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Roles of Non-coding RNAs in Human Diseases
[Introductory Editorial for the Theme: Roles of non-coding RNAs in Human Diseases]

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MAIN TEXT

Research centered on the molecular functions of proteins has uncovered signaling pathways that control pathophysiological processes in cells and tissues. A textbook view of many signaling pathways is that the master regulators are transcription factors that control signaling pathways via gene expression. The latter is influenced by epigenetic marks on genomic DNA; for example, the methylation status of histone proteins. After transcription from genomic DNA, the transcribed RNAs are decoded by ribosomes to produce polypeptides, which are then folded and modified into active proteins. However, over the last 15 years, it has become clear that the relationship of DNA to RNA to protein is not so straightforward.

Recent advancements in high-throughput sequencing technologies have uncovered that although the majority of a mammalian genome is transcribed to RNA, only a minor part encodes for functional polypeptides or proteins (1). Traditionally, RNAs that do not encode proteins have been well recognized for their function as housekeeping RNAs: for example, ribosomal RNAs (rRNAs), transfer RNAs (tRNAs) and small nuclear RNAs (snRNAs) have integral roles in translation of RNA into proteins and transcript splicing. Because such housekeeping functions are essential for cellular activities, the non-coding housekeeping RNAs are highly abundant in cells (2) (Fig. 1). For example, in rapidly growing mammalian cells such as HeLa cells, the composition of RNA species is ~80% rRNAs, 15% tRNAs, and 5% all the other RNAs, including protein-coding messenger RNAs (mRNAs) and other non-coding RNAs (ncRNAs) (2). It is now recognized that the other ncRNAs comprise a population of diverse types of ncRNA that control or modify diverse aspects of cell function. According to the latest annotations of human genes at the Ensembl genome database (Assembly: GRCh38.p12), there are 20,418 protein-coding genes; 15,195 pseudogenes, and 22,107 ncRNAs. NcRNAs include 4,871 small ncRNAs [e.g., small nuclear RNAs (snRNAs), small nucleolar RNAs (snoRNA), microRNAs (miRNAs), tRNAs];
15,014 long non-coding RNAs (lncRNAs), and 2,222 miscellaneous ncRNAs, which are ncRNAs that cannot be classified.

By definition, pseudogenes are sequence-similar to protein-coding genes but lack protein-coding potential. LncRNAs are any ncRNAs longer than 200 nucleotides (nt). Although it is a rather popular view that the complexity of an animal (e.g., humans vs. worms) correlates with the number of ncRNAs (3); in reality, the detailed annotation of the genome dictates this view (9). Furthermore, for even the most annotated animal genome, the human genome, the exact number of genes (including ncRNAs) is not currently defined (6). Thus, more detailed annotations of ncRNAs and their functional properties will be needed to fully understand the influence of ncRNAs in cellular activities. With regard to the evolution of ncRNAs, rRNAs can be found in Archae and Bacteria. In eukaryotes other than plants, RNA polymerase (Pol) I synthesizes pre-rRNA 45S and Pol III synthesizes tRNAs, rRNA 5S, and some small nuclear RNAs (snRNAs), while precursors of mRNAs, most of lncRNAs, and a large fraction of small housekeeping RNAs (e.g., miRNAs, snoRNAs, and the majority of snRNAs) are synthesized by Pol II (7). snoRNAs are important small RNAs that are relatively abundant. After synthesis, most of these RNAs are modified (e.g., addition of 5' capping, 3' polyadenylation, and RNA splicing) and localized to their specific subcellular locations to be functional, as in the case of the nuclear-enriched IncRNA, *Myolinc*, which binds to the DNA/RNA-binding protein, Tdp-43 (4).

Among the non-housekeeping, regulatory ncRNAs, one of the most well-studied classes is miRNA, for which the mature products are ~22 nt. The primary function of miRNAs is to bind sites in the 3'-untranslated regions (3'-UTR) of protein-coding transcripts, to block their translation. Because one miRNA can target hundreds of genes, miRNAs can be viewed as a machinery that fine-tunes cellular activities at a whole-cell level. Furthermore, due to their stability in circulation (e.g., elevated serum levels of *miR-141* in prostate cancer patients (5)), a growing number of miRNAs are under consideration for use as diagnostic biomarkers of various diseases. In addition, the function of a number of understudied classes of ncRNAs are beginning to be understood. Of these ncRNAs, lncRNAs are increasingly being studied. The current data suggest various functions and that dysregulation of lncRNA abundance is also linked to disease – for example, the lncRNA *CHRF* (8) functions as miRNA sponges in cardiovascular disease. Furthermore, the majority of hits from genome-wide association studies for human disease-associated loci map to non-coding regions, and to lncRNA loci in many cases.

In view of the growing evidence for important physiological roles of various forms of ncRNA, the Editors of AJP-Cell Physiology are pleased to start in this issue a thematic series of
Reviews on “Roles of non-coding RNAs in Human Diseases”. The first article by Zhang, Ma and
Pearce (10) considers the roles of miRNAs in brain development and the evidence that miRNAs
contribute to cerebrovascular pathophysiology. Future reviews in the series will also examine
roles of ncRNAs in the physiology and diseases of particular tissues or cell types, or will focus
on a specific ncRNA that is emerging in some form as a master-regulator. The Editors thank all
the authors for their time and effort in contributing these excellent Reviews. We hope that for
readers of AJP-Cell Physiology, these Reviews will provide contexts to consider how ncRNAs
may be involved in the cellular and molecular physiology of a multitude of biological processes.
Submissions of research articles that investigate the roles of ncRNAs in cell physiology are
welcome either as regular research articles or under any of the current Calls for Papers.

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GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Both authors drafted and revised the manuscript, prepared the figure, and approved the final version.

FIGURE LEGEND
Fig. 1. Major classes of cellular RNAs. Three types of RNA polymerases (Pol I, II, and III) synthesize different types of RNA species, yielding the indicated composition by weight of RNA transcripts in a typical human cell (left-hand pie chart). The gene number distribution is based on the latest genome annotation provided by the Ensembl genome database (Assembly: GRCh38.p12) (right-hand pie chart). piRNAs: Piwi-interacting RNAs; scRNAs: small cytoplasmic RNAs; snoRNA: small nucleolar RNA; and snRNAs: small nuclear RNAs.
**By Amount**
- rRNAs: 80%
- tRNAs: 15%
- Others: 5%
  - Protein-coding mRNAs
  - Small ncRNAs (e.g., miRNAs)
  - IncRNAs

**By Number**
- Pseudogenes: 26.3%
- Protein-Coding: 35.4%
- IncRNAs: 26.0%
- Misc. ncRNAs: 3.8%
- Small ncRNAs: 8.4%
  - miRNAs, piRNAs, scRNAs
  - snoRNA, snRNAs