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Non-Coding RNAs and Steroidogenesis

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Abstract

Non-coding RNAs have retained a prominent role in regulating gene expression. They are RNA species that are not transcribed but functional participate in almost every aspect of cellular function. One of the triggers of their discovery was the human genome project. The number of genes found in the human genome fluctuated during the analyses due to the abundant non-coding RNAs that were difficult to be judged as a gene or not. These non-coding RNAs are consisted of: microRNAs (mi-RNAs) that were found as RNAs transcribed form ultra-conserved regions; and other evolutionary conserved ones such as circular RNAs (circ-RNAs) and long non-coding RNAs (lnc-RNAs), as well as PIWI-interacting RNAs, small nucleolar RNAs, transcribed ultra conserved regions, and large intergenic non-coding RNAs. The amount of these functional non-coding RNAs have been increasing in a nearly exponential manner since their discoveries and have been listed up to more than half of the transcribed RNAs in the human cell. This review will focus on non-coding RNAs related with genes important for the function of the adrenal cortex.

Introduction

Adrenal Cortex and Non-Coding RNAs

In the human adrenal cortex, many intermediate steroids are metabolized from cholesterol by steroidogenic enzymes as shown in the "steroid map" of the adrenal cortex. The H295R cell line originates from adrenocortical cancer (ACC), and is commonly used for studying steroidogenesis from its steroid-producing features. From 2009, many studies searched for miRNAs in the adrenal gland as biomarkers to distinguish between adrenal cancer, adrenal adenomas, and normal adrenal cortex tissue. The discovery of *insulin-like growth factor 2* (IGF2) overexpressed in ACCs compared to adenomas makes it a useful biomarker [1]. A miRNA that is expressed from the intronic region of IGF2 also correlated with ACCs [2]. The mi-RNA that targets IGF2 in ACCs is mi-RNA-100[3], which is also known to target other cancers [4-7]. Mi-RNA-195 down-regulation and mi-RNA-483-5p up-regulation were found to be associated with poor prognosis in ACCs [8]. In later studies, these two mi-RNAs were found to be detectable in the serum of patients with high recurrence risk of ACCs [9]. Especially, mi-RNA-483-5p predicts recurrence and was shown to correlate with the amount of circulating tumor cells ACCs [10]. Other studies show mi-RNA-675, miRNA-139-3p, and micro-RNA-335 to be upregulated in ACCs compared to adrenal adenomas [11]. Combined with pathway analysis, miR-184 and mi-R-503 show higher and mi-R-511 and miR-214 show lower expression in ACCs involving the G2/M checkpoint [12]. In adrenocortical tumors microRNA profiles tend to differ from normal adrenal cortex. miRNA-24 was down-regulated in aldosterone-producing adenomas [13]. A bilateral adrenal hyperplasia form of adrenal adenoma called primary pigmented nodular adrenocortical disease (PPNAD) is known for its disorders of *protein kinase A (PKA) regulatory subunit type 1A (PRKARIA)* and leads to Cushing's syndrome in young people [14].

Let-7a was found to be upregulated in these patient's adrenal adenomas [15]. miR-200b and miR-203 were found to be down-regulated while miR-210 and miR-484 were up-regulated in a different study [16]. PPNADs were found to have up-regulated miRNA-449 expression, the miRNA that has been recently implicated in treatment of various cancers [17]. Though PPNAD rarely lead to ACC, there are some cases that do [18]. To this end, an extensive analysis of 45 ACCs by exome sequencing and SNP analysis revealed numerous mutations and methylation in the ACC group of poor prognosis and miRNA clusters in the ACC group with good prognosis. ZNRF3, encoding a cell surface E3 ubiquitin ligase was the most frequently altered in the study [19]. A genome wide DNA copy number report shows that whole genome duplication triggers massive DNA loss [20]. It is interesting that plants may have a defense mechanism relying on alternative splicing when this whole genome duplication occurs [21]. This would mean that if ACC cells survive whole genome duplication through alternative splicing, they would be prone to splicing inhibitors.

The recent discovery of circular RNAs (circRNAs) has given a large impact on human disease as well as RNA biology [22]. They are developed from back-splicing [23-25] and some function as micro-RNA sponges [26]. A recent report searching for circ-RNA by analyzing 123 r-RNA depleted RNA-seq data sets found a total of more than 300,000 of them, the majority of which are derived from coding regions of the gene, implying their role in translation or as backup RNAs. The tissue with the most circRNAs was the brain with 11.9% of circ-RNAs to be tissue-specific that may have a role in tissue development or differentiation. The circ-RNAs had many binding-sites for micro-RNA and RNA-binding protein. These tissue-specific circ-RNAs can be found as a database online (http://gb.whu.edu.cn/TSCD) [27]. Another report found nearly half of circ-RNAs expressed in a tissue-specific manner with more found in gland tissues: mammary gland has nearly 10,000; adrenal gland has more than 2,000; and the average of normal tissue is around 1,200 [28]. The characterization of these circRNAs have just started and functional relation with steroidogenesis has yet to be deciphered.

Steroidogenesis and Non-Coding RNAs

For functional studies targeting adrenocortical hormone production, there is scarce information of involving non-coding RNAs. Bioinformatic analyses of the 3' UTR of CYP11B1(11β-hydroxylase) and CYP11B2(aldosterone synthase) found mi-RNA-24 to be the common regulator that eventually regulates cortisol and aldosterone production, respectively [13]. The mi-RNA, let-7b was found to expressed in a negative correlated manner with cortisol levels of PPNAD patients [15]. Mi-RNA-21 was found to be upregulated in an angiotensin Ⅱ-stimulated screen of more than 200 mi-RNAs in H295R cells. Mi-RNA-21 per se induced aldosterone secretion as well as H295R cell proliferation [29]. All the steroidogenic enzymes are regulated by NR5A1, previously known as steroidogenic factor-1 (SF-1) [30] or Ad4-binding protein (Ad4BP) [31]. NR5A1 knockout mice lack the adrenal gland [32], which shows its importance in adrenal development as well as steroidogenic function. miRNAs targeting NR5A1 can be found in the ovary where miRNA-107 is involved in ovary development [33]. NR5A1 is also known for other targets in the adrenal gland implicating its multi-functional role in adrenocortical homeostasis [34].

Perspectives

The known CRH-ACTH-cortisol axis is well-defined and will probably be found to be more fine-tuned by functional analyses of related non-coding RNAs. Moreover, its interplay with neurosteroid production and maybe with their non-coding RNAs may unveil pathogenesis of diseases of unknown etiology such as schizophrenic states or mood- or neurotic-disorders.

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