Molecular and Cellular Endocrinology 336 (2011) 206–212

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

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

Review

Adrenocortical stem and progenitor cells: Unifying model of two proposed origins

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ARTICLE INFO

Article history:
Received 8 September 2010
Received in revised form
11 November 2010
Accepted 12 November 2010

Keywords:
Adrenal cortex
Stem cells
Adrenocortical cells
Adrenal development

ABSTRACT

The origins of our understanding of the cellular and molecular mechanisms by which signaling pathways and downstream transcription factors coordinate the specification of adrenocortical cells within the adrenal gland have arisen from studies on the role of Sf1 in steroidogenesis and adrenal development initiated 20 years ago in the laboratory of Dr. Keith Parker.

Adrenocortical stem/progenitor cells have been predicted to be undifferentiated and quiescent cells that remain at the periphery of the cortex until needed to replenish the organ, at which time they undergo proliferation and terminal differentiation. Identification of these stem/progenitor cells has only recently been explored. Recent efforts have examined signaling molecules, including Wnt, Shh, and Dax1, which may coordinate intricate lineage and signaling relationships between the adrenal capsule (stem cell niche) and underlying cortex (progenitor cell pool) to maintain organ homeostasis in the adrenal gland.

Contents

1. Introduction

Dr. Keith Parker serendipitously became a pioneer in the molecular study of adrenal gland development and organogenesis when he cloned the gene for steroidogenic factor 1 (*Sf1*) as a transcriptional regulator of genes encoding steroidogenic enzymes (Luo et al., 1994). Dr. Parker's work occurred concurrently with studies emerging from the Morohashi laboratory on the steroidogenic transcription factor Ad4BP, which turned out to be identical to Sf1 (Hatano et al., 1996). Together, these studies surprisingly found that the adrenal glands did not form in mice with a genetically modified null allele of *Sf1*. Studies of Sf1 for over two decades have provided the molecular framework for the emerging field of adrenocortical stem and progenitor biology. The current research in the emerging field of adrenal organogenesis and data supporting the presence of adrenocortical stem/progenitor cells was recently reviewed (Kim et al., 2009). The current summary herein highlights a working model of adrenocortical stem/progenitor cell biology and the pro-

Abbreviations: AGP, adrenogonadal primordium; FAdE, fetal adrenal enhancer; DAdE, definitive adrenal enhancer; Sf1, steroidogenic factor 1; E, embryonic day; Shh, sonic hedgehog; Cyp11b1, cytochrome P450, family 11, subfamily b, polypeptide 1; Cyp11b2, cytochrome P450, family 11, subfamily b, polypeptide 2; Gli1, GLI-Kruppel family member GLI1; Wnt, wingless-related MMTV integration site; ACTH, adrenocorticotropic hormone.

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doi:10.1016/j.mce.2010.11.012

posed stem cell niche and includes the emerging data supporting the hypothesis.

2. Adrenal anatomy

The adrenal glands are formed from two embryologically distinct tissues. The inner adrenal medulla is derived from neural crest cells of the neuroectoderm lineage and synthesizes catecholamines essential for the "fight-or-flight" response. The cortex is derived from cells of the intermediate mesoderm and is responsible for secretion of steroid hormones. The cortex is organized into three concentric zones, each with a discrete function, the synthesis and secretion of steroid hormones: (1) zona glomerulosa, mineralocorticoids; (2) zona fasciculata, glucocorticoids, and (3) zona reticularis, sex-steroid precursors.

3. Organogenesis

Adrenal gland organogenesis is orchestrated in discrete histological phases (Fig. 1; reviewed in Else and Hammer, 2005; Keegan and Hammer, 2002; Uotila, 1940). In the initial phase (4th week of gestation in humans, embryonic day (E) 9.0 in mice), the adrenogonadal primordium (AGP) is first distinguished and expresses the essential transcription factor SF1/Sf1 (Hatano et al., 1996; Luo et al., 1994). In the second phase (8th week gestation in humans, E10.5 in mice), the AGP separates into two distinct structures, the adrenal and the gonadal primordia. This phase is followed by migration of neural crest cells through the fetal cortex to establish the medulla and formation of a mesenchymal capsule around the fetal cortex (8–9th week of gestation in humans, E11.5–E12.5 in mice). As encapsulation progresses, the formation of the adult cortex (or definitive zone) is initiated. The human fetal zone histologically regresses at birth while the mouse fetal zone (X zone) regresses during puberty in males or at the time of first pregnancy in females.

4. Source of adrenocortical stem/progenitor cells

4.1. Evidence that the fetal cortex is the source of adrenocortical precursor cells

Sf1 expression is critical for proper adrenal organogenesis and is required for steroidogenic function in both the fetal and the adult cortex. As addressed by work of Zubair et al. (2006), the differential activity and regulation of Sf1 in the development and function of these two cell populations (fetal and adult cortex), is emerging as an essential mediator of adrenal gland organogenesis. These investigators identified a *F*etal *Ad*renal *E*nhancer (FAdE) that directs *Sf1* expression solely in the fetal cortex. During fetal adrenal development, a transcription complex containing the homeobox protein PKNOX1 (Prep1), homeobox gene 9b (Hox) and pre B-cell leukemia transcription factor 1 (Pbx1) are recruited to the FAdE upon separation of the adrenal primordium from the AGP. This complex initiates fetal zone expression of *Sf1*, which is later maintained through autoregulation by Sf1 itself (Zubair et al., 2006). Further studies of *Sf1* regulation by FAdE suggest that control of *Sf1* expression through the FAdE is abrogated at E14.5, at which time the fetal cortex begins to regress (Zubair et al., 2008). Through the use of lineage tracing studies in mouse, in which cells expressing *Sf1* driven by the FAdE are followed throughout development, Zubair et al. concluded that the adult cortex arises from cells of the fetal cortex (Fig. 2B). These studies propose a switch in the transcriptional regulation of *Sf1* in which the FAdE is inhibited and a presumed, yet-to-be identified, *D*efinitive *Ad*renal *E*nhancer (DAdE) is activated to perpetuate the expression of *Sf1* specifically in the adult cortex. The work from these studies allows important questions to be raised: (1) how is the FAdE inhibited at the transition to definitive cortex?, (2) where is the DAdE sequence and how is it activated? and (3) what are the molecular, cellular and organ-specific mechanisms that coordinate the overall fetal to adult transition? Emerging studies will address these questions to ascertain if fetal adrenal cells are indeed adrenocortical precursor cells of the definitive cortex.

4.2. Evidence that adrenocortical stem/progenitor cells reside within the adrenal capsule

The adult adrenal gland maintains organ homeostasis by replenishment of adrenocortical cells throughout life. Since the 1950s, numerous studies have provided evidence that cells from the capsule/subcapsular region of the adrenal gland are centripetally displaced inward to repopulate the adrenal cortex (reviewed in Kim et al., 2009). These studies have been primarily conducted using histology and markers of proliferation. Only within the last year has genetic data emerged to support this hypothesis. Three laboratories have provided evidence that the sonic hedgehog (Shh) signaling pathway is essential for adrenal gland development and maintenance (Ching and Vilain, 2009; Huang et al., 2010; King et al., 2009).

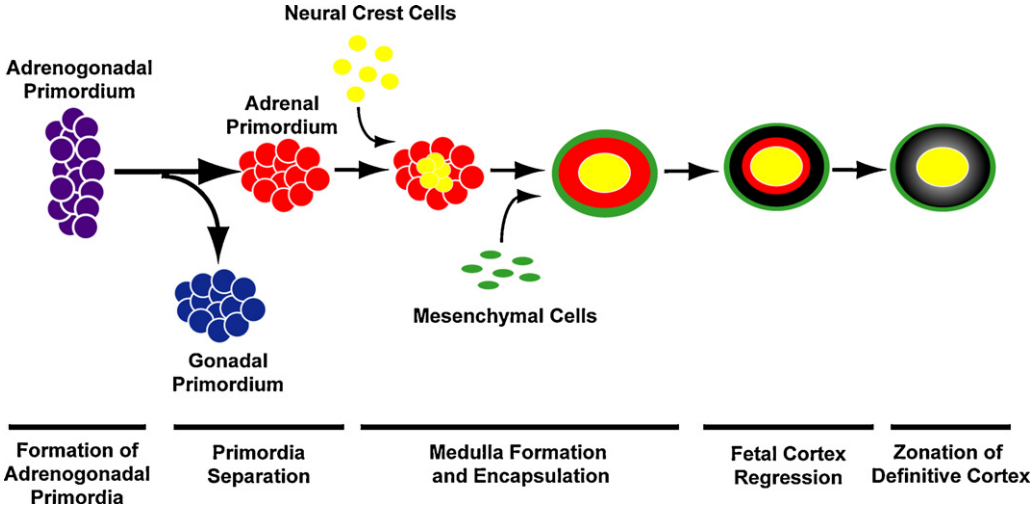

Fig. 1. Adrenal gland organogenesis. Model of adrenal gland formation from the adrenogonadal primordium through zonation of the definitive cortex. Note colors of the respective cell types: adrenogonadal primordium, purple; fetal adrenal cells, red; gonadal cells, blue; neural crest/medullary cells, yellow; mesenchymal/capsular cells, green; definitive cortex, black; fully differentiated and zonated definitive cells, gray.