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Review

Lessons from the gene expression pattern of the rat zona glomerulosa

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ABSTRACT

We recently identified hundreds of transcripts with differential expression in rat zona glomerulosa (zG) and zona fasciculata. Although the genes up-regulated in the zG may be playing important roles in aldosterone production, the relationship between most of these genes and aldosterone production has not been uncovered. Because aldosterone, in the presence of a high sodium diet, is now considered a significant cardiovascular risk factor, in this review we performed gene ontology and pathway analyses on the same microarray data to better define the genes that may influence zG function. Overall, we identified a number of genes that may be involved in aldosterone production through transforming growth factor β (TGF-β), WNT, calcium, potassium, and ACTH signaling pathways. The list of genes we present in the current report may become an important tool for researchers working on primary aldosteronism and aldosterone-related cardiovascular diseases.

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Contents

1. Introduction

Histologically the mammalian adrenal cortex consists of three concentric layers named the zona glomerulosa (zG), zona fasciculata (zF), and zona reticularis (zR) (Arnold, 1866). It is now accepted that these zones have distinct roles in steroid hormone production, with the zG synthesizing mineralocorticoids (aldosterone) and the zF producing glucocorticoids (Mitani et al., 1999; Vinson, 2003; Vinson and Ho, 1998). The role of zR varies between species but the primate zR is a source of the so-called adrenal androgens (Conley et al., 2004; Nakamura et al., 2009; Rainey et al., 2002). Thus, in addition to the zone-specific differences in histology, there is a functional zonation that allows the production of the adrenal zone-specific steroids.

Abbreviations: zG, zona glomerulosa; zF, zona fasciculata; zR, zona reticularis; *Cyp11b1*, steroid 11β-hydroxylase; *Cyp11b2*, aldosterone synthase; TGF-β, transforming growth factor β; *Gpc3*, glypican 3; *Kcnn2*, potassium intermediate/small conductance calcium-activated channel, subfamily N, member 2; *Fmod*, fibromodulin; *Sdc2*, syndecan 2; *Agtr1a*, angiotensin II receptor, type 1a; *Adcy4*, adenylate cyclase 4; *Agtr1b*, angiotensin II receptor, type 1b; *Ccnd1*, cyclin D1; *Col1a1*, type I collagen α1 chain; *Col1a2*, type I collagen α2 chain; *Sparcl1*, secreted protein acidic and rich in cysteine (SPARC)-like 1; *Atp2c1*, ATPase, Ca^{2+} sequestering; *Lum*, lumican; *Wee1*, WEE-1 homolog; *Ltbp1*, latent TGF-β binding protein 1; *Fn1*, fibronectin I; *Atp1b2*, ATPase, Na^+/K^+ transporting, β2 polypeptide; *Cacnb3*, calcium channel, voltage-dependent, β3 subunit; *Adcy3*, adenylate cyclase 3; *Cpz*, carboxypeptidase Z; *Atp2a2*, ATPase, Ca^{2+} transporting, cardiac muscle, slow twitch 2; *Cacna1c*, calcium channel, voltage-dependent, L type, α1C; *Vtn*, vitronectin; *Cacna1d*, calcium channel, voltage-dependent, L type, α1D.

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In humans and rodents, functional zonation relies in part on the zone-specific expression of two cytochrome P450 isozymes termed aldosterone synthase (CYP11B2) and steroid 11β-hydroxylase (CYP11B1) that catalyze the last steps in the biosynthesis of aldosterone and glucocorticoids (i.e. corticosterone in rodents and cortisol in humans), respectively. In human children and rodents, CYP11B2 is expressed in the histological zG (Domalik et al., 1991; Aiba and Fujibayashi, 2011; Ogishima et al., 1992); whereas in human adults, in addition to the histological zG, CYP11B2 expression is found in subcapsular aldosterone-producing cell clusters (APCCs) (Aiba and Fujibayashi, 2011; Nishimoto et al., 2010).

Not only are the functional roles of APCCs and molecular mechanisms of its formation unknown, but the exact molecular mechanisms causing the layered functional zonation remain poorly defined. The main regulators of aldosterone production are angiotensin II (AngII), K^+, and adrenocorticotropic hormone (ACTH) while that for glucocorticoid is ACTH (Hattangady et al., 2011). In the zG cells, the three agonists acutely (minutes after stimulation) increase the protein accumulation and phosphorylation of steroidogenic acute regulatory protein (StAR) and activate the aldosterone synthesis cascade. On the other hand, only AngII and K^+ can induce the chronic expression (hours to days) of zG-specific CYP11B2. As for glucocorticoid from the zF cells, ACTH is the main agonist that causes prompt expression of StAR and sustained induction of zF-specific CYP11B1. In the zG cells, AngII and K^+ together increase intracellular calcium, which is essential for the continued aldosterone secretory response (Barrett et al., 1989; Ganguly and Davis, 1994), while in both the zG and zF, ACTH binds to its cell surface receptor (melanocortin receptor 2) and activates downstream signaling molecules including adenylate cyclases (Stocco et al., 2005). Thus, hormone productions in the zG and zF cells are controlled by partly overlapping pathways; however, the differences in particular genes involved in these cells are not fully explored.

In order to understand global differences between the zG and zF, we recently identified the transcripts that are differentially expressed in rat zG versus zF (Nishimoto et al., 2012). As described in the report, laser-capture microdissection (LCM) was employed to isolate tissues from the zG and zF layers in Sprague–Dawley rats. An enriched population of zG cells was carefully captured from cells immediately beneath the capsule, whereas the zF cells were taken from the lipid-rich cells in the middle of this histological zone. RNAs from the zG and zF were isolated, biotin-labeled, amplified, and used for microarray analysis. The microarray revealed the unique gene expression profile of the zG, with 234 zG transcripts that have at least 2-fold greater expression than that in the adjacent zF. These genes may have important roles in zG maintenance and/or aldosterone production.

In order to better understand the biological meaning of the observed differences in gene expression, in this report we analyzed the same rat microarray data using gene ontology (GO) and pathway analyses. In both analyses, we focused on zG-specific genes in accordance with zG function since the most potent mineralocorticoid, aldosterone, is now thought to be a cardiovascular risk factor in the presence of a modern high sodium diet (Briet and Schiffrin, 2010; Conlin, 2005; Pimenta and Calhoun, 2006). First, we performed GO analysis using the GeneSpring 12 software. GO is a major bioinformatics initiative which provides a systematic language (ontology) in three key biological domains: biological processes, cellular components, and molecular functions (Gene Ontology Consortium, 2008). Second, we performed pathway analysis on 921 pathways defined in the Biological Pathway Exchange (BioPAX) (Demir et al., 2010). The *p*-value of the pathway analysis was determined based on the number of genes differentially expressed in each pathway. In addition, we manually analyzed genes related to the aldosterone synthetic pathway since this pathway was not included in the BioPAX pathway set. From these observations, we identified dozens of genes which may potentially play a role in aldosterone production.

2. GO analysis of zonally expressed genes

GO analysis using the 234 zG-upregulated genes could not identify any GO term with statistical significance ($p < 0.05$), but two terms showed an enrichment in the zG ($p < 0.1$): 'regulation of systemic arterial blood pressure by circulatory renin–angiotensin system' in the biological process term ($p = 0.096$, Table 1) and 'proteinaceous extracellular matrix (ECM)' in the cellular component term ($p = 0.084$, Table 2). The main function of zG is to produce aldosterone under the control of the renin–angiotensin system, and therefore the up-regulation of transcripts in Table 1 is consistent with the function of zG.

On the other hand, intriguingly, many transcripts belonging to the GO term 'proteinaceous ECM' have not been described in the zG (Table 2). For the purpose of reviewing these genes in this manuscript, we intuitively classified them into three groups based on their relationship with specific signaling pathways: transforming growth factor β (TGF-β) signaling, WNT signaling, and others. Fibromodulin (*Fmod*, 12.6×, gene #28 in Supplemental Table 1) and lumican (*Lum*, 5.7×, gene #86) are members of the structurally and functionally related family of small leucine-rich proteoglycans (Iozzo, 1999; Kresse et al., 1993). These proteins bind to the same region on type I collagen molecules, which consist of type I collagen α1 (*Col1a1*, 8.3×, $p = 0.051$) and α2 (*Col1a2*, 6.8×, gene #67) chains, and affect collagen fibrillogenesis *in vitro* (Rada et al., 1993; Svensson et al., 2000; Vogel et al., 1984). FMOD is known to interact with TGF-β and may silence TGF-β activities by sequestering TGF-β into the extracellular matrix (Hildebrand et al., 1994). Similarly, LUM is an endogenous inhibitor of TGF-β signaling (Nikitovic et al., 2011). In addition, latent TGF-β binding protein 1 (*Ltbp1*, 4.9×, gene #107) is a part of the TGF-β large latent complex, which binds TGF-β in the extracellular matrix (Horiguchi et al., 2012). It is reported that TGF-β signaling inhibits adrenal steroid production through inhibition of StAR, CYP11B1, and CYP11B2 (Brand et al., 2000; Liakos et al., 2003). Therefore, although the TGF-β binding proteins, *Fmod*, *Lum*, and *Ltbp1*, have not been described as genes related to the adrenal cortex, they may be involved in steroidgenesis in the zG by inhibiting TGF-β signaling pathways.

In addition, carboxypeptidase Z (*Cpz*, 3.0×, gene #172) and glypican 3 (*Gpc3*, 30.6×, gene #11) are known to modulate the WNT/β-catenin signaling pathway, which is involved in adrenal development (Heikkila et al., 2002; Mandel et al., 2008; Simon and Hammer, 2012). CPZ is a zinc-containing exopeptidase that catalyzes the removal of C-terminal amino acids from WNT4, thereby increasing WNT4 activity (Wang et al., 2009). In addition, GPC3 is a cell surface glycoprotein that has an ability to form complexes with WNTs and to stimulate the canonical WNT signaling pathway (Capurro et al., 2005). Although none of the 10 *Wnt* transcripts showed statistically significant up-regulation in the zG,

Table 1
Transcripts in GO term 'regulation of systemic arterial blood pressure renin–angiotensin system' in biological process ($p = 0.096$).

Symbol	Gene #	Fold change	Gene definition
Cyp11b2	1	214.2	Aldosterone synthase
Agtr1b	34	11.7	Angiotensin II receptor, type 1b
Agtr1a	37	11.1	Angiotensin II receptor, type 1a

The gene # is assigned in order of fold changes. See Supplemental Table 1.

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