Development of Adrenal Cortex Zonation

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KEYWORDS

• Adrenal cortex • Zonation • Development • Steroidogenesis

KEY POINTS

- The human adult adrenal cortex is composed of 3 different zones: zona glomerulosa (zG), zona fasciculata (zF), and zona reticularis (zR). These zones are responsible for production of mineralocorticoids, glucocorticoids, and adrenal androgens, respectively.
- The establishment of the adrenal zG and zF occurs late in fetal development with a transition from the fetal to adult cortex; however, the final completion of cortical zonation in humans does not occur until puberty with the establishment of the zR and its production of adrenal androgens; a process called adrenarche.
- The maintenance of the adrenal cortex involves the centripetal displacement and differentiation of peripheral Sonic hedgehog–positive progenitors cells into zG cells that later transition to zF cells and subsequently zR cells.

FETAL AND EARLY ADULT DEVELOPMENT OF THE ADRENAL CORTEX

Formation of the Adrenal Cortex

Origin of the adrenogonadal primordium

The adrenal glands develop from 2 separate embryologic tissues: the medulla is derived from neural crest cells originating in proximity to the dorsal aorta, whereas the cortex develops from the intermediate mesoderm.[1] The appearance of the adrenal gland in the form of the adrenogonadal primordium (AGP) at 28 to 30 days postconception (dpc) in humans (embryonic day [E] 9.0 in mice) is marked by the expression of steroidogenic factor 1 (SF1; NR5A1), a nuclear receptor essential for adrenal development and steroidogenesis.[2,3] The bilateral AGP first appears as a thickening of the coelomic epithelium between the urogenital ridge and the dorsal mesentery. Each

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AGP contains a mixed population of adrenocortical and somatic gonadal progenitor cells. SF1-positive AGP cells then delaminate from the epithelium and invade the underlying mesenchyme of the intermediate mesoderm.[4]

Separation of adrenogonadal primordium (formation of the adrenal gland)

Following delamination, most AGP cells migrate dorsolaterally to form the gonadal anlagen (gonadal primordial [GP]). A subset of AGP cells that express higher levels of SF1 migrate dorsomedially to form the adrenal anlagen (adrenal primordial [AP] or adrenal fetal zone [FZ]), ultimately settling ventrolateral to the dorsal aorta.[3] At about 48 dpc in humans (E11.5–E13.5 in mice), neural crest cells migrate from the dorsal midline just lateral to the neural tube to the area where the AP is developing.[5] These cells persist as discrete islands scattered throughout the embryonic adrenal until birth and ultimately coalesce and differentiate into the catecholamine-producing chromaffin cells of the adrenal medulla.[6,7] Meanwhile, the adrenal gland starts to separate from surrounding mesenchyme and becomes encapsulated with the formation of a fibrous layer overlying the developing cortical cells, a process largely complete by 52 dpc in humans (E14.5 in mice).[8]

Adrenocortical and chromaffin cells have an intimate relationship during embryonic development and postnatal homeostasis. Adrenal glucocorticoids play an essential role in chromaffin cell hormone production by regulating the expression of phenylethanolamine *N*-methyltransferase, which results in epinephrine (as opposed to norepinephrine) being the dominant catecholamine produced in the postnatal adrenal medulla.[9,10] However, mutant mice lacking the glucocorticoid receptor show normal embryonic neural crest cell migration to the adrenal and normal early fetal chromaffin cell development.[11] Similarly, even in the setting of a hypoplastic (*Sf1* heterozygous [$Sf1^{+/-}$] mice) or aplastic (*Sf1* null [$Sf1^{-/-}$] mice) adrenal cortex, a rudimentary adrenal medulla develops,[12] albeit in an ectopic location in the hypoplastic gland.[12,13] Further studies are needed to yield insights into the molecular mechanisms that dictate the interplay between the steroidogenic adrenocortical cells and the catecholamine-producing chromaffin cells of the adrenal gland.[14,15]

Fetal Development of the Adrenal Cortex

Fetal zone formation and function

After encapsulation, the embryonic adrenal cortex expands rapidly. In humans, the enlargement of the fetal cortex (FZ) accounts for most of the prenatal growth, especially during the last 6 weeks of gestation. The human fetal adrenal is one of the largest organs at term (0.2% of total body weight and nearly the size of the kidney), with 80% of the gland composed of FZ cells.[16] These large steroidogenic cells (20–50 mm) show a high cytoplasmic/nuclear ratio and robustly express cytochrome P450 17 alpha (CYP17), a bifunctional enzyme with both 17 hydroxylase and 17,20 lyase activities that convert pregnenolone to dehydroepiandrosterone (DHEA). Because of the high activity of CYP17 at this stage, the human fetal adrenal cortex produces large amounts of DHEA and DHEA-sulfate (S), which is then converted by the placenta to estrogens for the maintenance of normal pregnancy. Although large amounts of other sulfated $\Delta 5$ steroids, including pregnenolone sulfate and 17α-hydroxypregnenolone sulfate are also produced by FZ cells, it is unclear whether such steroids play a functional role in human biology.

Emergence of the definitive zone

By the eighth week of gestation, new adrenocortical cells emerge between the capsule and FZ, forming the definitive zone (DZ), which later develops into the adult cortex. The DZ is composed of SF1-positive, densely packed basophilic cells