Stem cells, evolutionary aspects and pathology of the adrenal medulla: A new developmental paradigm

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ABSTRACT

The mammalian adrenal gland is composed of two main components: the catecholaminergic neural crest-derived medulla, found in the center of the gland, and the mesoderm-derived cortex producing steroidogenic hormones. The medulla is composed of neuroendocrine chromaffin cells with oxygen-sensing properties and is dependent on tissue interactions with the overlying cortex, both during development and in adulthood. Other relevant organs include the Zuckerkerndl organ containing extra-adrenal chromaffin cells, and carotid oxygen-sensing bodies containing glomus cells. Chromaffin and glomus cells reveal a number of important similarities and are derived from the multipotent nerve-associated descendants of the neural crest, or Schwann cell precursors. Abnormalities in complex developmental processes during differentiation of nerve-associated and other progenitors into chromaffin and oxygen-sensing populations may result in different subtypes of paraganglioma, neuroblastoma and pheochromocytoma. Here, we summarize recent findings explaining the development of chromaffin and oxygen-sensing cells, as well as the potential mechanisms driving neuroendocrine tumor initiation.

1. Introduction

During mammalian embryonic development, all major cell lineages originate from multipotent, although fate-restricted, germ layers: the ectoderm, mesoderm and endoderm. The adrenal gland, similarly to other endocrine organs (such as the pituitary, pancreas, thyroid and parathyroid glands), integrates cell types from different origins into a functional and anatomical unit. Normal development and function of the adrenal gland is key for many bodily functions, especially as a part of the hypothalamic-pituitary-adrenal axis, responsible for controlling the response of our body to stressful external stimuli (Smith and Vale, 2006).

In mammals, the adult adrenal gland is mainly composed of neural crest-derived neurosecretory chromaffin cells found in the medulla, which are responsible for catecholamine release (adrenaline and noradrenaline) (Kohn, 1902; Euler, 1949). The medulla is surrounded by the mesoderm-derived cortical cells producing steroid hormones (synthesized from cholesterol), (reviewed by (Pihlajoki et al., 2015)). Intermingled with chromaffin cells, small groups of postganglionic neurons participate in currently underdefined functions (Dagerlind et al., 1996; Holgert et al., 1996). The whole gland is encapsulated in a thin mesodermal layer, the capsule, and is traversed by dense valvular transport of released hormones and neurotransmitters (Bandiera et al., 2013; Wood et al., 2013; Vidal et al., 2016). Last but not least, peripheral glial cells reside within the adrenal medulla in close association with chromaffin cells (satellite glia) and in adjacency to the paraganglionic spinal visceral motor nerves innervating the gland (Schwann cells) (Jessen and Mirsy, 2019).

The current opinion holds that chromaffin and adrenocortical lineages show a significant degree of cell subtype heterogeneity. In mouse, all chromaffin cells express tyrosine hydroxylase (TH) (necessary for the synthesis of DOPA from the amino acid tyrosine) and dopamine beta-hydroxylase (DBH) (catalyzing the conversion of dopamine to noradrenaline) (Axelrod, 1974; Nagatsu and Stjarne, 1998). At the same time, only a subpopulation of these chromaffin cells expresses phenyl-ethanolamine N-methyltransferase (PNMT), the enzyme that is responsible for conversion of noradrenaline into adrenaline. This discrepancy leads to two functional subpopulations of chromaffin cells; one that is capable mainly of noradrenaline synthesis while the second subpopulation synthesizes mainly adrenaline (Wurtman et al., 1968; Bohn et al.,

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Likewise, the mouse adrenal cortex is heterogeneous and organized in three main zones including the zona glomerulosa (in close contact with the capsule), zona fasciculata and X-zone (found in the innermost part of the cortex and in close contact with the medulla) as reviewed by (Pihlajoki et al., 2015) (Fig. 1). However, interspecies comparisons of the cellular composition and layers of the adrenal cortex have unveiled some important differences. In particular, in humans, an extra zone is found, known as zona reticularis, reviewed by (Yates et al., 2013). In all investigated mammalian species, each cortical layer is composed of cells that express a different set of enzymes responsible for the production of a spectrum of steroid hormones (mineralocorticoids – zona glomerulosa, glucocorticoids – zona fasciculata and zona reticularis) reviewed by (Vinson, 2016). The X-zone is only seen in young male mice or female mice prior to the first pregnancy and is hypothesized to participate in progesterone catabolism (Hirokawa and Ishikawa, 1974; Hershkovitz et al., 2000; Lim et al., 2000; Tsarovina et al., 2004; Huber, 2006; Wildner et al., 2008; Saito et al., 2012). During the second phase, the nerve-associated multipotent cells known as Schwann cell precursors generate the immediate progenitors of the chromaffin cells (called “bridge” cells) in the developing adrenal primordium proximally to the SF1+ (Nr5a1+) cells composing the adrenal cortex (Furlan and Adameyko, 2018; Lumb et al., 2018). (B) In the mouse model system, the adult adrenal gland is characterized by specific zonation: the chromaffin cell-containing medulla is surrounded by concentric layers of steroidogenic cells (derived from the SF1+ lineage), organized into zona fasciculata and zona glomerulosa (Pihlajoki et al., 2015). In young female mice, prior to the first pregnancy, an additional zone called x-zone can be identified (Hirokawa and Ishikawa, 1974; Morohashi and Zubair, 2011). NC(C): neural crest (cells), SCP: Schwann cell precursor, IML: interomedial column, DRG: dorsal root ganglion, SG: sympathetic ganglion, SRG: suprarenal ganglion, DA: dorsal aorta, zG: zona glomerulosa, zF: zona fasciculata.

11. Mechanisms of embryonic development of the adrenal medulla

During embryonic development, the early primordium of the adrenal gland develops in a spatial association with sympathetic neurons. This common primordium is referred to as the sympathoadrenal domain. Studies in chicken pointed to a common sympathoadrenal progenitor that was derived from neural crest cells (Le-Douarin and Teillet, 1974; Shukmaster et al., 2013). The neural crest is a migratory multipotent population characterized by the expression of Sox10 and Foxd3. The crest delaminates and migrates from the dorsal neuroepithelium (ectoderm) upon neural tube closure towards different destinations in the developing embryonic body. According to this model, following delamination, a portion of neural crest cells, referred to as sympathoadrenal neural crest, migrate ventrally towards the midline and reach the dorsal aorta (DA) (Loring and Erickson, 1987). Neural crest migration towards the DA is instructed by several ligand-receptor interactions mediated by BMPs and CXCL12 secreted by the DA (Reissmann et al., 1996; Shah et al., 1996; Britsch et al., 1998; Schneider et al., 1999; Huber, 2006; Schwarz et al., 2009; Kasemeier-Kulesa et al., 2010; Saito et al., 2012; Lumb et al., 2014) (Fig. 1). Additionally, class 3 SEMAPHORINS (SEMA3s) are secreted proteins that bind to transmembrane NEUROPILINS (NRPs) (Takahashi et al., 1999) expressed by neural crest cells and guide through cellular repulsion the cells towards their targets in the sympathoadrenal anlage (Schwarz et al., 2009; Sharma et al., 2012; Lumb et al., 2014).
Once neural crest cells reach the DA, they initiate the expression of a set of transcription factors necessary for sympathoadrenal specification and development: Ascl1 ( Mash1), Phox2a/b, Hand2, Gata2/3 and Insml (Güllomet et al., 1993; Pattyn et al., 1999; Schneider et al., 1999; Howard et al., 2000; Lim et al., 2000; Tsarovina et al., 2004; Wildner et al., 2008) (Fig. 1). Earlier studies concluded that following the arrival of the sympathoadrenal precursors at the vicinity of the DA, the cells undergo lineage segregation: the dorsal-most group of cells will give rise to sympathetic neurons, while the ventral-most group will give rise to chromaffin cells of the medulla (Takahashi et al., 2013). Following fate restriction, the two lineages will show spatial separation, with the chromaffin fate-committed cells migrating in between the cortical progenitors. Once the cells occupy their final location, both lineages start expressing specific markers, i.e. sympathoblasts will acquire neurofilaments, neuronal tubulin and TH, while chromaffin cells will express TH and all other components of catecholamine synthesis such as DBH and later on PNMT (Huber et al., 2009).

However, the original model of sympathoadrenal development through a common neural crest progenitor could not explain a few observations. Firstly, the sympathoadrenal progenitors are characterized by differential marker expression prior to their arrival to the DA or even the formation of the adrenal anlage. Specifically, neurofilament presence and Th expression unique to sympathoblasts was detected prior to the formation of the adrenal primordium, pointing to the presence of two distinct cellular populations in the vicinity of the future adrenal anlage (Ernsberger et al., 2005). This observation was replicated using CART as a neuroblast-specific marker absent in chromaffin cells (Ernsberger et al., 2005; Chan et al., 2016). Secondly, studies showed the presence of high numbers of SOX10+ glial cells in the adrenal primordium even before the generation of the majority of TH+ chromaffin cells and sympathoblasts (Gut et al., 2005; Reiprich et al., 2008).

The timing of the emergence of the first adrenal medulla cells (E11.5-E12.5 in mouse embryos) also suggests their origin from some enigmatic post-neural crest cellular source (Gut et al., 2005; Reiprich et al., 2008). Lastly, the specific involvement of axonal-derived signals such as neurogulin-1 (NRG1) in the establishment of the adrenal medulla had been hinted, which could not be explained by the traditional model in which sympathoadrenal cells were derived from a common neural crest progenitor population (Britsch et al., 1998).

Recent studies shed light on these events by revealing that chromaffin cells of the adrenal medulla are directly derived from the descendants of the neural crest, known as Schwann cell precursors (SCPs) (Furlan et al., 2017). SCPs are early embryonic nerve-associated cells of neural crest origin, which were historically described as cells of the peripheral glial lineage that were detected through expression of Mps even prior to myelination (Jessen and Mirsky, 1997; Lee et al., 1997; Lee et al., 2001). SCPs carry on some of the neural crest multipotency, giving rise to a wide range of cell types such as peripheral glia (Schwann cells), melanocytes, cranial parasympathetic neurons and other cell types (Furlan and Adameyko, 2018). In the vicinity of the sympathoadrenal primordium, cholinergic preganglionic neurons of the spinal cord (somas are located in the interomedial column) extend their axons in order to innervate the visceral organs. Using a sophisticated navigation system including class 3 SEMAPHORINS (SEMA3s) and their receptors NEUROPILIN-1 (NRP1) and NEUROPILIN-2 (NRP2) (Takahashi et al., 1999; Sharma et al., 2012), SCPs navigate along the axons guiding them to the developing sympathoadrenal primordium (Lamb et al., 2018). Once SCPs are delivered there, they differentiate via a transitory “bridge” transcriptional state into chromaffin cells of the adrenal medulla (Fig. 1).

Meanwhile, the analysis of the postnatal adrenal medulla in rodents has shown the existence of intramedullary postganglionic neurons organized into small ganglia, which are believed to partially innervate chromaffin and cortical cells (Dagerlind et al., 1990; Maubert et al., 1990; Oomori et al., 1994; Afework and Burnstock, 1995; Holgert et al., 1996). Of note, these neurons are grouped into type I NPY+/AChE+/TH−/NF− and type II VIP+/NOS+/TH− cells and are only observed in postnatal stages. This late onset of detection suggests their emergence during late developmental or even postnatal stages as compared to the early-born sympathetic neurons and chromaffin cells. In the mouse model system, cranial parasympathetic ganglia are derived from embryonic nerve-dwelling SCPs at stages during which neural crest migration is already complete (Dyachuk et al., 2014; Espinosa-Medina et al., 2014). Similarly, the neuronal ganglia found in the postnatal adrenal medulla might be derived from late embryonic or early postnatal SCPs or advanced nerve-associated glial progenitors that are supported within the growing gland by the visceral motor innervation.

In mice, the peak of the multipotency of SCPs throughout the body is seen between E11.0 to E13.5, a developmental window during which SCPs get dispersed to multiple locations via the peripheral nerves (Jessen and Mirsky, 2019). During this critical period, a subset of SCPs is driven into differentiation, potentially after receiving the enigmatic permissive signals produced by the organ primordia nearby.

Similarly to the dynamics described above, SCPs reach the adrenal primordium between E11.5 to E12.5 to produce the majority of the medullary chromaffin cells. This process requires high numbers of recruited SCPs, since they make very few cell divisions before differentiating into non-proliferative chromaffin cells. The lineage tracing shows that multipotency of SCPs and their capacity to produce chromaffin cells disappears almost completely by E15.5 (Furlan et al., 2017), when the medulla activates growth mechanisms based on chromaffin cell division until it reaches its full size. Remarkably, chromaffin cell divisions are rare in the postnatal adrenal medulla, posing questions about the mechanisms governing chromaffin cell turnover and self-renewal of the catecholaminergic neuroendocrine tissue.

Of note, the majority of SCPs will not differentiate and will keep developing into satellite glial cells found adjacent to neuronal somas in peripheral ganglia, or Schwann cells covering peripheral nerves. A bit later during development, a subset of immature nerve-associated Schwann cells will commit to myelination, while the rest will remain dormant on the nerves as Remak or non-myelinating Schwann cells (Jessen and Mirsky, 2005; Jessen et al., 2015).

1.2. Stem cells and turnover in the adult adrenal medulla

The regenerative capacity of the adrenal cortex is well recognized, especially given that cells of the zona glomerulosa and zona fasciculata are replaced throughout the lifetime both in human and rodents, also following adrenalectomy (Graham, 1916; Brogi and Pellegrino, 1959; Holzwarth et al., 1980; Hampel et al., 1994; Engeland et al., 1996; Gotlieb et al., 2018). Specifically, Finco and Lerario with co-authors revealed that Shh-expressing cells drive regeneration of the zona fasciculata through paracrine activation of Gli1 signaling in the cells of the capsule (Finco et al., 2018). At the same time, the regeneration of the entire cortex is kept in check through tight control exerted by ZNRD3 on Wnt/b-catenin-signaling (Basham et al., 2019). However, the regenerated adrenal tissue lacks medullary cells (Holzwarth et al., 1980; Hampel et al., 1994; Gotlieb et al., 2018).

Despite focus on the regenerating capacity of the adrenal gland, no study has been successful in proving the existence of de novo generation of chromaffin cells in vivo under normal circumstances. For decades, the adult adrenal medulla was considered a post mitotic cellular population. However, some studies showed that a very small number of chromaffin cells divide in the adult adrenal gland in rodents (Tischler et al., 1988; Tischler et al., 1989). The small numbers of detected chromaffin cell divisions are explained by the slow kinetics of chromaffin tissue turnover. For instance, a short-term BrdU chase ranging from 12 h to 7 days in adult rats resulted in less than 1% of chromaffin cells labelled in the medulla (Verhofstad, 1993). However, when the authors followed up the BrdU injection for 73 days, they were able to detect a turnover of approximately 40% of the entire chromaffin population within the gland. The proliferation rate of chromaffin cells increases in vitro, and is...
affected by external application of reserpine, which tampers with catecholamine synthesis in chromaffin cells, therefore posing the need for increase in catecholaminergic cell numbers as a homeostatic mechanism (Tischler et al., 1988; Tischler et al., 1989; Tischler et al., 1995). Additional factors shown to affect chromaffin cell proliferation are EGF, LIF and steroids naturally produced by the fetal adrenal cortex such as DHEA (dehydroepiandrosterone) and DHEA sulfate (DHEA-S) (Sicard et al., 2006; Sicard et al., 2007; Chung et al., 2011). Interestingly, all these factors have different effects on chromaffin cell proliferation depending on the age of the animal. The cells isolated from the young-animals demonstrated higher proliferation upon LIF treatment versus cells derived from the older-animal. On the opposite, EGF treatment induced proliferation of the “aged” chromaffin cells, but not of the “young” (Sicard et al., 2007). Overall, the fact remains, that proliferation of chromaffin cells in the adult adrenal gland is low under normal conditions and is enhanced once cells derived from young animals are cultured in vitro (Claude et al., 1988; Unsicker, 1993; Sicard et al., 2006; Sicard et al., 2007).

Although the adrenal medulla appears as a stable low proliferative tissue under normal conditions, there are putative stem cells responsive to stress. These stem-cell like populations, often referred to as “sustentacular” or “support” cells, are found both in the adult adrenal cortex
and medulla (Rubin de Celis, García-Martin et al., 2015; Steenblock et al., 2018) (Fig. 2). Furthermore, these sustentacular cells are characterized by Nestin expression and the presence of glial markers Sox10, Fthp7, S100b and Gfap (Rubin de Celis, García-Martin et al., 2015; Steenblock et al., 2018). Nestin+ cells in the adrenal medulla are found in close contact with the vasculature of the gland (Rubin de Celis, García-Martin et al., 2015). Notably, in mice, one study using lineage tracing with Nestin::CreERT2;R26YFP showed that Nestin+ cells might differentiate towards chromaffin cells upon induced immobilization stress, while the contribution of Nestin+ cells to glial and neuronal populations in the gland remains unaffected (Fig. 2) (Rubin de Celis, García-Martin et al., 2015). Even though this finding is especially meaningful in our understanding of the adrenal medulla turnover and the effect of stress on sustentacular cells, there has been no follow-up study. Further interrogation of the circumstances under which sustentacular cells are able to differentiate in the adult using additional lineage tracers (e.g. Gfap-, S100b- or Sox10-driven transgenic reporters) is necessary in order to fully understand their potential. These results suggest the presence of homeostatic mechanisms in the adrenal medulla mediated by the glial-like stem cells during stress response. This cellular mechanism of stress response might utilize the principles of the developmental generation of chromaffin cells by nerve-associated SCPs.

1.3. The adrenal medulla as an oxygen-sensing organ

Early observations on rats and humans have shown that adrenomedullary chromaffin cells are oxygen-sensing during perinatal stages, a transient property not mediated through the sympathetic innervation (Seidler and Slotkin, 1985; Mochizuki-Oda et al., 1997; Thompson et al., 1997; Rychkov et al., 1998; Garcia-Fernandez et al., 2007).

Another oxygen-sensing organ is the carotid body found at the bifurcation of the carotid arteries in the cervical region (Gonzalez et al., 2005). Carotid bodies are composed of type I cells, or catecholaminergic glomus cells, and type II sustentacular glial cells (Fig. 2). Glomus cells are able to sense hypoxia and respond by triggering increased respiration in order to counteract low oxygen levels (Lopez-Barneo et al., 2008). Interestingly, similarly to adrenal chromaffin cells, glomus cells belong to the neural crest-derived lineages and originate from nerve-associated SCPs in the mouse (Le Douarin, Le Lievre et al., 1972; Pearse et al., 1973; Pardal et al., 2007; Hochman et al., 2018). When considering their cellular properties and markers, oxygen-sensing perinatal chromaffin cells resemble glomus cells found in carotid bodies. Glomus cells, similarly to chromaffin cells, contain enzymes responsible for catecholamine synthesis and release, as well as the molecular machinery for the production and storage of neuropeptides such as NPY, enkephalins and the neurotransmitter serotonin (Chiocchio et al., 1966; Lawson, 1980; Oomori et al., 1994; Oomori et al., 1994; Kameda, 2002; Ramirez et al., 2012; Brindley et al., 2017). The similarities, however, do not stop here: the glial (type II) cells found in carotid bodies have stem-cell like properties, being able to produce new glomus cells in response to sustained hypoxia in adult animals (Pardal et al., 2007; Annese et al., 2017) (Fig. 2). Following the subjection to chronic hypoxia, carotid bodies increase in size in experimental animals. This is coherent with the observation revealing that carotid organs are larger in humans living in high altitudes (Arias-Stella and Valcarcel, 1976; Wang and Bisgard, 2002).

1.4. Diversity and dependencies of chromaffin cells

Specifically in mammals, in addition to the adrenal medulla and carotid body, other chromaffin cell accumulations are found next to the dorsal aorta between the kidneys. These include the Zuckerkand organ - the largest chromaffin accumulation in the body (Zuckerkand, 1901) and the transition from the suprarenal sympathetic ganglia towards the mesenteric ganglia - or transitional chromaffin body (Kastriti et al., 2019) (Fig. 3).

Chromaffin cells of the adrenal medulla are protected by the mesoderm-derived steroidogenic adrenal cortex, and in this respect differ from the extra-adrenal chromaffin cells. The Zuckerkand organ and transitional chromaffin body are not surrounded by any special tissue and might be exposed to different circulating factors in the retroperitoneal space (Fig. 3). However, there is evidence of molecular cross-talk between steroidogenic cells and chromaffin cells. Specifically, Sf-1 (Nr5a1) knock-out mice lacking an adrenal cortex develop chromaffin cells next to the suprarenal ganglion. However, these “medullary” chromaffin cells do not express PNMT, necessary for adrenaline synthesis and an indication of chromaffin cell maturation (Gut et al., 2005). Similarly, mice missing the glucocorticoid receptor (Gr+) or CYP21A (Cyp21a1a-/-), a key enzyme involved in steroidogenesis, develop a morphologically normal medulla, despite the fact that medullary cells present morphological abnormalities and are unable to secrete epinephrine (adrenaline) due to the lack of PNMT (Cole et al., 1995; Bornstein et al., 1999; Finotto et al., 1999; Tajima et al., 1999) (Fig. 4). Furthermore, ectopic development of steroidogenic tissue results in the recruitment of chromaffin cells and the formation of ectopic adrenal glands (Zuhair et al., 2009). In line with these findings supporting interactions between medulla and cortex, Th-/- mice show reduced catecholamine release, accompanied by decreased mitochondrial and increased liposomes in adrenocortical cells, as well as reduced corticosterone production (Bornstein et al., 2000).

In all cases, manipulation of either the steroidogenic cortex or catecholaminergic medulla results in cellular defects on the counterpart.
Cellular properties and maturation of steroidogenic and catecholaminergic cells

A Mature chromaffin cells (mouse)

Noradrenergic
20-30% TH CHGA/B NPY

Adrenergic
70-80% TH CHGA/B DBH NPY +PNMT

B Mature cortical cells (mouse)

capsule
zG - mineralocorticoid synthesis
STAR CYP11B2 CYP11A

zF - glucocorticoid synthesis
STAR CYP11B1 CYP11A CYP21A

Maturation of steroidogenic/catecholaminergic cells - reciprocal signaling (mouse)

C Normal fetal adrenal gland - only glucocorticoid synthesis

70-80% PNMT+

D Nr5a1 knock out (SF1 mutant)

No PNMT Retainment of RET

E Zuckerkandl organ

Absence of cortex-derived glucocorticoids

Cell death (postnatally)

F Perturbed signaling from the cortex (Glucocorticoid receptor knock out, Cyp21a knock out)

Cortex
Glucocorticoid synthesis
STAR CYP11B1 CYP11A CYP21A

Medulla
Glucocorticoid receptor
Noradrenaline Adrenaline

G Th knock out

Noradrenaline Adrenaline

Steroid hormone production

Decreased mitochondria

Increased liposomes

(caption on next page)
In line with the significance of the cortex-medulla interaction, the extra-adrenal Zuckerkandl organ, composed of chromaffin and glial cells alone, regresses after birth in all species where described (namely in mammals) (Coupland, 1954; Schober et al., 2013). The medulla, which is composed of the same chromaffin and glial cells, stays intact being immediately shielded by the adrenal cortex. Taken together, all these studies point to a co-dependency between the steroidogenic cortical cells and the neuroendocrine medullary cells making up the adrenal gland.

1.5. Evolution of chromaffin and oxygen-sensing cells

The continuity of chromaffin and related oxygen-sensing cells type suggests their common evolutionary origin and a subdivision of functions. Adrenal glands are considered as a feature of vertebrates, so it is logical to assume that the common ancestor of all vertebrates might have had the earliest form of this cell type. The studies of the “live fossil” agnathan, the lamprey (Petromyzon marinus, Lampetra lamontenti and Geotria australis gray), revealed the presence of chromaffin cells in the vicinity of the heart – extracardiac chromaffin cells - found both in larval and adult animals, as well as the intracardiac chromaffin cells (Paiment and McMillan, 1975; Epple et al., 1985). Extracardiac chromaffin cells of the lamprey are of the neural crest origin and their main function is considered to be oxygen-sensing. It has been hypothesized that they are analogous to the adrenal gland of gnathostomes (Gaskell, 1912; Païment and McMillan, 1975). However, a recent comparative study performed on lamprey and zebrafish suggested that these extracardiac chromaffin cells are in fact the predecessors of mammalian carotid bodies (Hockman et al., 2017). In line with this, bony fish also have oxygen-sensing catecholaminergic cells in a close association with blood vessels within the cardiac region (Stoyek et al., 2017).

Additionally, during the transition towards gnathostomes, an organ with high resemblance to the mammalian adrenal gland emerged in jawed fish. This organ, named interrenal organ, is steroidogenic and develops in close proximity to the embryonic kidney. Later during development, the interrenal organ is invaded by catecholaminergic chromaffin cells (Chai et al., 2003; Hsu et al., 2003; To et al., 2007). However, the cellular architecture of the interrenal organ differs greatly from the mammalian adrenal gland, similarly to other adrenal gland types found in anniotes, characterized by a variety of shapes and degrees of organization (Milano and Accardi, 1986; Grassi Milano, Basari et al., 1997).

Despite morphological and lineage-related differences, modern chromaffin cells are predominantly found in proximity to steroidogenic cells in oesteichthyes, amphibians, reptiles and ammniotes (birds and mammals). However, this might not be the case during the entire evolutionary history of the adrenal gland, as suggested by the presence of extra- and intra-cardiac oxygen-sensing cells in the lamprey. This might hint that steroidogenic cortical cell types and catecholaminergic medullary cells evolved in an anatomical separation and segregated together to form the composite gland at later evolutionary stages.

1.6. The adrenal medulla and pathophysiology

In humans, the sympathoadrenal domain gives rise to tumors composed of cells similar to sympathetic neurons, glomus or chromaffin cells, namely neuroblastoma, paraganglioma and pheochromocytoma, for reviews see (Matthay et al., 2016; Huber et al., 2018). Among those, neuroblastoma is a pediatric tumor of embryonic origin, which is highly heterogeneous in terms of tumor composition, location and potential outcome (Veschi et al., 2019). Paragangliomas and pheochromocytomas are rare, catecholamine-producing tumors in adults and are determined based on their location outside (i.e. paraganglioma) or inside the adrenal gland (i.e. pheochromocytoma). To this date, the cell of origin and mechanisms driving tumorigenesis of neuroblastoma and paraganglioma/pheochromocytoma is a major focus of research.

According to previous studies, the emergence of cancer may result from two consecutive mutagenic events, a hypothesis extended also to neuroblastoma and paraganglioma (Knudson and Strong, 1972; Knudson, 1996). In the case of sympathoadrenal tumors, the first event may take place during embryonic development. Such primary mutation may lead to neural crest anomalies, which can appear dormant until meeting permissive conditions (Kerosuo et al., 2018; Rabadán et al., 2013; Boeva et al., 2017; Tsutota and Kadomatsu, 2017). That would lead to composite postnatal tumors, often the case in neuroblastoma, but less in paraganglioma/pheochromocytoma (Sano et al., 2007; Rai et al., 2012; Rao et al., 2013; Shida et al., 2015). Subsequently, the “second hit” is likely a postnatal event. The vast heterogeneity of tumor composition and clinical outcome for neuroblastoma, pheochromocytoma and paraganglioma reflects the diverse genetic mechanisms that drive these diseases.

This can be explained, for instance, by reasoning that at the cellular level, the culprit for sympathoadrenal tumors can be rooted in neural crest cells and their derivatives including embryonic SCPs, sympathetic neurons, chromaffin cells or putative stem cells of the adult adrenal medulla (sustentacular cells/satellite glia). Depending on the particular stage in lineage progression when the mutagenic events took place, cancer-initiating cells might vary in multipotency, proliferation and differentiation potential. Thus, in regards to the initiation event, neuroblastoma and different subtypes of adult sympathoadrenal tumors (paraganglioma/pheochromocytoma) may result from differentially mature sympathoadrenal cells of origin.

The genetic mechanisms driving childhood or adult sympathoadrenal tumors can be distinct, even though their etiology has some common genes involved. Genetic analysis of neuroblastoma associate different genetic abnormalities with the three main subtypes of the disease, i.e. high risk, low risk and 4S neuroblastoma, a type characterized by spontaneous regression. In 90% of high risk neuroblastoma cases, research teams detected fragmental chromosomal alterations, often resulting in MYCN amplification, 17q gain or 11q loss (Pugh et al., 2013). Somatic mutations in single genes coding for ALK, FPTPN11, ATRX and others were seen in less than 25% of the cases in high-risk neuroblastoma. Additionally, genomic alterations in the telomerase reverse transcriptase (TERT) gene locus were reported in 20–30% of
high-risk neuroblastomas, resulting in upregulation of transcription of the gene (Peifer et al., 2015; Valentijn et al., 2015). Notably, around 30% of high-risk neuroblastomas still remain enigmatic with no obvious genetic mechanism. On the other hand, low-risk neuroblastoma was found to correlate with hyperploid cancer cells carrying multiple copies of whole chromosomes (Ambros et al., 2009). Furthermore, many aspects of a cross-talk utilizing signals from the micro-environment have been investigated over the years. For example, one of the studies suggested that cancer stem cells in neuroblastoma thrive under hypoxic conditions (Das et al., 2008).

The enigmatic regression of 4S neuroblastoma has been hypothesized to reflect the spontaneous apoptotic cell death sympathoblasts undergo at the end of the sympathoadrenal system maturation (Yuan and Yankner, 2000; Brodeur and Bagatell, 2014; Brodeur, 2018). However, it might also be that these tumors resemble the extra-adrenal chromaffin cells of the Zuckerkandl organ, which undergo cell death postnatally (Coupland, 1954; Schob et al., 2013) (Fig. 5).

Recent studies showed that neuroblastoma is governed by a mixed identity, being composed of adrenergic and neural crest-like mesenchymal lineages (Boeva et al., 2017; van Groningen et al., 2017). This points to the multipotency of the cancer precursor cell, such as the multipotency of neural crest cells and embryonic SCPs discussed above.
As opposed to neuroblastoma, both paraganglioma and pheochromocytoma are characterized by a high occurrence of familial germ line mutations (roughly 30% of total cases), whereas 40% of cases correspond to identified somatic mutations (Burnichon et al., 2011; Fishbein et al., 2017; Fishbein and Wilkerson, 2018). Among the genetic alterations identified in paraganglioma/ pheochromocytoma are gene fusions, gene copy alterations and drive mutations that have drastic effect on cell fitness. Importantly, some malignancies may be caused by epigenetic alterations. The genes involved in the pathogenesis of paraganglioma and pheochromocytoma cover a wide range of signaling pathways, i.e. kinase signaling (RET, NF1), transcription factors (MYCN, MAX), energy metabolism (SDHA, SDHB, SDHC, SDHD, SDHAF2), pseudohypoxia (VHL, EPAS1) and chromatin remodeling (ATRX, IDH1), as reviewed by (Fishbein and Wilkerson, 2018). Most acquired knowledge on the mechanisms driving these diseases has been inferred from analyses correlating the genetic constituents of the tumors with their phenotype in comparison to cells of the sympathoadrenal lineage. Based on these studies, paraganglioma and pheochromocytoma tumors can be classified into three main clusters: a kinase signaling cluster, a pseudohypoxia (VHL, EPAS1) and chromatin remodeling (ATRX, IDH1), as reviewed by (Fishbein and Wilkerson, 2018). This hypothesis is supported by the fact that tumors belonging to this cluster are almost exclusively intra-adrenal. On the other hand, pseudohypoxia cluster tumors are more aggressive, appear earlier in life and correlate with low PNMT and high VMA1/2, markers of noradrenergic cells and sympathetic neurons respectively. Almost all tumors of the pseudohypoxic phenotype carry mutations in the VHL, SDHx and EPAS1 genes and can be found both at intra- and extra-adrenal locations (Dahia et al., 2005; Burnichon et al., 2011; Fishbein et al., 2017; Fishbein and Wilkerson, 2018). Taking into consideration the oxygen-sensing potential of immature catecholaminergic and glial sustentacular cells of the carotid bodies, it is possible to hypothesize that SCs might be driven into abnormal proliferation and/or differentiation upon these hypoxic conditions.

The third cluster of pheochromocytoma and paraganglioma, or the Wnt-altered cluster, is characterized by the low but variable expression of noradrenergic and adrenergic markers, overexpression of GLI2, WNT4, MAML3 and ASCL1 with simultaneous decreased CARTPT expression (Fishbein et al., 2017; Fishbein and Wilkerson, 2018). Additionally, in most cases, these tumors are intra-adrenal. Developmental studies in mice confirmed that ASCL1 is associated with sympathoadrenal lineage. Thus, it is possible that in these mysterious types of paraganglioma and pheochromocytoma, the cell of origin is found earlier than currently expected in the sequence of developmental events in the sympathoadrenal system. Overall, we are far from pinpointing the cells of origin for a diversity of sympathoadrenal tumors. Often, studies tackling this question using the expression of stem cell markers in sympathoadrenal tumors reach contradictory results, as reviewed by (Scibba et al., 2020). The variable observations might be due to intratumoral and interpatient heterogeneity of paraganglioma and pheochromocytoma, which is not sufficiently characterized based on limited histological examination of the tumor biopsies.

1.7. Conclusions and future perspectives

In humans, a variety of adrenal gland-related syndromes affect the daily lives of many individuals. These syndromes range from hypo- or hyperplasia of the adrenal cortex, associated with lack of steroid hormone synthesis, to catecholamine-producing tumors within or proximal to the adrenal glands. The treatment upon intra-adrenal tumor diagnosis consists of surgical removal of the gland, which dictates the importance of establishing regenerative approaches for the whole adrenal gland, including complex adrenal organoids. Thus far, adrenal organoids consisting of cortex and medulla have not been achieved despite all recent advancements that might help to establish necessary protocols.

The recent state-of-the-art technological advances allow to uncover the transcriptional states connected to the physical positions of the individual cells, and are key for studying cellular populations characterized by high heterogeneity, such as the adrenal cortex, medulla or resulting tumors. The currently existing analysis tools and computational models will help to explain how the cell populations interact with each other using specific molecular toolkit. This might help to unmask the real intratumoral and interpatient heterogeneity of neuroblastoma, paraganglioma and pheochromocytoma, leading to targeted treatment approaches. Additionally, due to these novel technologies, we anticipate future progress in identifying rare cell populations in sympatho-adrenal domain. Lastly, obtaining much deeper insights into diverse physiological cell states mediating the response to stress or neural/endocrine signals will become possible with newly developed approaches.

Declaration of competing interest

The authors have no competing interests to declare.

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References

Afework, M., Burnstock, G., 1995. Colocalization of neuropeptides and NADPH-diaphorase in the intra-adrenal neuronal cell bodies and fibres of the rat. Cell Tissue Res. 280 (2), 291–295.

Ambros, P.F., Ambros, I.M., Brodeur, G.M., Haber, M., Khan, J., Nakagawara, A., Schlieämacher, G., Speleman, F., Spitz, R., London, W.B., Cohn, S.L., Pearson, A.D., Maris, J.M., 2009. International consensus for neuroblastoma molecular diagnostics: report from the international neuroblastoma risk group (INRG) biology committee. Br. J. Canc. 100 (9), 1471–1482.

Annes, V., Navarro-Guerrero, E., Rodriguez-Prieto, I., Pardal, R., 2017. Physiological plasticity of neural-crest-derived stem cells in the adult mammalian carotid body. Cell Reg. 19 (3), 471–478.

Arias-Stella, J., Valcarcel, J., 1976. Chief cell hyperplasia in the human carotid body at high altitudes; physiologic and pathologic significance. Hum. Pathol. 7 (4), 361–373.

Axelrod, J., 1974. Neuropeptidases. Sci. Am. 230 (6), 59–71.

Bandiera, R., Vidal, V.P., Motamedi, F.J., Clarkson, M., Sahut-Barnola, I., von Gise, A., Schlieämacher, G., Speleman, F., Spitz, R., London, W.B., Cohn, S.L., Pearson, A.D., Maris, J.M., 2009. International consensus for neuroblastoma molecular diagnostics: report from the international neuroblastoma risk group (INRG) biology committee. Br. J. Canc. 100 (9), 1471–1482.

Annes, V., Navarro-Guerrero, E., Rodriguez-Prieto, I., Pardal, R., 2017. Physiological plasticity of neural-crest-derived stem cells in the adult mammalian carotid body. Cell Reg. 19 (3), 471–478.

Arias-Stella, J., Valcarcel, J., 1976. Chief cell hyperplasia in the human carotid body at high altitudes; physiologic and pathologic significance. Hum. Pathol. 7 (4), 361–373.

Axelrod, J., 1974. Neuropeptidases. Sci. Am. 230 (6), 59–71.

Bandiera, R., Vidal, V.P., Motamedi, F.J., Clarkson, M., Sahut-Barnola, I., von Gise, A., Schlieämacher, G., Speleman, F., Spitz, R., London, W.B., Cohn, S.L., Pearson, A.D., Maris, J.M., 2009. International consensus for neuroblastoma molecular diagnostics: report from the international neuroblastoma risk group (INRG) biology committee. Br. J. Canc. 100 (9), 1471–1482.

Annes, V., Navarro-Guerrero, E., Rodriguez-Prieto, I., Pardal, R., 2017. Physiological plasticity of neural-crest-derived stem cells in the adult mammalian carotid body. Cell Reg. 19 (3), 471–478.

Arias-Stella, J., Valcarcel, J., 1976. Chief cell hyperplasia in the human carotid body at high altitudes; physiologic and pathologic significance. Hum. Pathol. 7 (4), 361–373.

Axelrod, J., 1974. Neuropeptidases. Sci. Am. 230 (6), 59–71.

Bandiera, R., Vidal, V.P., Motamedi, F.J., Clarkson, M., Sahut-Barnola, I., von Gise, A., Schlieämacher, G., Speleman, F., Spitz, R., London, W.B., Cohn, S.L., Pearson, A.D., Maris, J.M., 2009. International consensus for neuroblastoma molecular diagnostics: report from the international neuroblastoma risk group (INRG) biology committee. Br. J. Canc. 100 (9), 1471–1482.

Annes, V., Navarro-Guerrero, E., Rodriguez-Prieto, I., Pardal, R., 2017. Physiological plasticity of neural-crest-derived stem cells in the adult mammalian carotid body. Cell Reg. 19 (3), 471–478.
M.E. Kastriti et al.

Coupland, R.E., 1954. Post-natal fate of the abdominal para-aortic bodies in man.

Burnichon, N., Vescovo, L., Amar, L., Libe, R., de Reynies, A., Venisse, A., Jouanno, E., Brogi, M.P., Pellegrino, C., 1959. The secretion of corticosterone and aldosterone by the adrenal gland of the cat. Nature 212 (5064), 834–835.

Chan, W.H., Gonsalvez, D.G., Young, H.M., Southard-Smith, E.M., Cane, K.N., Brochi, S.R., Biscardi, A.M., Tramezzani, J.H., 1966. Catecholamines in the carotid body of the cat. Nature 212 (5064), 834–835.

Epple, A., Hilliard, R.W., Potter, I.C., 1985. The cardiovascular chromaffin cell system of the Southern Hemisphere lamprey, Geotria australis grayi. J. Morph. 183 (2), 229–231.

Emmerling, U., Esposito, L., Partimio, S., Huber, K., Lerario, A.M., Hammer, G.D., 2018. Sonic hedgehog and WNT signaling generate neuroendocrine cells of the adrenal medulla. Science 357 (6346), 643–646.

Unsicker, K., 2005. Expression of neuronal markers suggests heterogeneity of chick sympathetic neurons. Exp. Cell Res. 102 (2), 90–110.

Hirokawa, N., Ishikawa, H., 1974. Electron microscopic observations on postnatal development of sympathetic nerve endings in the adrenal gland of the rabbit. Am. J. Anat. 142 (1), 176–188.

Dahia, P.L., Ross, K.N., Wright, M.E., Hayashida, C.Y., Santagata, S., Barontini, M., Coppola, E., Brunet, J.F., 2014. Neurodevelopment. Parasympathetic ganglia derive from Schwann cell precursors. Science 345 (6203), 87–90.

Brown, G., Tsuchida, R., Malkin, D., Koren, G., Baruchel, S., Yeger, H., 2008. Hypoxia enhances tumor stemness by increasing the invasive and tumorigenic side population fraction. Stem Cell 26 (7), 1818–1830.

Dyachuk, V., Lefebvre, A., Beaudoin, A., Lacombe, B., Bresson, P., Grenier, V., Gaudet, C., Bouchard, P., Laporte, J., Karsenty, G., 2010. BMP2 regulates sympathetic neurogenesis and supports the differentiation of a novel population of neural progenitors. Dev. Biol. 343 (2), 153–164.

Honegger, P., Amore, P.A., Wagner, J.A., 1988. Acidic 'bHLH' factors dHAND is a downstream effector of BMPs in sympathetic neuron specification. Development 127 (18), 4073–4081.

Toledo, S.P., Nose, V., Li, C., Stiles, C.D., 2005. A HIF1alpha regulatory loop links hypoxia and TGFbeta signaling during sympatheural cell development. Dev. Neurobiol. 76 (2), 137–150.

Fischbein, L., Wilkerson, M.D., 2018. Chromaffin cell biology: inferences from the cancer genome atlas. Cell Tissue Res. 372 (2), 339–346.

Furlan, A., Adameyko, I., 2018. Schwann cell precursor: a neural crest cell in disguise? Curr. Top. Dev. Biol. 124, 107–132.

Brustle, O., Schambach, J., 2002. Defining the embryonic neural tube: insights from naturally occurring and experimentally induced neural tube defects. Nat. Rev. Neurosci. 3 (8), 537–544.

Kellendonk, C., Tronche, F., Schutz, G., Unsicker, K., 1999. Analysis of mice carrying targeted mutations of the glucocorticoid receptor gene argues against an essential role of glucocorticoid signaling in generating adrenal chromaffin cells. Development 126 (13), 2935–2944.

Fishlein, B., Leshchiner, I., Walter, V., Danilova, L., Robertson, A.G., Johnson, A.R., Lichtenberg, T.M., Murray, B.A., Ghayee, H.K., Else, T., Ling, S., Jefferys, S.R., de Cabas, A.A., Wenz, B., Koopman, E., Amelio, A.L., Makowski, L., Rathmell, W.K., Gonzalez-Crussi, F., Roqueplan, A.P., Giordano, T.J., Aas, A.L., Tischler, A.S., Cancer Genome Atlas Research Network, 2013. Reversal of functional chromaafin cell loss in mice lacking β-catenin. Nature 502 (7470), 643–646.

Benbenishty, A., Golomb, E., Ben-Eliyahu, S., 2015. Sympathoadrenal cell lineage: specification, diversification, and function. Cold Spring Harb. Perspect. Biol. 7 (4), 229–282.

Kellendonk, C., Tronche, F., Schutz, G., Unsicker, K., 1999. Analysis of mice carrying targeted mutations of the glucocorticoid receptor gene argues against an essential role of glucocorticoid signaling in generating adrenal chromaffin cells. Development 126 (13), 2935–2944.
neuropeptide Y and vasoactive intestinal polypeptide in the rat adrenal gland. Cell Tissue Res. 275 (2), 201–213.

Paimient, J.M., McMullen, I.C., 2019. The extracellular chromaffin cells of larval lampreys. Gen. Comp. Endocrinol. 27 (4), 495–508.

Pardal, R., Ortega-Saenz, P., Durán, R., López-Barneo, J. 2007. Glia-like stem cells sustain physiologic neurogenesis in the adult mammalian carotid body. Cell 131 (2), 364–377.

Pattyn, A., Morin, X., Cremers, H., Goridis, C., Brunet, J.F., 1999. The homeobox gene Phox2b is essential for the development of autonomic nerve crest derivatives. Nature 399 (6734), 366–372.

Pearce, A.G., Polak, J.M., Rost, F.W., Fontaine, J., Le Lievre, C., Le Douarin, N., 1973. Demonstration of the neural crest origin of type I (APUD) cells in the avian carotid body, using a cytochemical marker system. Histochemie 34 (3), 191–203.

Pfeifer, M., Horteguiz, C., Roels, F., Dreidax, D., Gartlgruber, M., Menon, R., Kramer, U., Roncaioli, J.J., Sand, F., Hermann, J.M., Ikrman, F., Schmidt, R., Ackermann, S., Engesser, A., Kahlert, Y., Vogel, W., Altmüller, J., Nurnberg, P., Thierry-Mieg, J., Thierry-Mieg, D., Mariappan, A., Heynck, S., Mariotti, E., Heinrich, G.O., Glöckner, G., Bosco, G., Leuschner, I., Schweiger, M.R., Savelyeva, L., Watkins, S.C., Zhou, S., Kunn, E., Eifor, T., Acher, V., Lang, U., Theisens, J., Volland, R., Saadati, M., Eggert, A., de Wilde, B., Berthold, P., Feng, Z., Zhao, C., Shi, L., Ortmann, M., Buttner, K., Sero, H., Bracham, A., Schulte, J., Hermann, O., Sullivan, R.J., Westermann, F., Thomas, R.K., Fischer, M., 2015. Telomerase activation by genomic rearrangements in high-risk neuroblastoma. Nature 526 (7575), 725–729.

Phlajoki, M., Domer, J., Cochran, R.S., Heinimoini, M., Wilson, D.B., 2015. Adrenocortical zonation, renewal, and remodeling. Front. Endocrinol. (Lausanne) 6, 27.

Pugh, T.J., Morozova, O., Attiyeh, E.F., Agharezhadeh, S., Wei, J.S., Auclair, D., Carter, S. L., Cibulskis, K., Hanson, M., Kizian, A., Kim, J., Lawrence, M.S., Lichtenstein, L., McKenna, A., Pedamallu, C., 2013, 135–140.

Kudrnod Jr., A.G., Strong, L.C., 1972. Mutation and cancer: neuroblastoma and pheochromocytoma. Am. J. Hum. Genet. 45 (2), 514–532.

Kohn, A., 1902. Das chromaffine gewebe. Gebr. anat. Entwickl. 12, 253–348.

Lancaster, W., 2008. The neuroendocrine nature of the glomus cells: an experimental, ultrastructural, and histochemical tissue culture study. Laryngoscope 90 (1), 120–144.

Le Douarin, N., Le Lievre, C., Fontaine, J., 1972. Experimental research on the embryologic origin of the carotid body in birds. P R Acad Helv Seances Acad Sc. 275 (4), 583–586.

Le Douarin, N.M., Teillet, M.A., 1974. Experimental analysis of the migration and differention of neuroblasts of the autonomic inner nervous system of and neuroectodermal neural crest derivatives, using a biological cell marking technique. Dev. Biol. 41 (1), 162–184.

Lee, M., Brennan, A., Blanchard, A., Zoidl, G., Dong, Z., Tabernero, A., Zoidl, C., Dent, M. A., Jensen, K.R., Mirsky, R., 2019. Schwann cell precursors; multipotent glial cells in embryonic nerves. Front. Mol. Neurosci. 12, 69.

Jessen, K.R., Mirsky, R., Lloyd, A.C., 2015. Schwann cell development and role in nerve repair. Cold Spring Harb. Perspect. Biol. 7 (7) a028478.

Kasemeier-Kulesa, J.C., McLennan, R., Romine, M.H., Kulesa, P.M., Lefcort, F., 2010. Co-localization of noradrenaline, serotonin and gamma-aminobutyric acid in chief cells of the mouse carotid body. Cell Tissue Res. 328 (2), 249–254.

Komiya, Y., Nakaya, K., Tanaka, H., Iuchi, H., Ishikawa, K., Satoh, Y., Ono, K., 1994a. Immunohistochemical and histochemical evidence for the presence of noradrenaline, serotonin and gamma-aminobutyric acid in chief cells of the mouse carotid body. Cell Tissue Res. 278 (2), 249–254.

Komiya, Y., Okuno, S., Fujisawa, H., Iuchi, H., Ishikawa, K., Satoh, Y., Ono, K., 1994b. Noradrenaline cells are neuroactive for catecholamine-synthesizing enzymes. Molecular and Cellular Endocrinology 518 (2020) 110998
Shah, N.M., Groves, A.K., Anderson, D.J., 1996. Alternative neural crest cell fates are instructively promoted by TGFbeta superfamily members. Cell 85 (3), 331-343.

Sharma, A., Verhaegen, J., Harvey, A.R., 2012. Receptor complexes for each of the class 3 semaphorins. Front. Cell. Neurosci. 6, 28.

Shida, Y., Iigawa, T., Abe, K., Hakariya, T., Takehara, K., Onita, T., Sakai, H., 2015. Composite pheochromocytoma of the adrenal gland: a case series. BMC Res. Notes 8, 257.

Shuitkmaster, S., Schier, M.C., Huber, K., Krispin, S., Kalcheim, C., Unsicker, K., 2013. Sympathetic neurons and chromaffin cells share a common progenitor in the neural crest in vivo. Neuronal Dev. 8, 12.

Sidik, F., Ehrhart-Bornstein, M., Corbell, D., Sperber, S., Krug, A.W., Ziegler, C.G., Rettori, V., McCann, S.M., Bornstein, S.R., 2007. Age-dependent regulation of chromaffin cell proliferation by growth factors, dehydroepiandrosterone (DHEA), and DHEA sulfate. Proc. Natl. Acad. Sci. U. S. A. 104 (6), 2007-2012.

Sidik, F., Krug, A.W., Ziegler, C.G., Sperber, S., Ehrhart-Bornstein, M., Bornstein, S.R., 2006. Role of DHEA and growth factors in chromaffin cell proliferation. Ann. N. Y. Acad. Sci. 1073, 312-316.

Smith, S.M., Vale, W.W., 2006. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. Dialogues Clin. Neurosci. 8 (4), 383-395.

Stoyek, M.R., Jonz, M.G., Smith, F.M., Croll, R.P., 2017. Distribution and chronotropic effects of serotonin in the zebrafish heart. Auton. Neurosci. 206, 43.

Tajima, T., Okada, T., Ma, X.M., Ramsey, W., Bornstein, S., Aguilera, G., 1999. Kinetics of adrenal medullary cells. J. Anat. 183 (Pt 2), 315-322.

Tischler, A.S., Ruzicka, L.A., Donahue, S.R., DeLellis, R.A., 1989. Chromaffin cell chemosensitivity in rat adrenomedullary chromaffin cells. J. Physiol. 498 (Pt 2), 503-510.

Tischler, A.S., Delellis, R.A., Nunnemacher, G., Wolfe, H.J., 1988. Acute stimulation of chromaffin cell proliferation in the adult rat adrenal medulla. Lab. Invest. 58 (6), 733-735.

Tischler, A.S., Ruzicka, L.A., Donahue, S.R., Delellis, R.A., 1989. Chromaffin cell proliferation in the adult rat adrenal medulla. Int. J. Dev. Neurosci. 7 (5), 439-448.

Tischler, A.S., Zlat, J., Downing, J.C., McClain, R.M., 1995. Sustained stimulation of rat adrenal chromaffin cell proliferation by reresiphe. Toxicol. Appl. Pharmacol. 135 (2), 254-257.

To, T.T., Hahner, S., Nica, G., Rohr, K.B., Hammerschmidt, M., Winkler, C., Allolio, B., 2007. Pituitary-interrenal interaction in zebrafish interrenal organ development. Mol. Endocrinol. 21 (2), 472-485.

Tsarova, K., Pattyn, A., Stubbsbus, J., Muller, F., van der Wees, J., Schneider, C., Brunet, J.F., Rohrer, H., 2004. Essential role of Gata transcription factors in sympathetic neuron development. Development 131 (19), 4775-4786.

Tsutbota, S., Kadomatsu, K., 2017. Origin and mechanism of neuroblastoma. Oncoscience 4 (7-8), 70-72.

Utsicker, K., 1993. The chromaffin cell: paradigm in cell, developmental and growth factor biology. J. Anat. 183 (Pt 2), 207-221.

Valentinij, L.I., Koster, J., Zwiernburg, D.A., Hasselt, N.E., van Sluis, P., Volckmann, R., van Noesel, M.M., George, R.E., Tytgat, G.A., Molenaa, J.J., Versteeg, R., 2015. TERT rearrangements are frequent in neuroblastoma and identify aggressive tumors. Nat. Genet. 47 (12), 1411-1414.

van Groningen, T., Koster, J., Valentinij, L.I., Zwiernburg, D.A., Akogul, N., Hasselt, N.E., Broekmans, M., Hazenveld, F., Nowakowska, N.E., Bras, J., van Noesel, C.J.M., Jongejans, A., van Kamps, A.H., Koster, L., Bas, F., van Diijk-Kerkhoven, L., Huizer-Smit, M., Lecca, M.C., Chan, A., Lakomaa, M., Molenaa, P., Volckmann, R., Westerhout, E.M., Hamdi, M., van Sluis, P.G., Ebus, M.E., Molenaa, J.J., Tytgat, G.A., Westerman, B.A., van Nes, J., Versteeg, R., 2017. Neuroblastoma is composed of two super-enhancer-associated differentiation states. Nat. Genet. 49 (8), 1261-1266.

Veschi, V., Verona, F., Thielle, C.J., 2019. Cancer stem cells and neuroblastoma: characteristics and therapeutic targeting options. Front. Endocrinol. (Lausanne) 10, 762.

Vidal, V., Sacco, S., Rocha, A.S., da Silva, F., Panzolini, C., Dumontet, T., Doan, T.M., Shan, J., Rak-Raszewska, A., Bird, T., Vainio, S., Martinez, A., Schell, A., 2016. The adrenal capsule is a signaling center controlling cell renewal and zonation through Rspo3. Genes Dev. 30 (12), 1389-1394.

Vinson, G.P., 2016. Functional zonation of the adult mammalian adrenal cortex. Front. Neurosci. 10, 238.

Wang, Z.Y., Biegard, G.E., 2002. Chronic hyposia-induced morphological and neurochemical changes in the carotid body. Microsc. Res. Tech. 59 (3), 168-177.

Wildner, H., Gierl, M.S., Strehe, M., Pla, P., Birchmeier, C., 2008. Insm1 (IA-1) is a crucial component of the transcriptional network that controls differentiation of the sympathetic-adrenal lineage. Development 135 (3), 473-481.

Wood, M.A., Achnawa, A., Finco, L., Swonger, J.M., Elston, M.J., Talquist, M.D., Hammer, G.D., 2013. Fetal adrenal capsular cells serve as progenitor cells for steroidogenic and stromal adrenocortical cell lineages in M. musculus. Development 140 (22), 4522-4532.

Wurman, R.J., Axelrod, J., Vesell, E.S., Ross, G.T., 1968. Species differences in inducibility of phenylethanolamine-N-methyl transferase. Endocrinology 82 (3), 584-596.

Yates, R., Katugampola, H., Cavlan, D., Coger, K., Meirandous, E., Hughes, C., Metherell, L., Guasti, L., King, P., 2013. Adrenocortical development, maintenance, and disease. Curr. Top. Dev. Biol. 106, 239-312.

Yuan, J., Yankner, B.A., 2000. Apoptosis in the nervous system. Nature 407 (6805), 802-809.

Zubair, M., Oka, S., Parker, K.L., Morohashi, K., 2009. Transgenic expression of Ad4Bp/ SF-1 in fetal adrenal progenitor cells leads to ectopic adrenal formation. Mol. Endocrinol. 23 (10), 1657-1667.

Zuckerkanid, E., 1901. About sympathetic paranganglia in the retropertioneal space of man. (Über Nebenniere des sympathicus im retroperitonealraum des menschen). Verhandlungen Anat. Ges. 15, 95-107.