Molecular and Cellular Endocrinology 445 (2017) 42–54

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

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

Cell signaling pathways in the adrenal cortex: Links to stem/progenitor biology and neoplasia

Morgan K. Penny [a, b], Isabella Finco [b], Gary D. Hammer [a, b, c, *]

[a] Cancer Biology Graduate Program, University of Michigan Medical School, Ann Arbor, MI 48109, USA
[b] Department of Internal Medicine, Division of Metabolism, Endocrinology and Diabetes, University of Michigan, Ann Arbor, MI 48109, USA
[c] Endocrine Oncology Program, Comprehensive Cancer Center, University of Michigan Health System, 109 Zina Pitcher Place, 1528 BSRB, Ann Arbor, MI 48109, USA

ARTICLE INFO

Article history:
Received 5 August 2016
Received in revised form
17 November 2016
Accepted 7 December 2016
Available online 8 December 2016

Keywords:
Adrenal cortex
Stem cells
Progenitor cells
Adrenocortical adenoma
Adrenal tumor
Adrenocortical carcinoma

ABSTRACT

The adrenal cortex is a dynamic tissue responsible for the synthesis of steroid hormones, including mineralocorticoids, glucocorticoids, and androgens in humans. Advances have been made in understanding the role of adrenocortical stem/progenitor cell populations in cortex homeostasis and self-renewal. Recently, large molecular profiling studies of adrenocortical carcinoma (ACC) have given insights into proteins and signaling pathways involved in normal tissue homeostasis that become dysregulated in cancer. These data provide an impetus to examine the cellular pathways implicated in adrenocortical disease and study connections, or lack thereof, between adrenal homeostasis and tumorigenesis, with a particular focus on stem and progenitor cell pathways. In this review, we discuss evidence for stem/progenitor cells in the adrenal cortex, proteins and signaling pathways that may regulate these cells, and the role these proteins play in pathologic and neoplastic conditions. In turn, we also examine common perturbations in adrenocortical tumors (ACT) and how these proteins and pathways may be involved in adrenal homeostasis.

1. Introduction

The adrenal glands are bilateral endocrine organs positioned above the kidneys. The highly dynamic gland is composed of an outer mesenchymal capsule, underneath which lies the adrenal cortex, and an inner adrenal medulla. The cortex and medulla are separate tissues that carry out disparate functions: the former is responsible for synthesis and secretion of steroid hormones and the latter is a neuroendocrine tissue that produces catecholamines. In the human adrenal, the cortex can be divided into three different zones: the outer zona glomerulosa (zG) that secretes mineralocorticoids; the zona fasciculata (zF) that produces glucocorticoids; and the innermost zona reticularis (zR) that synthetizes adrenal androgens. In the mouse and rat adrenal, the zR is absent.

Over recent decades, several groups have demonstrated that dysregulation of the signaling pathways involved in organogenesis and homeostasis of the adrenal cortex plays a central role in human adrenocortical disease. Conversely, the elucidation of the molecular pathogenesis of different types of genetic disorders that exhibit adrenocortical manifestations has allowed a better understanding of adrenal cortex homeostasis, building a paradigm that integrates physiologic and pathologic processes. The insulin-like growth factor (IGF), Wnt, hedgehog (HH), and protein kinase A (PKA) signaling pathways play major roles during both embryonic development and homeostasis, and have pathogenic roles in a variety of inherited and acquired adrenocortical disorders. Additionally, telomere protection and maintenance is involved in both adrenocortical function and dysfunction. Genetically engineered animal models specifically built to scrutinize the importance of these pathways have provided further evidence regarding their roles in the long-term maintenance and differentiation of stem and progenitor cell populations in the adrenal cortex (see Fig. 1). More recently, molecular profiling studies of large cohorts of patients with adrenocortical carcinoma (ACC) (Assié et al., 2014; Juhlin et al., 2014; Pinto et al., 2015), particularly the recently published data from the TCGA project in ACC (Zheng et al., 2016), have identified novel molecules and signaling pathways that are commonly perturbed in adrenocortical malignancy. These studies have provided further clues

* Corresponding author. Endocrine Oncology Program, Comprehensive Cancer Center, University of Michigan Health System, 109 Zina Pitcher Place, 1528 BSRB, Ann Arbor, MI 48109, USA.
E-mail address: ghammer@med.umich.edu (G.D. Hammer).

http://dx.doi.org/10.1016/j.mce.2016.12.005
0303-7207/

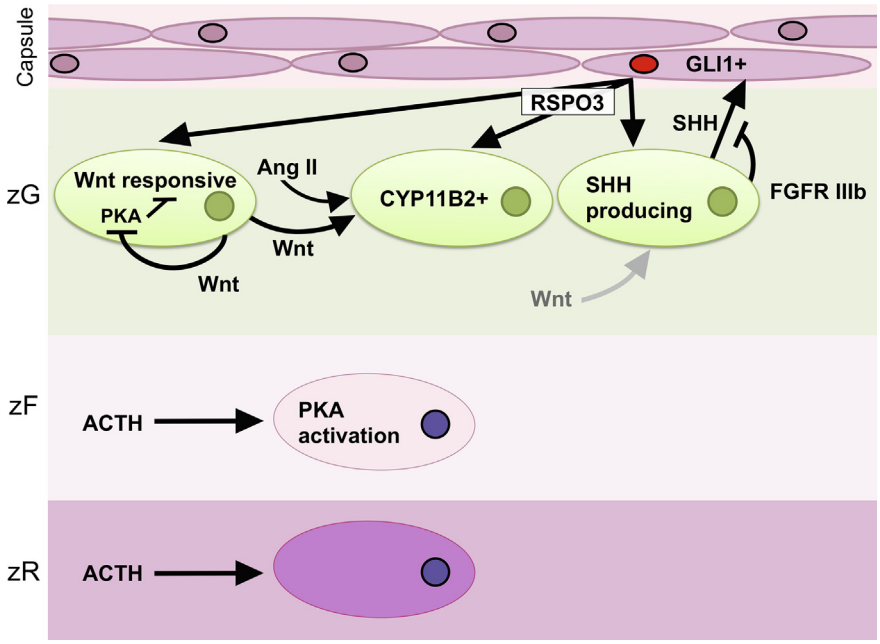

Fig. 1. Homeostatic paracrine and endocrine signaling pathways in the adrenal cortex. Sonic hedgehog (SHH) ligand is produced by clusters of cells in the zG (SHH producing cells), which serve as a stem/progenitor population for the embryonic and postnatal adrenal cortex. SHH acts on capsular cells, causing GLI1 expression and activation (GLI1+). Signaling downstream of FGFR IIIb in subcapsular zG cells is thought to reduce SHH signaling in the embryonic mouse. GLI1+ cells are also putative stem/progenitors that populate the adrenal cortex embryonically and post-natally in the mouse. Wnt responsive cells are those with active canonical Wnt signaling. WNT4 ligand, an effector and presumptive target of canonical Wnt signaling, acts on zG cells that secrete aldosterone in response to angiotensin II (Ang II) levels. WNT4 expression increases CYP11B2 expression and aldosterone levels. In the absence of WNT4 or in the presence of increased ACTH stimulation, PKA inhibits canonical Wnt signaling. RSPO3 ligand potentiates Wnt signaling, and is necessary for SHH, WNT4, and CYP11B2 expression both embryonically and in the post-natal adrenal. The majority of RSPO3 is produced by capsular GLI1+ cells. Known mechanisms of RSPO3 are mediated by the presence of Wnt ligands, though significant involvement of specific Wnts on SHH-producing cells (indicated by the grey arrow) has not been demonstrated in the adrenal cortex. In the zF, ACTH stimulates PKA activity, which is associated with growth and cortisol production in ACTs.

regarding the molecular processes that regulate adrenal growth, differentiation, and self-maintenance and how they become deregulated.

While a number of prior theories have been put forth regarding the maintenance of adrenocortical growth, recent evidence has defined peripheral capsular and subcapsular cell populations as critical mediators of homeostatic repopulation of the whole adrenal cortex. Pioneering experiments of unilateral rat adrenal enucleation, removing the inner content of the adrenal and leaving behind only the capsule and a layer of cells underneath the capsule, documented complete regeneration of the adrenal cortex. These experiments provide evidence that the stem cell niche is contained in the capsular and/or subcapsular cell compartments (Ingle and Higgins, 1938). Moreover, cell labeling studies support the hypothesis of progressive centripetal displacement of adrenocortical cells throughout life. Cells proliferate in the region under the capsule and are displaced centripetally towards the inner corticomedullary boundary where they undergo apoptosis (Vinson, 2003).

The adrenal capsule has also recently been proposed to serve as a niche for adult adrenocortical stem and progenitor cells located within and/or underneath the capsule (Freedman et al., 2013; King et al., 2009). Several studies by different research groups have indicated that the capsule contains adult stem/progenitor cells nurtured by a population of subcapsular cells that maintain the capsular niche (Huang et al., 2010; Kim et al., 2009; Vidal et al., 2016; Wood and Hammer, 2011) and these subcapsular cells may serve as stem/progenitor cells as well (King et al., 2009). While the available data suggest stem and progenitor characteristics in certain cell populations, the current challenge is still to identify adrenocortical stem cell markers, both for embryonic stem cells involved in the gland's development, and for adult stem cells, which maintain homeostatic processes.

There is also evidence supporting a hypothesis that repopulation is a zone-specific process. It is well established that zG-specific growth can be stimulated by serum potassium and angiotensin to maintain electrolytic balance, whereas the zF is stimulated by ACTH to produce glucocorticoids. Zone-specific proliferation can be reconciled with centripetal displacement by acknowledgment that there are likely both endocrine mechanisms that rely on expansion of transit amplifying cells and additionally organ-specific homeostatic mechanisms that rely on repopulation by descendants of capsular and subcapsular stem and progenitor cells. These separate mechanisms would be necessary for gland maintenance and allowing a specific zone to expand to respond to increased needs for selective steroidogenesis.

Ongoing research continues to uncover critical pathways involved in adrenocortical homeostasis, hyperplasia, and neoplasia and the connections that can be made between these processes. In particular, discoveries of the underpinnings of the genetic syndromes that predispose patients to adrenocortical adenomas (ACAs) and/or carcinomas, such as Beckwith-Widemann syndrome (BWS) and Carney complex (CNC), have allowed insights to signaling pathways central to both neoplasia and homeostasis (Mussa et al., 2016b; Stratakis et al., 1996). This review will focus on the contribution of cell signaling pathways as it pertains to stem/progenitor biology and neoplasia, especially cancer.

2. SHH signaling

Sonic hedgehog (SHH), together with Indian hedgehog (IHH) and Desert hedgehog (DHH) are secreted ligands of the hedgehog family of morphogenic proteins. The signaling pathway activated by these ligands has been shown to be crucial for stem cell biology and proper organogenesis. Perturbation of any aspect of the system