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Informosomes, East and West

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Abstract—Although Alexander Spirin was most known for his ribosome work, his earlier research on RNA synthesis during vertebrate embryogenesis was also pioneering. There he introduced the idea that messenger RNA exists as a complex with proteins. He named these particles "informosomes", mainly for the RNA species they contained but also hinting that this ribonucleoprotein form might underlie control of the mRNA's translation. Although the notion that mRNA is complexed with proteins was entirely plausible and had considerable supporting data, it was received with skepticism in some quarters. Here I briefly summarize this phase of Spirin's early work and offer my perspectives and speculations on why its acceptance was unduly delayed.

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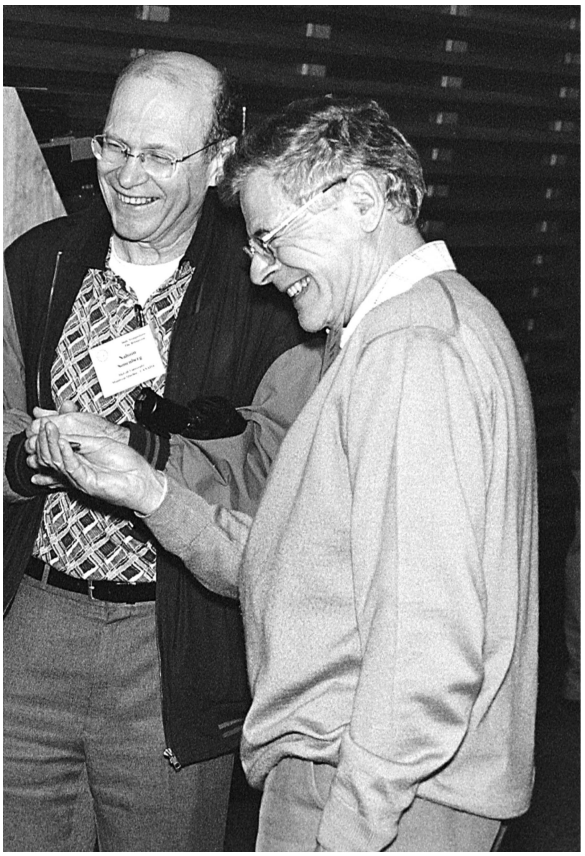
INTRODUCTION

Alexander Spirin's early work included some of the first studies of RNA synthesis in fish embryos. Notwithstanding his later ribosome work, so more widely known, this early work was seminal. The majority of research on this at the time was in sea urchin embryos and although this system had been productive [1], the leading figures in embryology all recognized this phyletic limitation and were well aware of and admired Spirin's work [2], which focused on the immediacy with which stored vs. new mRNA is deployed during embryogenesis of the teleost *Misgurnus fossilis* [3, 4].

During the course of this work Spirin and colleagues obtained evidence that the newly synthesized, cytoplasmic RNA in these embryos was protein bound. (They showed along the way that new ribosomes are not built until later embryonic stages, removing the possibility that their labeled RNA could be ribosomal RNA). The ribonucleoprotein status of the labeled RNA was indicated by three observations. One was that the sucrose gradient sedimentation of this labeled RNA was faster than that of the deproteinized RNA (but slower than the ribosomes, tracked by the UV absorbance). The second was that incorporated radioactive amino acids co-sedimented with the labeled RNA. The third was that if the cytoplasmic extracts' putative particles were subjected to formaldehyde fixation, the labeled RNA displayed a density in cesium chloride gradients indicative of a RNA–protein complex, not free RNA.

Spirin and colleagues published this work in 1964 [3, 4] and by then, the idea had been picked up in the West [5, 6] and indeed Spirin came to Philadelphia, U. S. in 1964-1965 to pursue the informosome concept in sea urchin embryos, confirming it [7]. But just a few months later it was reported that deproteinized RNA added to a HeLa cell extract became protein-bound [8], raising skepticism about any claims of endogenous RNA-protein complexes.

Spirin and colleagues immediately investigated this further in their system and made a number of important findings. They found that *E. coli* ribosomal RNA added to cytoplasmic extracts from *M. fossilis* embryos indeed became protein bound. Pursuing this, they ran these complexes on a sucrose gradient, and fixed them with formaldehyde followed by isopycnic banding in CsCl gradients. This revealed that these "artificial" complexes had lost much of their protein, having been separated (in the sucrose gradient) from the pool of cytoplasmic proteins that had not bound to the RNA. When they did similar experiments on the endogenous particles (informosomes), no such instability was observed. These critical experiments, *inter alia*, were summarized in a comprehensive paper based on the Second Sir Hans Krebs Lecture that Spirin gave at the 6th Federation of European Biochemical Societies Meeting in Madrid [9],



mRNA regulation across half a century. Nahum Sonenberg and Alexander Spirin, 2001 Cold Spring Harbor Symposia on Quantitative Biology: The Ribosome. Reproduced with permission of the Cold Spring Harbor Laboratory Archives.

a paper I recommend to anyone who wishes a more in-depth summary of his work in this field. This distinguished invitation reflected the growing recognition of Spirin's informosome work at the time, before his reputation in the ribosome field emerged.

Messenger RNP was soon defined in numerous other systems throughout 1971-1975 [10-23] and then a key epistemological and methodological advance occurred, namely the use of UV crosslinking to capture mRNA–protein complexes in live cells [24], removing or at least greatly minimizing any lingering doubts. Meanwhile, the field of translational control had gotten underway and soon expanded.

PERSONAL PERSPECTIVES

Alex Spirin's death has stimulated me to reflect on his informosome work after some years, from which I have come away with even greater admiration than I may have had then, although admiration I did have at the time. I can now see, hindsight being 20-20 of course, how a "dichotomy of theaters" was in operation for how the informosome concept played out. To the embryologists, the notion that some of the mRNA is "masked" and thus is being held for later deployment was very appealing. But to some of those in the West, working with HeLa and other rapidly growing cells with no inactive mRNA, the concept was less relevant (to their primary focus). And to those molecular biologists who discovered mRNA in 1961 and went on to dissect its ribosome-linked activity, there was no conceptual need for mRNA-associated proteins. A third perspective is one that I have considered not mentioning but must, and it is no surprise to anyone. Even in the 1960s when Spirin's work was evolving, there were many scientists in the West who were suspicious of work from Russia. We who were not, and I was not, were pained to observe this, and it pains me now that some in my country felt this way.

I am happy that Alexander Sergeyevich Spirin came to be so admired in my country, and throughout the world. Others in this volume vividly describe all he did in the ribosome field and for molecular biology in his country in Pushchino and Moscow, and beyond. I last saw him at the 2001 Cold Spring Harbor Symposium, where we enjoyably shared memories of the informosome/mRNA era. I, and all of us, shall always remember him for his breadth, prescience and overall scientific penetration (figure).

Ethics declarations. The author declares that he has no conflict of interest. This article does not contain description of studies with the involvement of humans or animal subjects.

REFERENCES

1. Pederson, T. (2006) The sea urchin's siren, *Dev. Biol.*, **300**, 9-14, doi: 10.1016/j.ydbio.2006.10.006.
2. Davidson, E. H. (1968) *Gene Activity in Early Development*, Academic Press, New York.
3. Ajtkhozhin, M. A., Belitsina, N. V., and Spirin, A. S. (1964) Nucleic acids in the early developmental stages of fish embryos (based on the loach Misgurnis fossilis), *Biochemistry (Moscow)*, **29**, 169-175.
4. Belitsina, N. V., Ajtkhozhin, M. A., Gavrilova, L. P., and Spirin, A. S. (1964) Messenger RNA of differentiating animals cells, *Biochemistry (Moscow)*, **29**, 363-374.
5. Henshaw, E. C., Revel, M., and Hiatt, H. H. (1965) A cytoplasmic particle bearing messenger ribonucleic acid in rat liver, *J. Mol. Biol.*, **4**, 241-256, doi: 10.1016/s0022-2836(65)80233-3.
6. McConkey, E. H., and Hopkins, J. W. (1965) Subribosomal particles and the transport of messenger RNA in HeLa cells, *J. Mol. Biol.*, **14**, 257-270, doi: 10.1016/s0022-2836(65)80245-5.
7. Spirin, A. S., and Nemer, M. (1965) Messenger RNA in early sea-urchin embryos: cytoplasmic particles, *Science (Washington)*, **150**, 214-217, doi: 10.1126/science.150.3693.214.
8. Girard, M., and Baltimore, D. (1966) The effect of HeLa cell cytoplasm on the rate of sedimentation of RNA, *Proc.*

Natl. Acad. Sc. USA, **56**, 999-1002, doi: 10.1073/pnas.56.3.999.

9. Spirin, A. S. (1969) The second Hans Krebs lecture: informosomes, *Eur. J. Biochem.*, **10**, 20-35, doi: 10.1111/j.1432-1033.1969.tb00651.x.
10. Perry, R. P., and Kelley, D. E. (1968) Messenger RNA–protein complexes and newly synthesized ribosomal subunits: analysis of free particles and components of polyribosomes, *J. Mol. Biol.*, **35**, 37-59, doi: 10.1016/S0022-28361(68)80035-X.
11. Burny, A., Huez, G., Marbaix, G., and Chantrenne, H. (1969) On a messenger ribonucleoprotein complex from rabbit reticulocytes, *Biochim. Biophys. Acta*, **190**, 228-231, doi: 10.1016/0005-2787(69)90176-2.
12. Cartouzou, G., Poirée, J. C., and Lissitzky, S. (1969) Rapidly-labelled ribonucleic acid-protein complexes of the thyroid tissue, *Eur. J. Biochem.*, **8**, 357-359, doi: 10.1111/j.1432-1033.1969.tb00536.x.
13. Lebleu, B., Marbaix, G., Huez, G., Temmerman, J., Burny, A., and Chantrenne, H. (1971) Characterization of the messenger ribonucleoprotein released from reticulocyte polyribosomes by EDTA treatment, *Eur. J. Biochem.*, **19**, 264-269, doi: 10.1111/j.143201033.1971.tb01313.x.
14. Morel, C., Kayibanda, B., and Scherrer, K. (1971) Proteins associated with globin messenger RNA in avian erythroblasts: isolation and comparison with the proteins bound to nuclear messenger-like RNA, *FEBS Lett.*, **18**, 84-88, doi: 10.1016/0014-5793(71)80413-1.
15. Blobel, G. (1972) Protein tightly bound to globin mRNA, *Biochem. Biophys. Res. Commun.*, **47**, 88-95, doi: 10.1016/s0006-291x(72)80014-7.
16. Kumar, A., and Lindberg, U. (1972) Characterization of messenger ribonucleoprotein and messenger RNA from KB cells, *Proc. Natl. Acad. Sci. USA*, **69**, 681-685, doi: 10.1073/pnas.69.3.681.
17. Kwan, S.-W., and Brawerman, G. (1972) A particle associated with the polyadenylate segment in mammalian messenger RNA, *Proc. Natl. Acad. Si. USA*, **69**, 3247-3250, doi: 10.1073/pna.69.11.3247.
18. Blobel, G. (1973) A protein of molecular weight 78,000 bound to the polyadenylate region of eukaryotic messenger RNAs, *Proc. Natl. Acad. Sci. USA*, **70**, 924-928, doi: 10.1073/pnas.70.3.924.
19. Bryan, R. N., and Hayashi, M. (1973) Two proteins are bound to most species of polysomal mRNA, *Nat. New Biol.*, **244**, 271-274, doi: 10.1038/newbio244271a0.
20. Lindberg, U., and Sundquist, B. (1974) Isolation of messenger ribonucleoproteins from mammalian cells, *J. Mol. Biol.*, **86**, 451-468, doi: 10.1016/0022-2836(74)90030-8.
21. Auerbach, S., and Pederson, T. (1975) Phosphorylation of messenger RNA-bound proteins in HeLa cells, *Biochem. Biophys. Res. Comm.*, **63**, 149-156, doi: 10.1016/0304-4165(75)90351-7.
22. Auerbach, S., and Pederson, T. (1975) Metabolic stability of messenger ribonucleoprotein in HeLa cells, *Biochim. Biophys. Acta*, **395**, 388-391, doi: 10.1016/0005-2787(75)90211-7.
23. Kumar, A., and Pederson, T. (1975) Comparison of proteins bound to heterogeneous nuclear RNA and messenger RNA in HeLa cells, *J. Mol. Biol.*, **96**, 353-365, doi: 10.1016/0022-2836(75)90165-5.
24. Wagenmakers, A. J. M., Reinders, R. J., and Van Venrooij, W. J. (1980) Cross-linking of mRNA to proteins by irradiation of intact cells with ultraviolet light, *Eur. J. Biochem.*, **112**, 323-330, doi: 10.1111/j.1432-1033.1980.tb04780.x.