This Week's Citation Classic®

Weinberg R A & Penman S. Small molecular weight monodisperse nuclear RNA.
J. Mol. Biol. 38:289-304, 1968.
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A novel class of nuclear RNA is described which has properties quite distinct from those of all other RNA types described to date. This RNA consists of a group of low molecular weight, highly stable, methylated species. [The *SCI*® indicates that this paper has been cited in more than 385 publications.]

A Discovery of snRNA

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When we began this work in 1967, the molecular biology of eukaryotic RNA metabolism was still in its infancy. We thought then that the basic plan of life had been puzzled out in *E. coli*. Our challenge was to extend the bacterial scheme to mammalian cells. The experiments lay there, waiting to be done. These were exciting times!

Just when I began work in Sheldon Penman's lab, as a doctoral student in the MIT graduate program, the use of gel electrophoresis was extended to include RNA analysis. RNA species that were previously seen as broad sedimentation peaks could now be resolved as sharp bands. Measurement of radioactive peaks was easy: We would run each RNA sample through a cylindrical gel cast in a Plexiglas tube, freeze the gel in the tube, and shove it out onto the bed of a homemade salami slicer. The 1mm slices could then be counted by placing them in individual planchettes in a gas phase gamma counter, or, later on, in a fully automatic liquid scintillation counter. Analysis of a single RNA sample only took one and a half to two days!

The prevailing dogma was that all nuclear RNA was highly unstable, being destined for processing and export to the cytoplasm or rapid intranuclear degradation. Indeed, I spent a year documenting the processing paths of the nucleolar ribosomal RNA precursors and their brief, 50-minute sojourn en route to the cytoplasm. The rest of the nucleus, the "nucleoplasm," was known to contain heterogeneous nuclear RNA (hnRNA) having a very short lifetime (10-20 minutes) and of very obscure function.

I occasionally saw low molecular weight material upon gel electrophoresis of nucleoplasmic RNA following pulse-chase labeling protocols and ascribed this to DNA fragments that had managed somehow to acquire a uridine label and survive the DNase treatment used to prepare the nucleoplasmic RNAs. But, we soon found that what we had dismissed as junk was really a collection of as many as 10 distinct, low molecular weight, highly methylated RNA species—a whole new class of RNA! There was even one in the nucleolus. Unlike all the other RNAs in the nucleus, these RNAs seemed stable, turning over very slowly if at all.

This RNA seemed important, as some of its species were present in a million molecules per cell! (The cytoplasm only carries five million ribosomes.) Later we called this class snRNA (small nuclear RNA), a name that has stuck.[1] The labels we attached to the individual RNAs haven't. They were superseded by those used by Harris Busch's group which had, unknown to us, discovered these RNAs independently and spent the next decade doing detailed biochemical characterization of them.[2,3] His terms (U1, U2, U3...) are well embedded in the now-extensive literature on snRNA.

I gave all this up in 1969. Surely, one good reason to quit was the backbreaking work of processing 150 gel slices each time I wanted to analyze a single RNA sample. It remained for the technically more imaginative to introduce the procedure of autoradiography of slab gels—a procedure that allowed data collection to proceed 50-100 times more rapidly. Of course, there was another, very compelling reason to give up snRNA: I hadn't the vaguest clue of how to determine its functions.

Who could have imagined the central role of snRNA in splicing and hnRNA processing?[4] In fact, who could have imagined splicing? I found, though never reported, that these RNAs were present in some ill-defined ribonucleoprotein complex. Years later, the exciting discovery that lupus erythematosus patients showed antibody responses to these ribonucleoproteins made possible the characterization of snRNPs and spliceosomes, and laid the groundwork for understanding the mechanisms of splicing and polyadenylation.[5] I almost bumped into splicing once more. Five years later, while trying to associate SV40 mRNAs with different parts of the viral genome, I found puzzling, noncontinuous mapping patterns. In so doing, I came very close to stumbling upon RNA splicing. In the end, minds more astute than mine figured out what was really going on. But that is another big fish story!

1. **Weinberg R A.** Nuclear RNA metabolism. *Annu. Rev. Biochem.* 42:329-54, 1973. (Cited 230 times.)
2. **Reddy R & Busch H.** U snRNAs of nuclear snRNPs in the cell nucleus. (Busch H, ed.) *The cell nucleus*. Academic Press, 1986. p. 261-305.
3. **Busch H, Reddy R & Rothblum L.** SnRNAs, snRNPs and RNA processing. *Annu. Rev. Biochem.* 51:617-54, 1982. (Cited 315 times.)
4. **Padgett R A, Mount S M, Steitz J A & Sharp P A.** Splicing of messenger RNA precursors is inhibited by antisera to small ribonucleoproteins. *Cell* 35:101-7, 1983. (Cited 255 times.)
5. **Lerner M R & Steitz J A.** Antibodies to small nuclear RNAs complexed with proteins are produced by patients with systemic lupus erythematosus. *Proc. Nat. Acad. Sci. USA* 76:5495-9, 1979. (Cited 695 times.)

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