Journal of Steroid Biochemistry & Molecular Biology 137 (2013) 93–98

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

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

Review

Major enzymes controlling the androgenic pressure in the developing lung

Yves Tremblay[a,b,c,*], Pierre R. Provost[a,b,c]

[a] Reproduction Axis, Perinatal and Child Health, Rm T-1-49, CHUQ Research Center, Canada
[b] Department of Obstetrics/Gynecology & Reproduction, Faculty of Medicine, Laval University, Québec City, Québec, Canada
[c] Centre de Recherche en Biologie de la Reproduction (CRBR), Laval University, Québec City, Québec, Canada

ARTICLE INFO

Article history:
Received 5 October 2012
Received in revised form 15 March 2013
Accepted 18 March 2013

Keywords:
5α-Reductase
Budding
Fetal
IGF-I
Surfactant

ABSTRACT

A sex difference is observed in the incidence and morbidity of respiratory distress syndrome (RDS) of the neonate and in bronchopulmonary dysplasia (BPD). The involvement of androgens is well evidenced in RDS and it is suspected in BPD. Interestingly, the developing lung is not an inert tissue just exposed to circulating androgens, but is rather an active androgen metabolizing tissue, expressing enzymes involved in both androgen synthesis and inactivation. The present review focuses on the major enzymes involved in androgen metabolism within the developing lung. Testosterone synthesis and inactivation by AKR1C3/Akr1c6 (human/mouse 17β-hydroxysteroid dehydrogenases (HSDs) type 5) and HSD17B2 (17β-HSD type 2), respectively, play an important role in the developing lung. Akr1c14 (3α-HSD) shows a strong increase in expression according to developmental time. The canalicular stage of lung development corresponding to the surge of surfactant lipid synthesis, which is linked to RDS, as well as saccularization/alveolarization, which are linked to BPD, are covered by this review for the mouse and human species. The androgen metabolizing enzymes expressed within the developing lung can become potential pharmaceutical targets in the objective of accelerating lung maturation by specific treatments. The classic deleterious effects of androgens on lung maturation and the surge of surfactant synthesis in males are well known. Conversely, androgens also have positive impacts on the development of both male and female lungs. Steroidogenic enzymes are key regulators of these positive effects.

This article is part of a Special Issue entitled 'CSR 2013'.

1. Introduction

Lung development is classified into five stages. The embryonic stage (gestation day (GD) 9.0–9.5 in the mouse; 3–8 weeks of pregnancy in the human) corresponds to the formation of the lung bud. During the pseudoglandular stage (GD 9.5–16.5 in the mouse; 8–16 weeks of pregnancy in the human), branching morphogenesis occurs to form the conductive airway tree including the terminal bronchioles. The canalicular stage (GD 16.5–17.5 in the mouse; 16–25 weeks of pregnancy in the human) refers to the expansion of the airway tree, organ growth, differentiation of epithelium cell types, and increase in the number of capillaries. The terminal bronchioles evolve into primitive respiratory bronchioles containing terminal sacs. The saccular stage (GD 17.5 to postnatal day (PN) 5 in the mouse; 25–36 weeks of pregnancy in the human) corresponds to the subdivision of saccules, resulting in primitive alveoli which are pouches in the walls of saccules. Finally, during the alveolar stage (PN 5–30 in the mouse; from 36 weeks of pregnancy to 2 years after birth in the human), development of true vascularized alveoli occurs. Secondary septa grow into the airspaces, increasing the exchange surface area of the lung. The terminal saccules, alveolar ducts, and alveoli increase in number. Fig. 1 describes lung development and shows variations in sex steroid levels over developmental time for human and mouse.

In the human and mouse, the peak of circulating testosterone of testicular origin is observed before the surge of surfactant synthesis, which occurs on GD 17.5 in the mouse and between the 28th and 34th weeks of pregnancy in the human. A sex difference is observed in the surge of surfactant synthesis. The emergence of mature type II pneumonocytes (PTII) responsible for surfactant synthesis occurs with a delay for males. This delay results from circulating testosterone of testicular origin. Respiratory distress syndrome (RDS) is a consequence of birth before the emergence of mature PTII cells. A sex difference in RDS is observed in the newborn with a higher prevalence for males. The major cause of this disease is the lack

Abbreviations: 3α,17β-diol, 5α-androstane-3α,17β-diol; 3β-HSD, 3β-hydroxysteroid dehydrogenase/Δ^5–Δ^4 isomerase; DHEA, dehydroepiandrosterone; DHT, 5α-dihydrotestosterone; E_1, estrone; E_2, estradiol; GD, gestation day; IGF-I, insulin-like growth factor I; IHC, immunohistochemistry; ISH, in situ hybridization; PN, post-natal day; PTII, type II pneumonocytes.

* Corresponding author at: Dept. Ob/Gyn & Reproduction, Reproduction Axis, Perinatal and Child Health, CHUQ Research Center, 2705 Laurier Boulevard, Rm T-1-49, Québec, QC, Canada G1V 4G2. Tel.: +1 418 525 4444x46158; fax: +1 418 654 2765.
E-mail address: yves.tremblay@crchul.ulaval.ca (Y. Tremblay).

0960-0760/$ – see front matter.
http://dx.doi.org/10.1016/j.jsbmb.2013.03.006

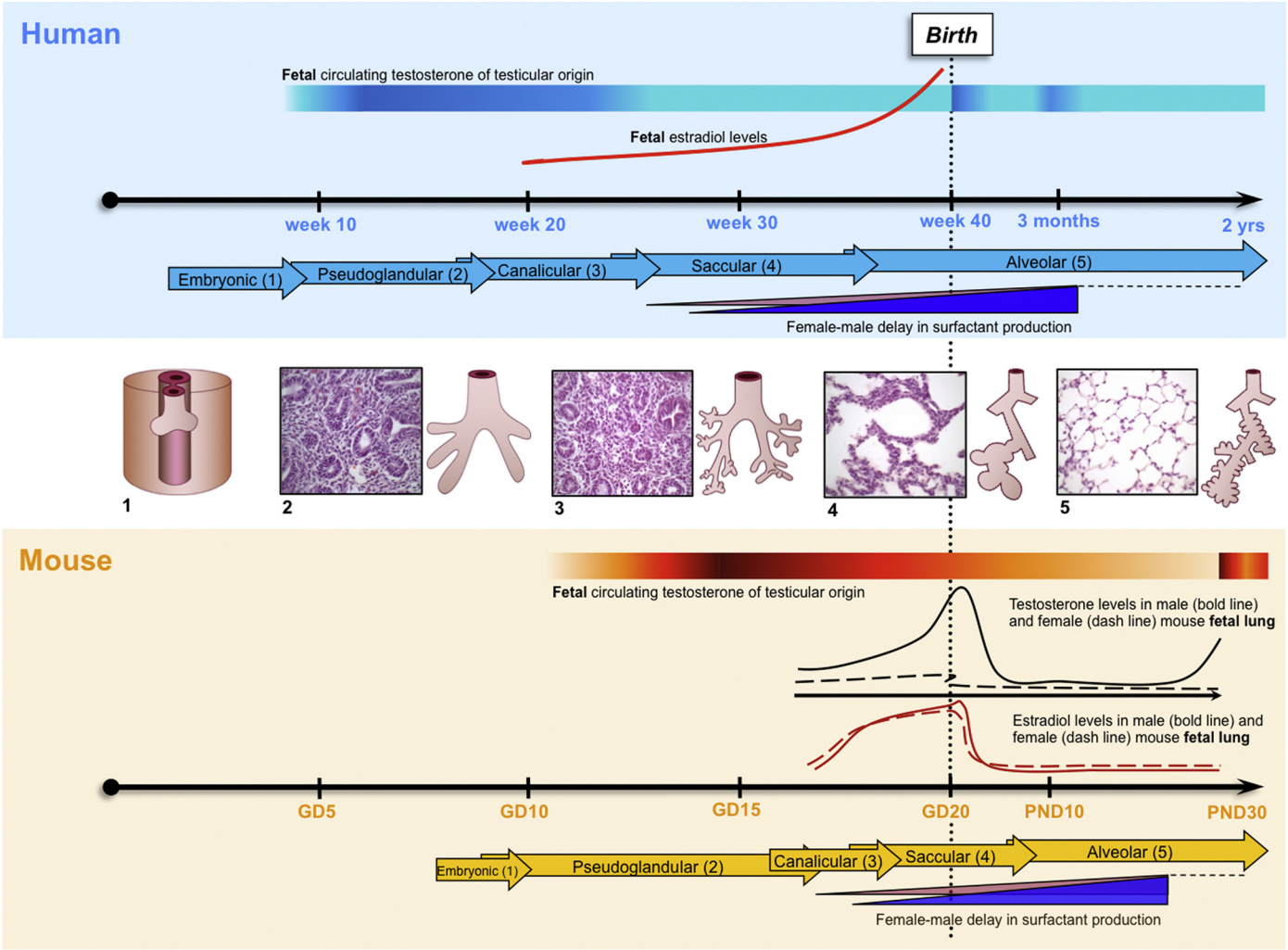

Fig. 1. *Lung development and sex steroid levels.* Human (blue background) and mouse (orange background) lung developmental stages in relation to testosterone and estradiol levels in fetal circulation and in fetal lung. Hormone levels in human fetal lung and estradiol levels in the mouse fetal circulation are not available. Human fetal circulating estradiol levels are not available individually for each sex. Surfactant production is also indicated for both female and male by the pink and blue triangles, respectively, underneath each graph. Histologic photographs and schematic illustrations show mouse lung tissues at the corresponding developmental stages (center panel). Fetal levels of circulating testosterone are represented by colored strips (blue for human and red for mouse) in which the gradient indicates the intensity level (the darker color represents higher levels). GD, gestation day; PND, post-natal day.

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of surfactant as a consequence of premature birth. The sex difference in PTII cell maturation and consequently in the surge of surfactant synthesis is proposed to explain the sex difference in RDS. For more information, see [1]. Bronchopulmonary dysplasia (BPD) is the product of a heterogeneous group of lung disorders that begin in the neonatal period as a consequence of preterm birth and neonatal care. New BPD is characterized by impaired alveolar and capillary growth and development. A sex difference is observed in new BPD [2–5], but it is undetermined whether testosterone is involved.

Albeit the deleterious effects of androgens on lung maturation, many data suggest that androgens must play a positive role in lung development in both sexes and that the sex difference in circulating testosterone just exacerbates the normal effects of androgens. Accordingly, androgen receptor expression and testosterone are found in the lung of both male and female fetuses [6]. A peak of expression for some steroidogenic enzymes occurs in correlation with the emergence of mature PTII cells in the lung of both sexes [7]. No sex difference was found in the expression of steroidogenic enzymes involved in androgen synthesis and inactivation in the developing lung, except in the precise timing of expression [7]. Even though the presence of a functional androgen receptor is not necessary to survival as shown by the *Tfm* mouse model, a role for androgens and lung androgen metabolism is possibly essential for obtaining optimal lung development. In this review, we summarize the knowledge on the enzymes involved in the androgen metabolism in the developing lung. Normal roles for these enzymes in male and female lung developments are proposed.

The androgen receptor is an androgen-activable transcription factor. Once activated by binding to testosterone or 5α-dihydrotestosterone (DHT, the most potent androgen) in the cytoplasm, the androgen receptor rapidly translocates to the nucleus and binds to its *cis*-acting promoter element. In addition to this classical action, androgens can also exert non-genomic actions [8–10]. In our study of the effects of the anti-androgen flutamide on the developing lung transcriptome, we reported multiple androgen targeted genes [11]. The effects of androgens on the surge of surfactant synthesis are exerted through the androgen receptor [12].