenchymal cell–cell interactions. In support of that process, the PTHrP Receptor duplicated during the vertebrate water–land transition some 300 mya [28], amplifying the PTHrP signaling pathways of the lung, skin and bone. The causal nature of this interrelationship is supported by the deletion of PTHrP in developing mice, causing failure of lung, skin and bone development. PTHrP is also expressed in the developing swim bladder along with many other genes expressed in the lung [29], establishing the functional homology between these organs. Moreover, the gas gland epithelial cells that line the swim bladder secrete cholesterol, the most primitive lung surfactant, preventing the walls of the bladder from sticking to one another. That functional homology relates ancestrally to the advent of cholesterol in the cell membranes of evolving unicellular eukaryotes from prokaryotes, acting to thin the phospholipid bilayer, facilitating oxygenation, metabolism and locomotion, the fundamental properties of vertebrate physiologic evolution [30].

According to the de Duve Hypothesis [31], oxidant stress-induced disruption of intracellular calcium homeostasis caused selection pressure for peroxisome evolution, counterbalancing calcium dyshomeostasis by utilizing lipids. This same scenario applies to the alveolar extracellular space, in which calcium and lipid homeostasis are of critical importance in controlling the alternating assembly and breakdown of tubular myelin, the structure that reduces surface tension in the alveolar hypophase. Tubular myelin is a mesh-like structure composed of lipids and proteins, among them Surfactant Proteins and antimicrobial peptides, packaged together as lamellar bodies within the alveolar type II cell, actively secreted into the alveolar space. The homologous mechanism of lamellar body secretion is observed in the stratum corneum of the skin, where the secreted lipid-antimicrobial peptide gemisch forms a lipid barrier protecting the skin against both infection and unregulated transudation of fluids; lung surfactant serves these same dual purposes in the alveolus, demonstrating the functional homology between the lung and skin as barriers against the environment, likely due to their common origin in the plasmalemmas of unicellular organisms.

4. The role of the lipofibroblast in chronic lung disease

The cited cell/molecular events that evolutionarily determine alveolar homeostasis follow a sequence consistent with the phylogeny and ontogeny of the vertebrate lung in both the forward and reverse directions, the latter seen under pathologic conditions, suggesting an approach to lung biology and pathophysiology consistent with Evolutionary Medicine. This is exemplified by the failure to explain the reduction in CLD by surfactant replacement in the surfactant–deficient premature infant when conventional wisdom would predict its reduction due to improvement in oxygenation and ventilation following provision of the deficient substance, namely, pulmonary surfactant. That is because CLD is not simply due to the lack of surfactant in the alveolus, but more fundamentally, it is due to the lack of fully established ATII–LIF homeostatic communications in the alveolar wall, leading to surfactant insufficiency [32]. The failure of homeostatic regulation is characterized by the deficiency of PTHrP in the airways of those premature infants who develop Bronchopulmonary Dysplasia (BPD) [33]. Therefore, unless such homeostatic communications are established, regardless of what treatment is provided, it will not prevent or reverse BPD. This principle is likely the basis for the success of continuous positive airway pressure (CPAP), providing just the right amount of alveolar distension, exploiting billions of years of lung evolutionary phylogeny and development, stimulating the ATII–LIF cross talk developmentally induced by PTHrP,

leading to a more physiologic cellular–molecular milieu. That is why premature infants supported on CPAP are less likely to develop BPD [34].

5. LIF-to-MYF transdifferentiation is a cardinal feature in BPD pathogenesis

Using a variety of isolated cellular and animal models, in a series of studies from our laboratory we have shown that in the presence of deranged mesenchymal–epithelial signaling, for example, on exposure to hyperoxia, infection, volutrauma, and other insults that lead to BPD, pulmonary LIFs rapidly lose their lipogenic phenotype and transdifferentiate into a myogenic phenotype, that is, MYFs. Transdifferentiated LIFs (i.e., MYFs) are unable to maintain pulmonary epithelial cell growth and differentiation [35], resulting in failed alveolarization, seen characteristically in BPD and other Chronic Lung Diseases (CLDs), unequivocally signifying the importance of LIFs in lung development and injury repair. Using oxotrauma as a prototype, as detailed below, in these disease models, using PPARγ agonists we have effectively abrogated specific alveolar molecular changes following oxotrauma, barotrauma, and infection that are known to lead to BPD.

6. Prevention of oxotrauma by PTHrP/PPARγ signaling pathway agonists

We initially studied the effects of hyperoxia on the fibroblast phenotype in immature and relatively mature rat lungs, and found that exposure to hyperoxia down-regulated PTHrP/PPARγ signaling, augmenting the transdifferentiation of pulmonary LIFs to MYFs [36]. Cells were maintained either in normoxia (21% O2) or subjected to hyperoxia for 24 h (95% O2) at passages 1 and 5. Serial passaging and maintenance of cells in normoxia resulted in a significant decrease in the expression of the lipogenic markers, based on molecular (reverse transcription–polymerase chain reaction [RT–PCR] for the PTHrP receptor, PPARγ, and ADRP) and functional (triglyceride uptake) criteria, from postnatal day P1–P5. This decrease was greater for relatively immature (e18) than for more mature (e21) fibroblasts, consistent with the developmentally-dependent nature of BPD. Exposing LIFs to hyperoxia augmented the loss of the lipogenic markers, and gain of the myogenic marker α-SMA from P1–P5 in comparison to cells maintained in normoxia. This augmentation was also greater for e18 versus e21 LIFs. These data suggested that exposure to hyperoxia augmented the transdifferentiation of pulmonary LIFs to MYFs. Importantly, we also reported that pretreatment with an endogenous PPARγ signaling pathway agonist, prostaglandin J_2 (PGJ_2), at least partially attenuated the hyperoxia-augmented LIF-to-MYF transdifferentiation.

Following these in vitro studies, we determined whether in vivo exposure to hyperoxia also resulted in pulmonary alveolar LIF-to-MYF transdifferentiation, and whether treatment with a potent PPARγ signaling pathway agonist, rosiglitazone (RGZ), would prevent transdifferentiation [37]. Newborn Sprague Dawley rat pups were exposed to normoxia (21% O2), hyperoxia alone (95% O_2 for 24 h), or hyperoxia with RGZ (95% O_2 for 24 h+RGZ, 3 mg/kg, administered intraperitoneally). Hyperoxia-exposed lungs exhibited arrest of alveolarization, characterized by large air spaces, thinned interstitial septa, and decreased secondary septal crest formation. Accompanying these morphometric changes, there was a significant decrease in the expression of lipogenic markers, and a significant increase in the expression of myogenic markers in the hyperoxia-alone group. The hyperoxia-induced morphologic, molecular, and immunohistochemical changes were virtually prevented by pretreatment with RGZ, providing the first evidence for the in vivo efficacy of exogenously administered PPARγ agonists in preventing hyperoxia-induced neonatal lung injury.

7. Nature favors implementation of lipofibroblasts to maintain homeostasis

Besnard et al. [38] found that when they specifically deleted a gene necessary for the synthesis of cholesterol in ATII cells, the lungs appeared to function normally even though cholesterol is necessary for effective surfactant surface activity. However, it was found that the lung developmentally compensated for this deficiency by overexpressing the LIF population in the alveoli, sensing alveolar dyshomeostasis due to cholesterol-less surfactant having poorer surface-active quality. Hence, the alveoli invoked the atavistic LIF evolutionary strategy to facilitate surfactant production, both ontogenetically and phylogenetically.

It should be abundantly clear from the work reviewed above that LIF PPARγ signaling plays a central role in epithelial–mesenchymal interactions, maintaining alveolar homeostasis and aiding lung injury repair. The LIF expresses PPARγ in response to PTHrP signaling from the ATII cell, resulting in both the direct protection of the mesoderm against oxidant injury [39], and protection against atelectasis by augmenting surfactant protein and phospholipid [39] synthesis. Injury to either ATIIs or LIFs down-regulates this molecular signaling pathway, causing MYF transdifferentiation—MYFs cannot support ATII cell proliferation and differentiation [35], leading to the failed alveolarization characteristic of BPD. By contrast, the LIF phenotype supports ATII cell proliferation and differentiation even under the influence of factors implicated in the pathogenesis of BPD [32]. Importantly, these studies show that exogenously administered PPARγ agonists can prevent or reverse MFY transdifferentiation, potentially preventing the inhibition of alveolarization in the developing lung, the hallmark of BPD of the newborn.

In summary, by identifying deep homologous mechanisms that have determined both the phylogeny and ontogeny of the lung, we have experimentally used exogenously administered PPARγ agonists to exploit the lung's evolved reliance on LIFs to combat hyperoxia and prevent neonatal lung injury leading to BPD, the CLD of prematurity. We speculate that a diagnostic and therapeutic approach predicated on mechanisms that have resulted in the evolution of human lung under the selection pressure of increased atmospheric oxygen [11] can be exploited to understand homeostasis, representing health, and dyshomeostasis, representing disease.

Acknowledgments

John S. Torday has been supported by National Institutes of Health (NIH) Grant HL055268. Virender K. Rehan has been supported by NIH (HL075405, HD51857, HD058948, HL107118, and HD071731) and Tobacco-Related Disease Research Program (TRDRP) (15IT-0250, 17RT-0170, and 23RT-0018).

References

[1] K. Hitchcock O'Hare, M.N. Sheridan, Electron microscopic observations on the morphogenesis of the albino rat lung, with special reference to pulmonary epithelial cells, Am. J. Anat. 127 (1970) 181–206.
[2] C. Vaccaro, J.S. Brody, Ultrastructure of developing alveoli. I. The role of the interstitial fibroblast, Anat. Rec. 192 (1978) 467–480.
[3] J.S. Brody, Cell-to-cell interactions in lung development, Pediatr. Pulmonol. 1

(2009) S42–S48.
[4] S.E. McGowan, J.S. Torday, The pulmonary lipofibroblast (lipid interstitial cell) and its contributions to alveolar development, Annu. Rev. Physiol. 59 (1997) 43–62.
[5] C. Tordet, L. Marin, F. Dameron, Pulmonary di- and tri-glycerides during the perinatal development of the rat, Experientia 37 (1981) 333–334.
[6] H.J. Maksvytis, C. Vaccaro, J.S. Brody, Isolation and characterization of the lipid-containing interstitial cell from the developing rat lung, Lab. Investig. 45 (1981) 248–259.
[7] J.S. Brody, N.B. Kaplan, Proliferation of alveolar interstitial cells during postnatal lung growth. Evidence for two distinct populations of pulmonary fibroblasts, Am. Rev. Respir. Dis. 127 (1983) 763–770.
[8] F. Awonusonu, S. Srinivasan, J. Strange, W. Al-Jumaily, M.C. Bruce, Developmental shift in the relative percentages of lung fibroblast subsets: role of apoptosis postseptation, Am. J. Physiol. 277 (1999) L848–L859.
[9] N.B. Kaplan, M.M. Grant, J.S. Brody, The lipid interstitial cell of the pulmonary alveolus. Age and species differences, Am. Rev. Respir. Dis. 132 (1985) 1307–1312.
[10] J. Torday, J. Hua, R. Slavin, Metabolism and fate of neutral lipids of fetal lung fibroblast origin, Biochim. Biophys. Acta 1254 (1995) 198–206.
[11] J.S. Torday, V.K. Rehan., The evolutionary continuum from lung development to homeostasis and repair, Am. J. Physiol. Lung Cell. Mol. Physiol. 292 (2007) L608–L611.
[12] J.S. Torday, V.K. Rehan., Evolutionary Biology, Cell–Cell Communication and Compex Disease, Wiley, Hoboken, New Jersey, 2012.
[13] K. Bloch, Summing up, Annu. Rev. Biochem. 56 (1987) 1–19.
[14] M. Csete, J. Walikonis, N. Slawny, Y. Wei, S. Korsnes, D.C. Doyle, B. Wold, Oxygen- mediated regulation of skeletal muscle satellite cell proliferation and adipogenesis in culture, J. Cell. Physiol. 189 (2001) 189–196.
[15] V.K. Rehan, S. Sugano, Y. Wang, J. Santos, S. Romero, C. Dasgupta, M.P. Keane, M.T. Stahlman, J.S. Torday, Evidence for the presence of lipofibroblasts in human lung, Exp. Lung Res. 32 (2006) 379–393.
[16] L. Frank, J.R. Bucher, R.J. Roberts, Oxygen toxicity in neonatal and adult animals of various species, J. Appl. Physiol. Respir. Environ. Exerc. Physiol. 45 (1978) 699–704.
[17] D.J. Mostello, M. Hamosh, P. Hamosh, Effect of dexamethasone on lipoprotein lipase activity of fetal rat lung, Biol. Neonate 40 (1981) 121–128.
[18] J.S. Torday, D.P. Torday, J. Gutnick, J. Qin, V. Rehan, Biologic role of fetal lung fibroblast triglycerides as antioxidants, Pediatr. Res. 49 (2001) 843–849.
[19] C.J. Schultz, E. Torres, C. Londos, J.S. Torday, Role of adipocyte differentiation-related protein in surfactant phospholipid synthesis by type II cells, Am. J. Physiol. Lung Cell. Mol. Physiol. 283 (2) (2002) L288–L296.
[20] I. Wyszogrodski, K. Kyei-Aboagye, H.W. Taeusch Jr., M.E. Avery, Surfactant inactivation by hyperventilation: conservation by end-expiratory pressure, J. Appl. Physiol. 38 (1975) 461–466.
[21] T.E. Nicholas, H.A. Barr, Control of release of surfactant phospholipids in the isolated perfused rat lung, J. Appl. Physiol. 51 (1981) (1981) 90–98.
[22] J.S. Torday, H. Sun, J. Qin, Prostaglandin E2 integrates the effects of fluid distension and glucocorticoid on lung maturation, Am. J. Physiol. 274 (1998) L106–L111.
[23] J.S. Torday, H. Sun, L. Wang, E. Torres, M.E. Sunday, L.P. Rubin, Leptin mediates the parathyroid hormone-related protein paracrine stimulation of fetal lung maturation, Am. J. Physiol. Lung Cell. Mol. Physiol. 282 (2002) L405–L410.
[24] L.P. Rubin, C.S. Kovacs, M.E. De Paepe, S.W. Tsai, J.S. Torday, H.M. Kronenberg, Arrested pulmonary alveolar cytodifferentiation and defective surfactant synthesis in mice missing the gene for parathyroid hormone-related protein, Dev. Dyn. 230 (2004) 278–289.
[25] L.P. Rubin, O. Kifor, J. Hua, E.M. Brown, J.S. Torday, Parathyroid hormone (PTH) and PTH-related protein stimulate surfactant phospholipid synthesis in rat fetal lung, apparently by a mesenchymal–epithelial mechanism, Biochim. Biophys. Acta 1223 (1) (1994) 91–100.
[26] J.S. Torday, V.K. Rehan, Up-regulation of fetal rat lung parathyroid hormone-related protein gene regulatory network down-regulates the Sonic Hedgehog/Wnt/betacatenin gene regulatory network, Pediatr. Res. 60 (2006) 382–388.
[27] T.E. Nicholas, Pulmonary surfactant: no mere paint on the alveolar wall, Respirology 1 (1996) 247–257.
[28] P.L. Pinheiro, J.C. Cardoso, D.M. Power, A.V. Canário, Functional characterization and evolution of PTH/PTHrP receptors: insights from the chicken, BMC Evol. Biol. 12 (2012) 110.
[29] W. Zheng, Z. Wang, J.E. Collins, R.M. Andrews, D. Stemple, Z. Gong, Comparative transcriptome analyses indicate molecular homology of zebrafish swimbladder and mammalian lung, Plos One 6 (2011) e24019.
[30] S.F. Perry, D.R. Carrier, The coupled evolution of breathing and locomotion as a game of leapfrog, Physiol. Biochem. Zool. 79 (2006) 997–999.
[31] C. De Duve, Evolution of the peroxisome, Ann. N.Y. Acad. Sci. 168 (1969) 369–381.
[32] L. Cerny, J.S. Torday, V.K. Rehan, Prevention and treatment of bronchopulmonary dysplasia: contemporary status and future outlook, Lung 186 (2008) 75–89.
[33] V.K. Rehan, J.S. Torday, Lower parathyroid hormone-related protein content of tracheal aspirates in very low birth weight infants who develop bronchopulmonary dysplasia, Pediatr. Res. 60 (2006) 216–220.
[34] C.A. Friedman, R.C. Menchaca, M.C. Baker, C.K. Rivas, R.N. Laberge, E.H. Rios, S. H. Haider, E.J. Romero, E.B. Eason, J.K. Fraley, M. Woldesenbet, Bubble nasal CPAP, early surfactant treatment, and rapid extubation are associated with decreased incidence of bronchopulmonary dysplasia in very-low-birth-weight newborns: efficacy and safety considerations, Respir. Care 58 (2013) 1134–1142.
[35] J.S. Torday, E. Torres, The role of fibroblast transdifferentiation in lung epithelial cell proliferation, differentiation, and repair in vitro, Pediatr. Pathol. Mol. Med. 22 (2003) 189–207.
[36] V. Rehan, J. Torday, Hyperoxia augments pulmonary lipofibroblast-to-myofibroblast transdifferentiation, Cell Biochem. Biophys. 38 (2003) 239–250.
[37] V.K. Rehan, R. Sakurai, J. Corral, M. Krebs, B. Ibe, K. Ihida-Stansbury, J.S. Torday. Antenatally administered PPAR-gamma agonist rosiglitazone prevents hyperoxia-induced neonatal rat lung injury, Am. J. Physiol. Lung Cell. Mol. Physiol. 299 (2010) L672–L680.
[38] V. Besnard, S.E. Wert, M.T. Stahlman, A.D. Postle, Y. Xu, M. Ikegami, J. A. Whitsett, Deletion of Scap in alveolar type II cells influences lung lipid homeostasis and identifies a compensatory role for pulmonary lipofibroblasts, J. Biol. Chem. 284 (2009) 4018–4030.
[39] V.K. Rehan, J. Fong, R. Lee, R. Sakurai, Z.M. Wang, M.J. Dahl, R.H. Lane, K. H. Albertine, J.S. Torday, Mechanism of reduced lung injury by high-frequency nasal ventilation in a preterm lamb model of neonatal chronic lung disease, Pediatr. Res. 70 (2011) 462–466.