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The expanding world of noncoding RNA biology

We highlight the expanding world of noncoding RNA biology in a Collection of articles from Nature research journals that discuss recent technological advances, approaches and emerging models driving this rapidly advancing field.

Although most of the genome is transcribed to RNA, less than 2% of the mammalian genome encodes proteins. The vast majority of synthesized RNAs are noncoding RNAs (ncRNAs) such as long noncoding RNAs (lncRNAs), circular RNAs (circRNAs) and small noncoding RNAs (sncRNAs). Although ncRNAs were initially considered to be degradation products of RNA turnover and metabolism, and were often neglected, increasing evidence has demonstrated their regulatory and functional roles in diverse cellular compartments and macromolecular structures and in a wide range of contexts spanning differentiation, disease and metabolism. In their study featured on our cover this month, Beucher et al. show that the *HASTER* lncRNA promoter, which is antisense to *HNF1A*, is a cell-specific *cis*-regulatory element that maintains *HNF1A* at an appropriate level through positive and negative feedback loops, and disruption of this lncRNA promoter can cause diabetes.

Technologies to study coding and noncoding RNAs have revolutionized this field and continue to open avenues of inquiry and drive discoveries. In light of its considerable growth and high interest to our broad cell biology audience, we are delighted to highlight recently published articles discussing advances in this field, with two Perspectives and a Review, which are featured in a cross-journal Collection that focuses on methods to study noncoding RNAs. This selection also includes recent methods and key resource articles that enable researchers to further explore the biology of non-coding RNA. The Collection can be found on a dedicated page, where readers can also access an online library of related content published across Nature research journals.

Many lncRNAs are expressed at much lower levels than their co-factors or targets. How do they effectively exert cellular functions despite this stoichiometric disadvantage? In their Perspective, Unfried and Ulitsky propose several models to tackle this question. The first model involves the formation of phase-separated condensates, exemplified by the lncRNAs NORAD and Xist. The second model also relies on lncRNA-seeded cellular compartments, but they do not necessarily have phase separation properties. Although biological condensates are appealing models to explain the substoichiometric action of lncRNAs, some lncRNAs use a 'recycling' or 'chaperone' model to act on their targets, which are much more abundantly expressed in cells. An example of the recycling model is the lncRNA Cyrano, which can be repeatedly recycled for the degradation of up to 17 miR-7 molecules. In the RNA chaperone model, the lncRNA SLERT acts as a chaperone to induce conformational changes of its target DDX21, which is around 1,000 times more abundant than SLERT in cells.

The sncRNA world is expanding from small interfering RNAs (siRNAs), microRNAs (miRNAs) and Piwi-interacting RNAs (piRNAs) to various types of non-canonical sncRNA. In their Perspective, Chen and colleagues discuss biases and caveats associated with traditional sncRNA sequencing methods and approaches to overcome these limitations to facilitate sncRNA identification. They also consider common problems associated with the analysis and interpretation of sncRNA sequencing data. Finally, they discuss emerging methods to directly map RNA modifications in sncRNAs, focusing on mass spectrometry and nanopore technologies, and propose ways to improve these methods. These rapidly advancing technological innovations should enhance our understanding of the identities and functions of sncRNAs.

The ability to observe RNA with high spatial and temporal resolution is crucial for understanding several aspects of RNA processing including transcription, translation, splicing, transport, localization and degradation, as well as understanding noncoding RNA and viral RNA. In their Review, Yeo and colleagues comprehensively discuss technological advances in RNA imaging in both fixed and live cells. The authors provide a historic view of innovation in fluorescent microscopy, image processing, DNA chemistry and next-generation sequencing to achieve many milestones in RNA imaging. They go on to highlight the knowledge gained from these methodological advances that continue to propel the field of RNA biology.

Much remains to be discovered, and we look forward to *Nature Cell Biology* continuing to be a key outlet for new methods and advances in this stimulating and rapidly developing area of research. We thank our authors and referees for their contributions, and hope that this Collection serves as both information and inspiration for our readers.

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