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Original article

Adrenal stem cell niches are located between adrenal and renal capsules

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Proceedings

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Stem cells: present and future
Guest Editors: Gavino Faa (Cagliari, Italy), Vassilios Fanos (Cagliari, Italy), Antonio Giordano (Philadelphia, USA)

Abstract

The human adrenal glands arise around the 4th week of gestation and during the intrauterine life produce many substances that are responsible for the maintenance of fetal homeostasis and organ maturation. Stem cell niches represent the microenvironment suitable for life and replication of adrenal stem cells.

Adrenal gland stem cells have the capacity to self-renew and generate functional differentiated daughter cells that replenish lost cells. Morphologically the adrenal stem cells appeared as small, polymorphic cells, closed together, with basophilic nucleus, located between adrenal and renal capsules. This study was mainly based on a morphological and immunohistochemical approach, particularly on characterization and localization of the multiple stem/progenitor cells that contribute to the development of the human adrenal gland.

Keywords

Stem/progenitor cells, adrenal glands, adrenal gland stem cell niches, adrenal gland capsule, adrenal gland morphogenesis, adrenal gland development.

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Introduction

The relevant role played by adrenal glands in fetal metabolism is mainly represented by a specific component of the developing gland: the fetal zone of the adrenal cortex, that occupies the core of the fetal adrenal gland, and represents the vast majority of the adrenal cells at all the gestational ages, till birth. In the early phases of gestation, fetal zone cells produce androgens, including dehydroepiandrosterone (DHEA) and DHEA-sulfate, that are precursors of the placental estrogens. At late gestation, fetal zone cells produce aldosterone and cortisol, factors responsible for the maintenance of fetal homeostasis and organ maturation [1].

Maternal diet, stress, hypertension, antibiotics, non-steroid anti-inflammatory drugs, prematurity, low birth weight and intrauterine growth restriction may disturb adrenal gland development, ending with malfunction in the perinatal period and adrenal insufficiency later in life [2]. Stem cell niches represent the microenvironment suitable for life and replication of adrenal stem cells. Stem cell niches often contain one or more blood vessels, necessary to provide oxygen and nutrients. Adrenal gland stem cells have the capacity to self-renew and generate functional differentiated daughter cells that replenish lost cells [3].

The aim of this paper was to review adrenal glands organogenesis in humans, with particular attention to the characterization and localization of the multiple stem/progenitor cells, playing a role in adrenal gland development.

This study was mainly based on a morphological and immunohistochemical approach.

Development of the adrenal glands

During the intrauterine life, the adrenal gland plays a fundamental role in the maintainance of pregnancy and in the general homeostasis of the fetus [4]. Human fetal adrenal glands arise from the intermediate mesoderm, near the developing mesonephros, around the 4th week of gestation, when the adrenogonadal primordium (AGP), constituted by primordial adrenal cells and primordial gonadal cells, develops. Around the 8th and the 9th week of gestation, when separation of the AGP into adrenal primordium (AP) and gonadal primordium (GP) takes place, stem cells encapsulate the developing fetal adrenal gland [5] (**Fig. 1**). At this time, the cortex appears separated into two different zones: the definitive zone, which is localized in the outer cortical zone, in close proximity to the adrenal capsule, and the fetal zone [6] (**Fig. 2**).

From the neural crest, neuroblastic precursors migrate inside the developing adrenal gland to give rise to the adrenal medulla. Through nerve fibers originating from the sympathetic ganglia, medullary precursors penetrate into the adrenal primordium [7]. During gestation, small islands of medullary cells are scattered in the body of the cortex and during the 1st postnatal week, the vast majority of medullary cells are localized around the central vein. Around the 4th postnatal week medullary cells have clustered in the center of the gland [8] (**Fig. 2**).

Adrenal stem/progenitor cell niches

An important function of the stem cell niches is to regulate the balance between cellular self-renewal and differentiation. During asymmetric division stem cells divide into two daughter cells; one daughter cell remains in the niche as a stem cell and the other daughter cell leaves the niche to produce a large number of progeny. During symmetric division stem cells divide into two identical daughter cells, both remaining in the niche as stem cells. Under different physiological conditions the switching between symmetric and asymmetric division can occur in multiple stem cells that occupy the same niche [9, 10].

It is believed that stem/progenitor cells of the adrenal cortex are localized at the periphery of the gland and remain undifferentiated and quiescent until needed to replenish the gland, when they undergo proliferation and differentiation. It has

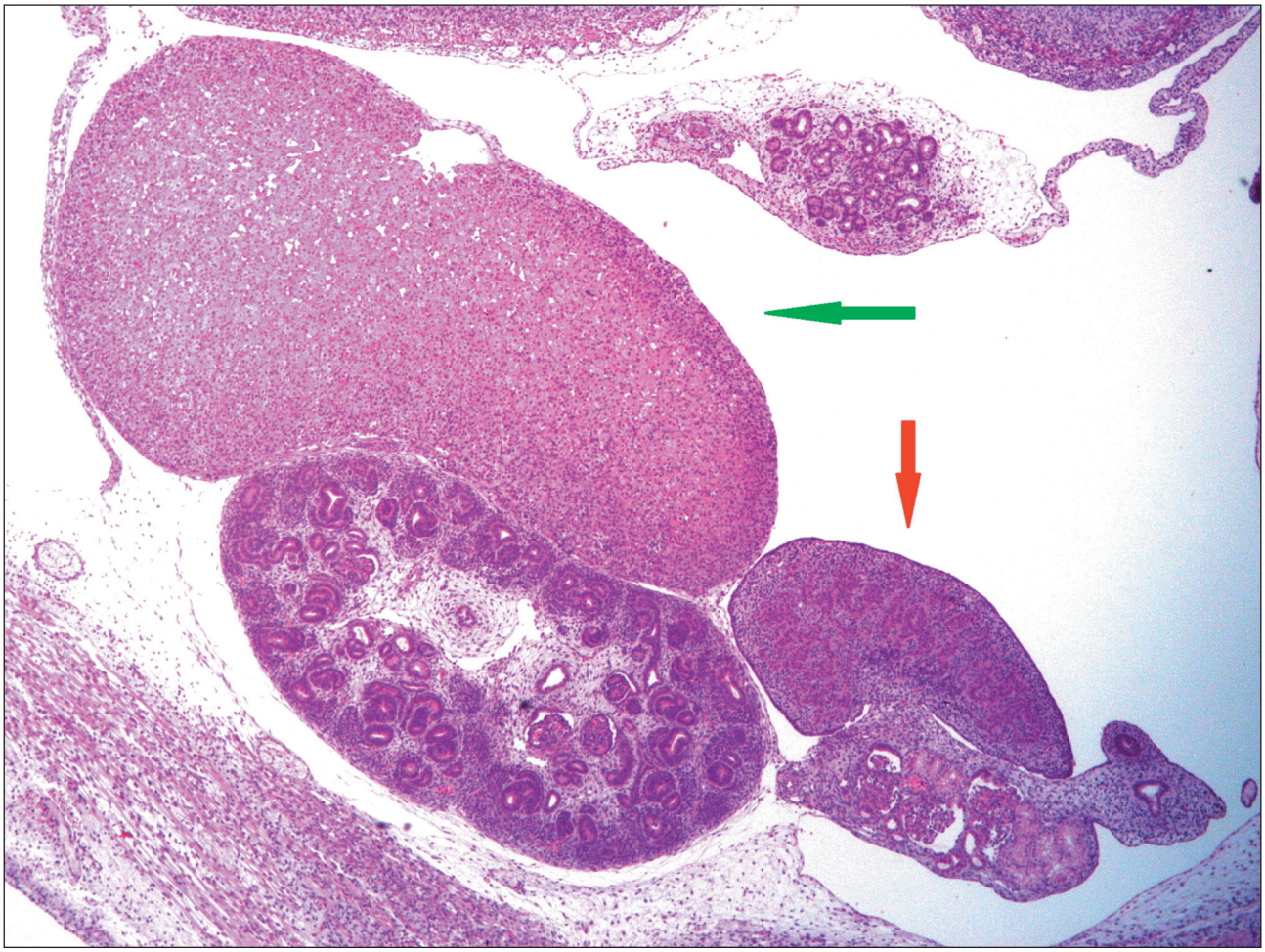

Figure 1. Adrenal primordium (AP) (green arrow) and gonadal primordium (GP) (red arrow) in a human fetus of 9 weeks of gestation.

been recently proposed that the adrenal capsule serves as a stem cell niche/residence for adult adrenocortical stem/progenitor cells that reside within and/or underneath the capsule [11, 12].

The adrenocortical capsule and the underlying undifferentiated cortical cells are emerging as critical components of the stem/progenitor cell niche [13]. It has been suggested that the slowly proliferating cells present in the capsule generate daughter cells that could be centripetally displaced to populate the adrenal cortex [14].

Recent data support the hypothesis that the homeostasis of the adrenal cortex occurs through an inward centripetal displacement of cortical cells from the periphery of the gland (capsule and/or subcapsular region) toward the cortico-medullary boundary, where apoptosis occurs [15]. The continuous centripetal repopulation of the adrenal cortex is consistent with a cell population endowed with the stem/progenitor cell properties of self-renewal and pluripotency.

Adrenal stem cells features: where are they located and which is their morphology?

Human adrenal gland stem cells may be identified for the first time at the periphery of the adrenal cortex at 7-10 weeks of gestation (**Fig. 3**): they are generally described as small cells with iperchromatic nuclei. At 16 weeks of gestation, medullary cells appear and the adrenal stem cells are located at the periphery of the cortex, in the cortical parenchyma, cortico-medullary junction and in the core of the adrenal gland. The adrenal essential architecture is established around 20 weeks, however there are still stem cells. At term of gestation there are few stem cells [16] (**Fig. 4**).

Preliminary personal data

Histological sections of human adrenal glands in fetuses of 9, 11, 12 weeks of gestation and in a

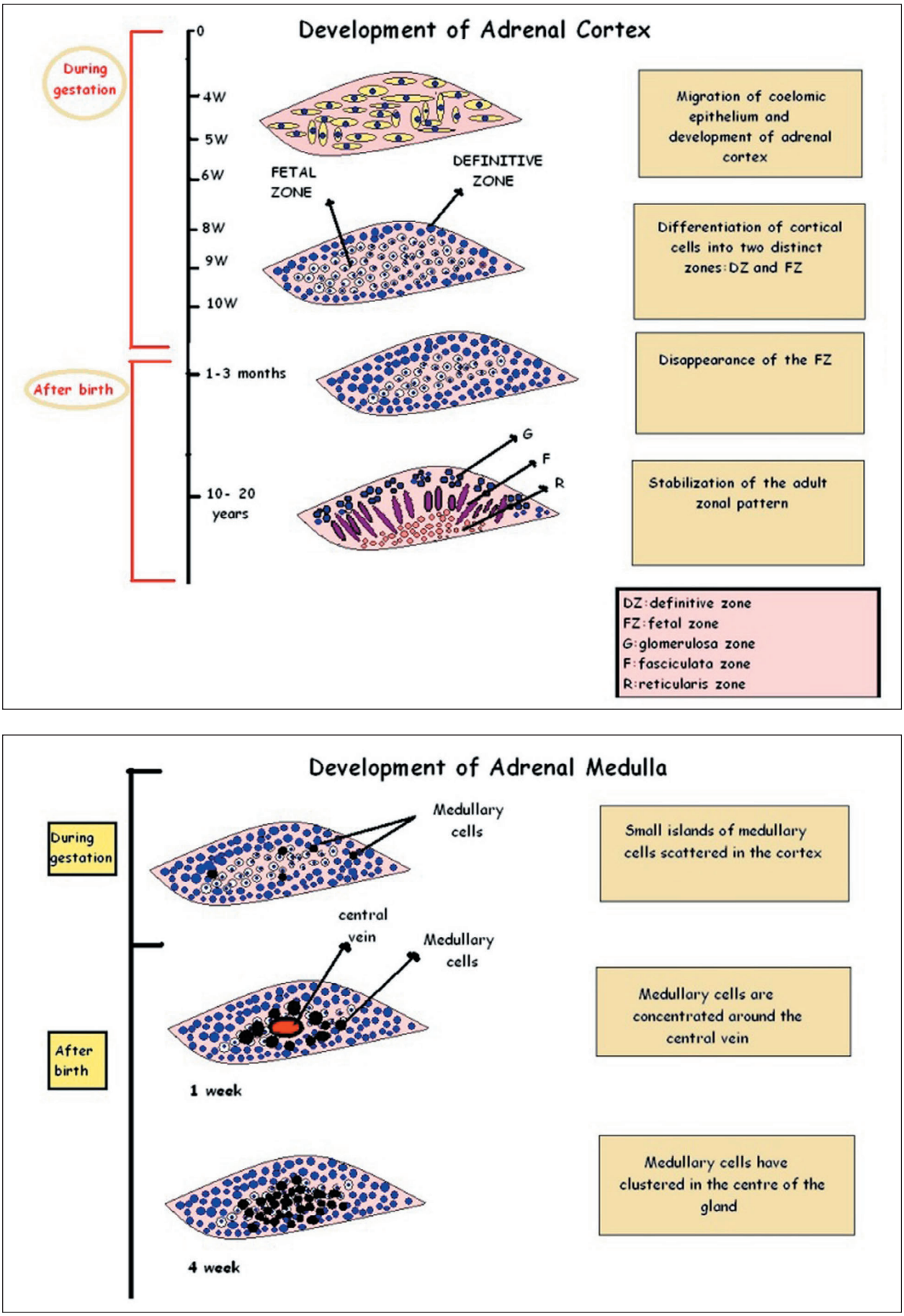

Figure 2. Stages of development of the adrenal cortex (**A**) and the adrenal medulla (**B**) in a human adrenal gland.

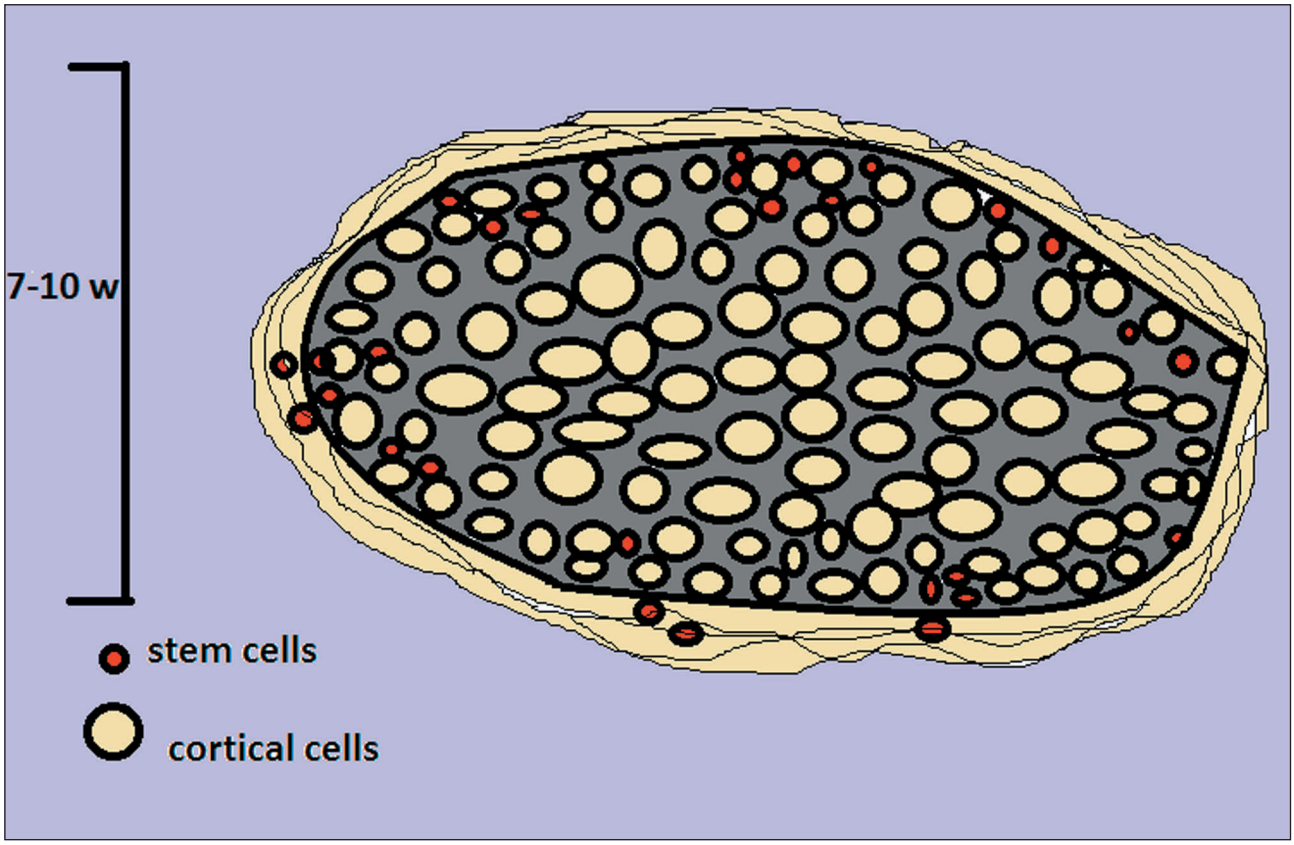

Figure 3. Human adrenal gland stem cells may be identified at the periphery of the adrenal cortex at 7-10 weeks of gestation.

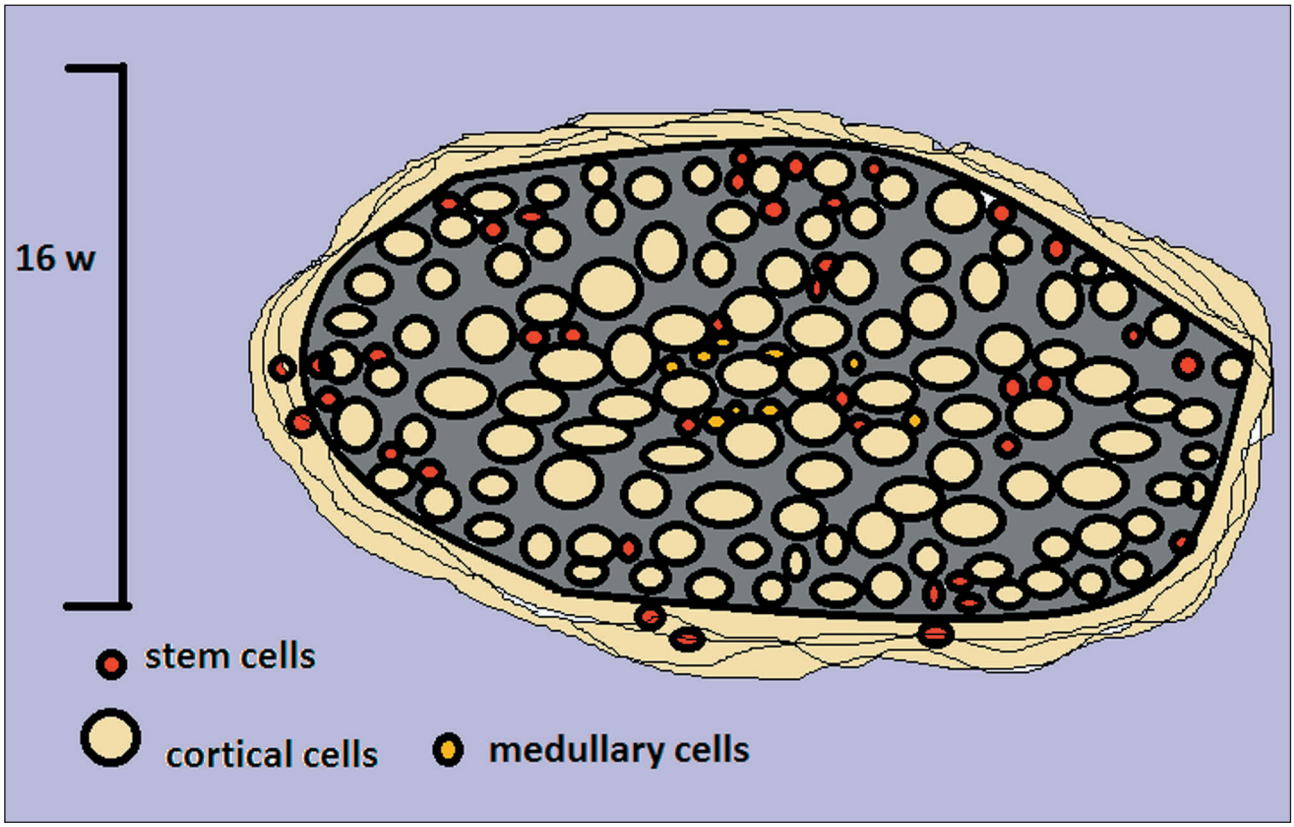

Figure 4. Human adrenal gland stem cells may be identified at the periphery of the cortex, in the cortical parenchyma, cortico-medullary junction and in the core of the adrenal gland at 16 weeks of gestation.

newborn of 1 day of life, colored by hematoxylin and eosin, were examined at microscope.

The characterization and the location of stem/progenitor cell niches in human fetal adrenal glands appeared complex. Stem cell niches often contained one or more blood vessels, necessary to provide oxygen and nutrients.

The stem cell niches were not visible at low power. At high power (40-60 PF) stem cell niches appeared scattered inside the capsule and in subcapsular zone. They were located between adrenal and renal capsules. There was a strong evidence for the variability of the number and morphology of the stem/progenitor cells, according to increasing gestational age. As the development went on, the number of stem cells and niches were gradually reduced.

In a human embryo of 9 weeks of gestation, the adrenal gland appears constituted by a cortical zone where we recognized the definitive zone, at the periphery of the gland, and the fetal zone, that represented the biggest part of the gland. The adrenal glands appeared surrounded by a fibrous capsule in which we recognized, in addition to fibroblasts, nests of polymorphous cells of about 10-15 micron of size, very close together, often near a blood vessel, with the nucleus intensely basophilic and poor cytoplasm. Nests of cells with the same characteristics were observed in the subcapsular zone (**Fig. 5**, **Fig. 6**).

These cells sometimes contained prominent cherry red nucleoli (**Fig. 7**).

Frequently we observed mitotic figures in the proximity of the stem/progenitor cell niches, inside

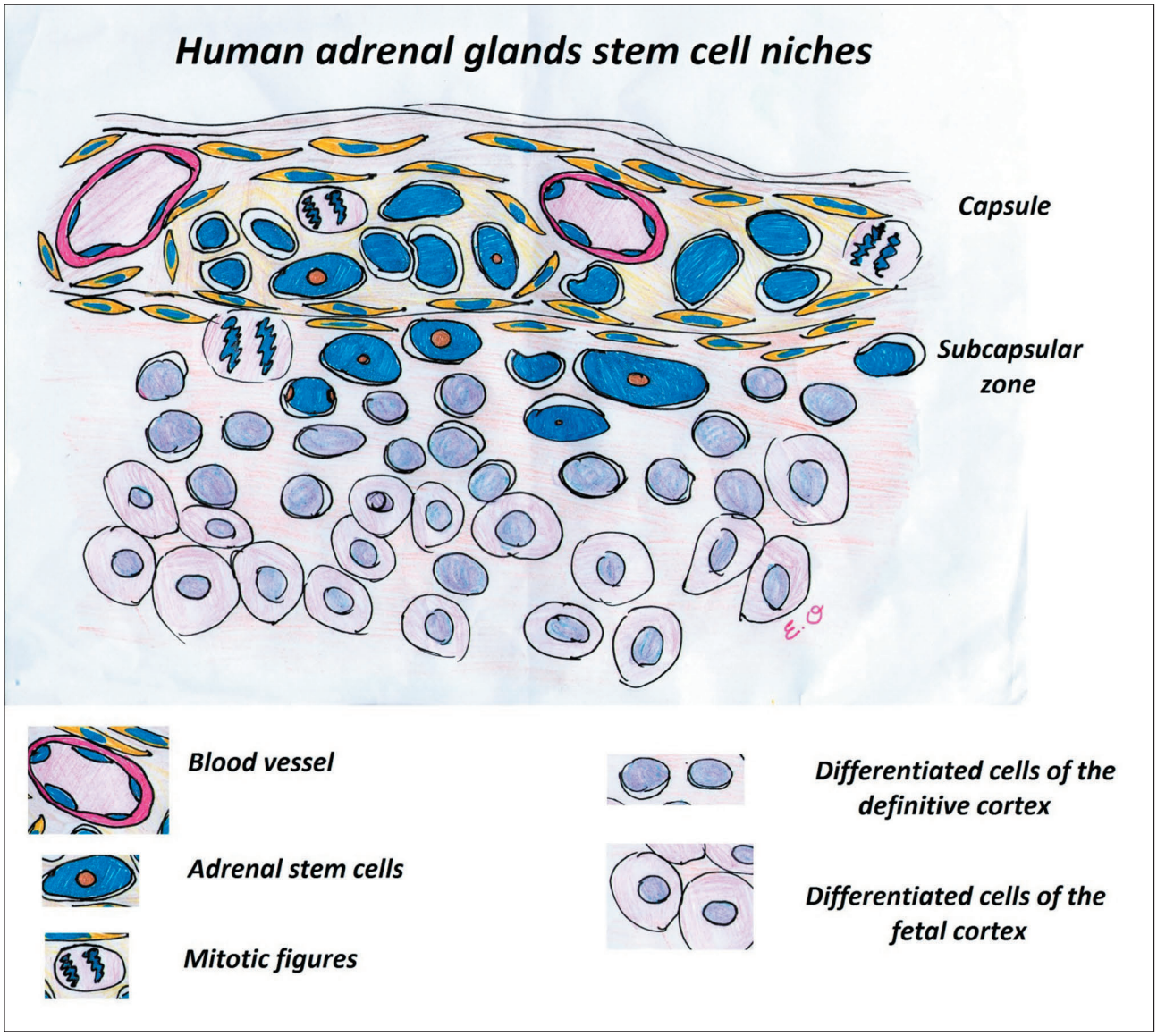

Figure 5. Representation of the adrenal glands stem cell niches in a human fetus of 9 weeks of gestation.

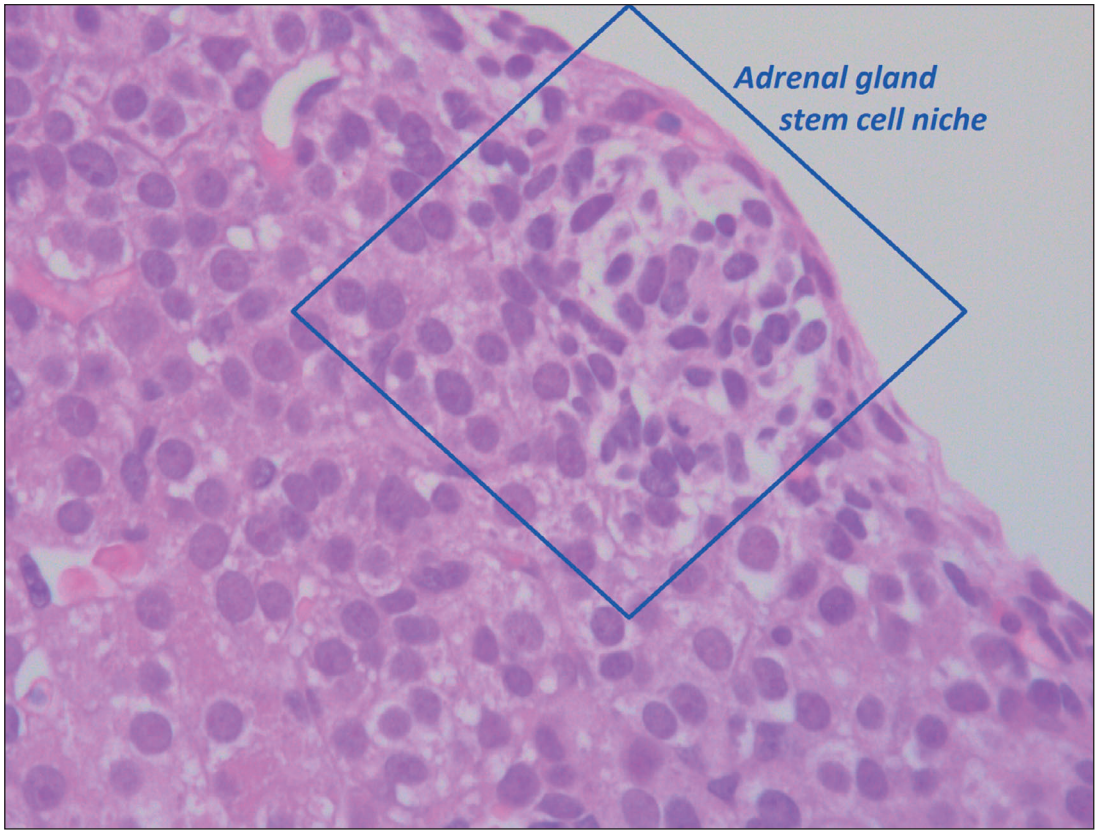

Figure 6. Adrenal gland stem cell niches appeared inside the capsule of the adrenal glands in a human fetus of 9 weeks of gestation.

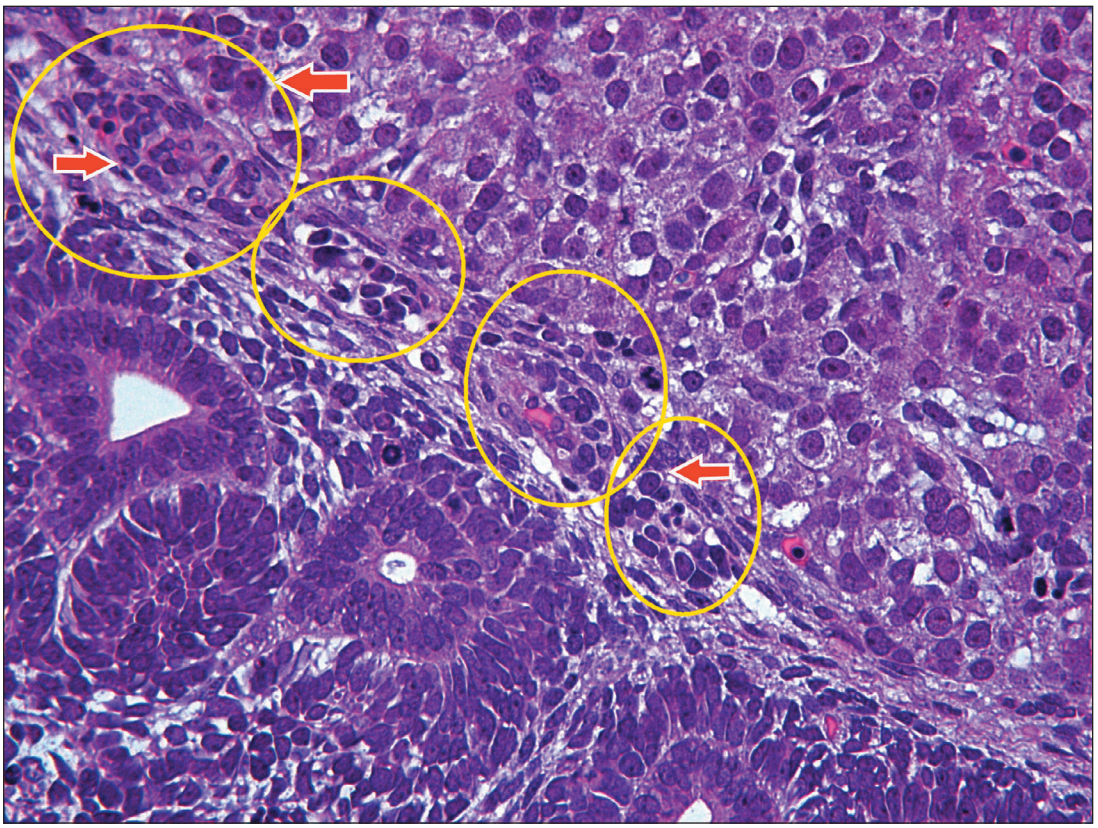

Figure 7. Adrenal gland stem cells appeared as polymorphous cells, very close together, often near a blood vessel, aggregated in nests. Adrenal gland stem cells sometimes contained prominent cherry red nucleoli.

and under the adrenal capsule (**Fig. 8**). These cells showed different morphology as compared to the other cells of the gland, and tended to aggregate in nests inside the stem cell niches.

In a human newborn of two days of life, adrenal stem cell niches were not evident inside the capsule and in the subcapsular zone of the adrenal gland. The cortex of the adrenal gland appeared organized into glomerular and fasciculate zone.

Adrenal gland stem cells: recent immunohistochemical data

Recent studies in multiple human embryonic adrenal glands between 7 and 40 weeks of gestation demonstrated that at immunohistochemistry the stem cells were positive for neural cell adhesion molecule, as CD117, Neuron Specific Enolase (NSE), Platelet-Derived Growth Factor receptor alpha (PDGFr alpha), Synaptophysin, Hepatocyte Growth Factor receptor (HGFR), and Alpha fetoprotein. The stem cells were also negative for Chromogranin, ErbB2 and Bcl-2 and for some cytokeratins [16].

Discussion

Adrenal gland stem cells have the capacity to self-renew and generate functional differentiated daughter cells that replenish lost cells [3]. Stem/progenitor cells are localized inside the niches, virtual spaces in which these cells reside, proliferate and differentiate in daughter cells. The niches, located near a blood vessel, contain stem cells, giving them a protective environment and ensuring a constant supply of oxygen and nutrients.

Every situation that can cause hypoxia, such as maternal hypertension, thrombosis of placental vessels, could cause death of stem cells by hypoxia.

Our preliminary study has set a goal to highlight, based on morphological findings, the stem cell niches, containing stem/progenitor cells

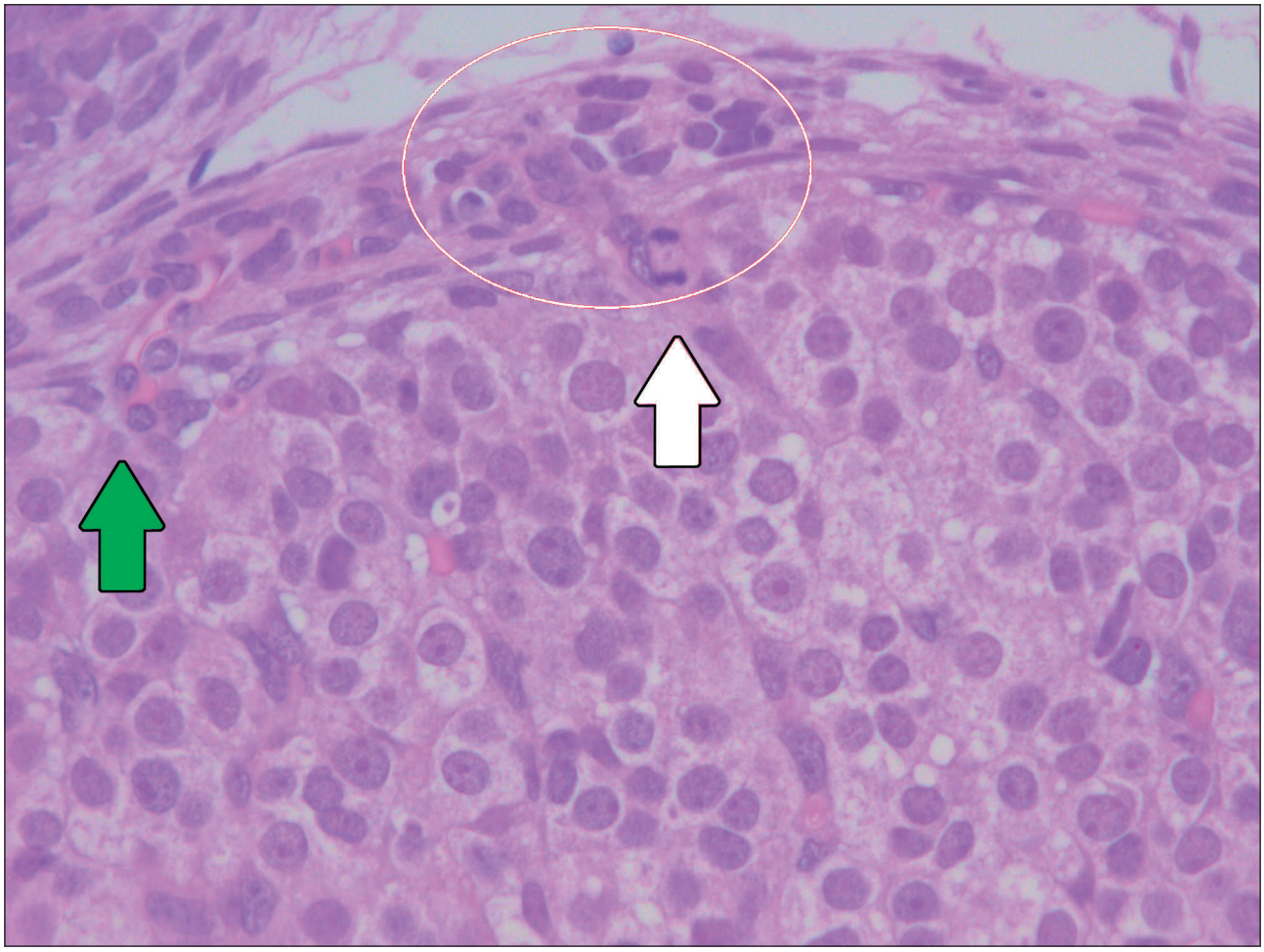

Figure 8. Adrenal gland stem niches appeared inside the capsule and in the subcapsular zone of the adrenal glands in a human fetus of 9 weeks of gestation. The white arrow indicates a mitotic figure. The green arrow indicates a blood vessel inside the stem cell niche.

of the adrenal gland. They were clearly identified during the development of the human fetus.

There were many morphological differences among the stem cells of the adrenal gland during gestation: stem/progenitor cells were numerous in the earlier period of development of the adrenal gland, whereas at term of gestation we could see only few stem cells. Stem/progenitor cells appeared small, polymorphic, with scant cytoplasm, very close together. Some cells showed prominent cherry red nucleoli. This morphological diversity could be explained as the presence, inside the stem cell niche, of cells in different state of activation. The future goal, using immunohistochemical techniques, is to better characterize the stem cell niche and, on the basis of expression of specific markers, identifying which of them are quiescent and which of them are activated to generate a population of mature and different daughter cells.

The research and the identification of stem/progenitor cells in the human adrenal gland is very interesting because they could be utilized as regenerative cell therapy in the treatment of neonatal and adult degenerative deseases.

Declaration of interest

The Authors declare that no conflict of interest exists.

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