RNA metabolism

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The birth of stable introns

In 2012, Joseph Gall and colleagues published a paper reporting the observation of extensive levels of stable introns in the oocyte nucleus of the frog *Xenopus tropicalis*. As a final-year graduate student looking for a postdoctoral position, I had an interview at Gall's laboratory at the Carnegie Institution in the autumn of 2011. I was (and still am) interested in studying the roles of long non-coding RNAs in intergenerational inheritance, and Gall showed me an unusual observation made in his laboratory — genome-wide occurrence of intronic RNA fragments that were stable for days in the frog oocyte nucleus or germinal vesicle.

We did not understand the potential biological importance of these stable introns, and Gall suggested we look at this phenomenon in a genetically tractable model organism, *Drosophila melanogaster*, which I had experience with. At first, I was sceptical about whether this observation was convincing enough to devote my postdoctoral career to: it was too unusual — why had others not seen it before? Furthermore, the unique method of nuclear RNA isolation required the 'gelling' of the nucleus, which made me wonder whether it could affect the RNA.

Nevertheless, several aspects of this study piqued my curiosity: the serendipitous nature of the discovery (the original aim was to identify nascent transcripts from lampbrush chromosomes) and the carefully designed isolation method that required the removal of the nuclear envelope to obtain essentially pure nuclear RNA, which explained why stable introns were not observed before

> "... it was too unusual — why had others not seen it before?"

owing to contamination with cytoplasmic mRNA. Importantly, Gall's deep understanding of the biological system helped to place the observation in a cellular and developmental context that warranted further investigation.

This paper guided my research at the Gall lab, and subsequently once I established my own group, led me to explore the functions of stable introns in vivo in *D. melanogaster*. Reflecting on the progress we have made in the decade since the original discovery, we now know that stable introns exist in both linear and circular forms and localize to the nucleus and the cytoplasm. They function in germline stem cells and are required for a nutritional stress response during oogenesis. What is even more gratifying is that maternally deposited stable introns regulate offspring development in several ways.

This story highlights the importance of chance in scientific research and of following one's intuition and curiosity when pursuing unusual observations.

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Original article: Gardner, E. J. et al. Stable intronic sequence RNA (sisRNA), a new class of noncoding RNA from the oocyte nucleus of *Xenopus tropicalis*. *Genes Dev.* **26**, 2550–2559 (2012)

Related article: Pek, J. W. et al. Stable intronic sequence RNAs have possible regulatory roles in *Drosophila melanogaster*. *J. Cell Biol.* **211**, 243–251 (2015)