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Review

Human adrenocortical carcinoma cell lines

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ABSTRACT

The human adrenal cortex secretes mineralocorticoids, glucocorticoids and adrenal androgens. These steroids are produced from unique cell types located within the three distinct zones of the adrenal cortex. Disruption of adrenal steroid production results in a variety of diseases that can lead to hypertension, metabolic syndrome, infertility and androgen excess. The adrenal cortex is also a common site for the development of adenomas, and rarely the site for the development of carcinomas. The adenomas can lead to diseases associated with adrenal steroid excess, while the carcinomas are particularly aggressive and have a poor prognosis. *In vitro* cell culture models provide important tools to examine molecular and cellular mechanisms controlling both the normal and pathologic function of the adrenal cortex. Herein, we discuss currently available human adrenocortical carcinoma cell lines and their use as model systems for adrenal studies.

Contents

1. Introduction

The adrenal cortex is composed of three functionally distinct regions, the zona glomerulosa (ZG), zona fasciculata (ZF), and zona reticularis (ZR). The ZG synthesizes mineralocorticoids; the ZF produces cortisol and the ZR secretes the so called adrenal androgens, DHEA and DHEA-sulfate. Each zone is preferentially regulated by different circulating factors that include angiotensin II (Ang II) and potassium (K^+) for the ZG, adrenocorticotropic hormone (ACTH) for the ZF, and ACTH plus other yet to be determined factors for the ZR (Parker and Rainey, 2004) (Fig. 1). It has been established that the reason each zone secretes a unique set of steroids is related to the selective expression of steroid-metabolizing enzymes within each zone (Rainey, 1999; Rainey et al., 2002; Vinson, 2003; Nguyen and Conley, 2008) (Fig. 2). However, the molecular mechanisms that cause zone-specific expression patterns of enzymes are yet to be resolved.

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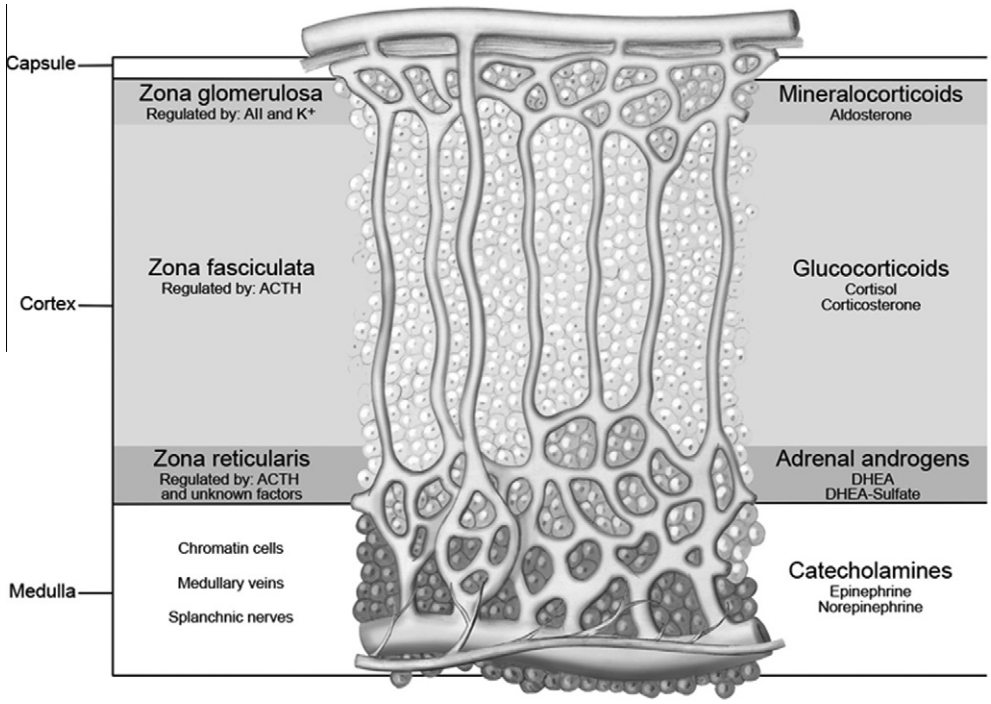

Fig. 1. The adrenal cortex is divided into three histological and functionally distinct zones: the zona glomerulosa synthesizes mineralocorticoids; zona fasciculata produces cortisol and zona reticularis secrets the so called adrenal androgens, DHEA and DHEA-sulfate.

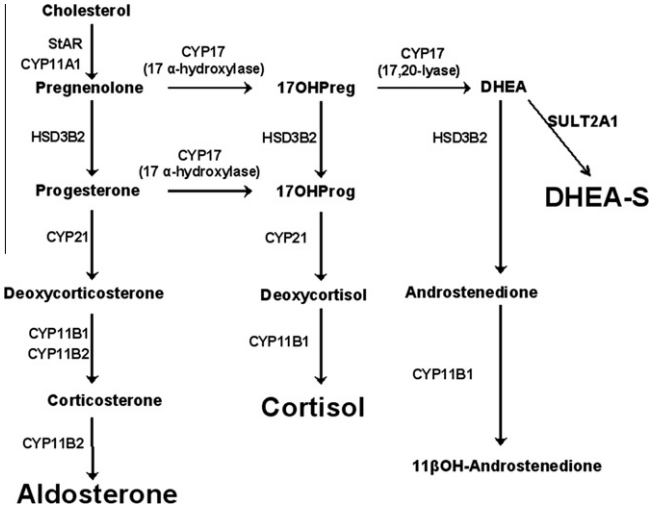

Fig. 2. Human adrenal steroid biosynthetic pathways illustrating the three main products of the human adrenal cortex: aldosterone, cortisol, and adrenal androgens (DHEA, DHEA-S) as well as the enzymes that synthesize these steroids. StAR = steroidogenic acute regulatory protein; CYP11A1 = cholesterol side-chain cleavage enzyme; HSD3B2 = 3β-hydroxysteroid dehydrogenase type II; CYP21 = 21-hydroxylase; CYP11B1 = 11β-hydroxylase; CYP11B2 = aldosterone synthase; CYP17 = 17α-hydroxylase/17, 20 lyase; SULT2A1 = steroid-sulfotransferase.

Adrenal steroid production remains an area of active research, which supports the need to develop appropriate cell models that can mimic adrenal physiology or pathology. Primary cultures of adrenocortical cells have proven to be useful for examining the mechanisms controlling many aspects of adrenal physiology (Chen and Hornsby, 2006; Kuulasmaa et al., 2008; Cardoso et al., 2009; Xing et al., 2010, 2011). However, several issues have limited the use of primary adrenal cells as *in vitro* models. The most common limitations are the constant requirement for fresh tissue and the difficulties associated with the isolation of adequate cortical cells. In addition, cells from different human donors are subject to considerable variability; whereas cells from rodents do not produce cortisol or adrenal androgens due to the lack of steroid 17α-hydroxylase (CYP17) expression. To overcome the problems with tissue accessibility and quality, many groups have attempted to establish cell lines from adrenocortical carcinomas. This approach has been somewhat successful leading to adrenal cell lines from several species and we have previously reviewed the overall development of these models (Rainey et al., 1994, 2004). Herein, we focus only on the human adrenocortical cell lines and provide details with regard to their development and utility.

2. Human adrenocortical carcinoma cell lines

2.1. NCI-H295 derived cell lines

The NCI-H295 cell line was established from a female patient diagnosed with an adrenocortical carcinoma (Gazdar et al., 1990). A large invasive adrenocortical tumor was detected in this patient and was later reported to have metastasized to the lungs and liver. Following tumor extraction, the tissue was finely minced, defragmented and maintained in various serum-containing and serum-free culture media for a one year period. The most vigorous growing cells were selected and designated as the NCI-H295. Radioimmunoassay (RIA) and gas chromatography/mass spectroscopy (GCMS) analysis demonstrated that the selected cells could produce a variety of steroids (Gazdar et al., 1990).

Because the original NCI-H295 cells grow very slowly as loosely attached cell clusters, alternative growth conditions were sought to segregate a population of cells with better monolayer attachment and more rapid growth. To achieve this goal, cells were continuously flushed with growth medium to remove the floating suspended cells and retain the attached subtype. Based on the serum supplement used for growth, three strains were developed and have been termed H295R-S1, H295R-S2 and H295R-S3 (Rainey et al., 2004). All three strains grow as adherent monolayer cultures