The RNA–Protein World

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ABSTRACT

Following the naming of the RNA World for the hypothetical biochemical world during very early life forms, the current world was named the Protein World. However, the astonishing high level of transcripts from virtually all chromosomes in an organism now found in eucaryotes, as well as their extensive roles in regulating gene expression, suggests that today's world should be labeled as the RNA–Protein World.

Keywords: regulatory RNA; transcription; stress

The overwhelming number of efficient, protein enzymes observed in the biochemical makeup of today's living organisms has led to a general description: The Protein World. That picture was acceptable until ~15 yr ago when the first evidence of specific, regulatory cellular RNAs was presented (Lee et al. 1993; Wightman et al. 1993). Although some other RNAs not directly involved in the mechanics of protein synthesis had been identified previously, there were not many and very few had catalytic activity. The discovery of the first two RNAs that had catalytic activity (one was a veritable RNA enzyme) (Kruger et al. 1982; Guerrier-Takada et al. 1983) led Walter Gilbert (Gilbert 1986) to coin the phrase "the RNA World" for the picture of primitive cells and the origin of life. That term was appropriate, but over the years the description of the Protein World and even the RNA World had to be altered, as is the case with virtually all general hypotheses in science.

The identification of miRNAs, piRNAs, lncRNAs, and RNAi in eucaryotes (Grimson et al. 2008) and small RNAs in procaryotes (Gottesman and Storz 2011), as well as numerous noncoding RNAs of viruses, and perhaps many more RNAs with similar attributes to regulatory RNAs, has changed the view of intracellular biochemistry. With the first identification of regulatory cellular RNAs in *Caenorhabditis elegans*, the total number of such RNAs in many organisms is now overwhelming. There are many hundreds of miRNAs of 22 nucleotides (nt) in length in mammalian cells, and many more piRNAs. The number of lncRNAs, of length from a few hundred to thousands of nucleotides (see Lee 2012, the Xist RNA in humans), is being more accurately estimated but only several have associated functions. Junk DNA does not exist: The previously described "blank" stretches of DNA are transcribed into RNA, probably lncRNA.

Is there a biological basis for this multitude of regulatory RNAs? In bacteria, no small RNAs are made unless a bacterium is under stress. Stress, depending on how you define it, could be hot or cold temperatures, ambient oxygen concentration in aerobes, pH, and other factors. Is the same true for eucaryotes? Are miRNAs, lncRNAs only made when "stress" occurs? If mammalian cells are under normal homeostasis growing happily, or bacteria are under no stress, how does stress occur? There could be a number of ways of defining stress, but in *C. elegans*, regulatory RNAs are made that govern developmental events, and the same is true of mammals. Are development and differentiation, with the function of other molecules included, stress? This is a sweeping generalization but "stress" that utilizes the primary importance of regulatory RNA can be contained within it.

A recent summary of the results of analysis of the human genome lists the number of RNA "genes" (Anonymous 2012), at about 20,000, as very close to that of protein coding genes. Although the function of all these RNAs is not known, a consideration of biochemical pathways and their control—and the ensuing role of these miRNAs and lncRNA in controlling the phenotype of human disease—supports the view that our current world is not the Protein World but, rather, the RNA–Protein World. An understanding of all these new RNAs, structurally and functionally, is imperative and will push the advancement of molecular biology and medicine for the next generation.

The RNA World might have existed, but the exclusivity of RNA and the neglect of DNA could have been overstated. Certainly, single-stranded fragments of DNA could have existed along with similar fragments of RNA. RNA could have been the replicating enzyme that would have been required for both single-stranded nucleic acids. Such a replicative function for RNA has been demonstrated in vitro (Lincoln and Joyce

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Article and publication date are at http://www.rnajournal.org/cgi/doi/10.1261/rna.038687.113.

2009). Single-stranded DNA can also function as an enzyme (Breaker and Joyce 1995), but there is no indication today that was the case in nature many years ago. The roles during evolution of these two nucleic acids are not clear, but what is definite is that double-stranded DNA, which is much less susceptible to mutation and chemical change than RNA, took over as the carrier of genetic information. Whether stress at an early time of evolution led to the multiple roles of RNA cannot be said, but the variety of RNA structures and the possibility of a primitive ribosome (Krupkin et al. 2011) and catalytic RNAs are an indication that RNA led the charge to more modern biochemistry and, recognizable to us, new organisms.

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