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INTRODUCTION

Molecular versatility: the many faces and functions of noncoding RNA

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Abbreviations

eRNA	enhancer-associated RNA
lncRNA	long noncoding RNA
mRNA	messenger RNA
meiRNAs	meiotic ncRNAs
ncRNA	noncoding RNA
piRNA	Piwi-interacting RNA
rRNA	ribosomal RNA
siRNA	small interfering RNA
snRNA	small nuclear RNA
snoRNA	small nucleolar RNA
TERRA	telomeric repeat containing RNA
tRNA	transfer RNA
XIST/Xist	X-inactive specific transcript

Over a decade ago, as postdocs, we sat on opposite sides of a laboratory building in Cleveland, Ohio. We both were studying noncoding RNAs (ncRNAs), but, analogous to our physical distance, we worked in vastly different organisms and utilized distinct experimental approaches in our daily scientific endeavors. Our contrasting experimental philosophies, however, led to an accelerated increase of both knowledge and appreciation of the many functions of ncRNAs. Thus, when the editors Beth Sullivan and Conly Reider invited us to develop this Special Issue, we not only embraced the opportunity but also knew that, between the two of us, we would include reviews from every corner of the current ncRNA world. This was a challenging task, since the versatility of ncRNAs in biological processes has significantly expanded since our postdoctoral days. Although it was impossible to include reviews on every aspect of ncRNA biology, all of the reviews in this Special Issue highlight ncRNA molecules as key regulators of the eukaryotic genome.

Despite less than 2 % of our DNA coding for protein (Lander et al. 2001), most of the genome is transcribed into RNA (Kapranov et al. 2007a, b; Hangauer et al. 2013). The biological significance for much of this transcription is unclear, but at least some of it corresponds to the multitude of ncRNA types. ncRNA is central to numerous processes from providing priming sites for DNA replication to templating telomere sequence for telomerase. Collectively, the ncRNAome is highly diverse as outlined in Fig. 1. These include ncRNAs involved in regulation of transcription, splicing, and translation, as well as maturation of other ncRNA, such as the processing of ribosomal RNA (rRNA) by small nucleolar RNAs (snoRNA). One intriguing question is how many other ncRNA types remain undiscovered? Figure 2 shows a timeline from the middle of the last century to the present day. The mid-1950s through the 1960s witnessed groundbreaking advances in RNA research including defining functions of tRNAs (Hecht et al. 1959) and rRNAs (Littlefield et al. 1955; Siekevitz and Palade 1959), as well as the discovery of messenger RNA (mRNA)

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(Brenner et al. 1961; Gros et al. 1961). This was followed by a quiet period before an era beginning in the early 1990s that witnessed the discovery of a variety of different small RNA species.

Small ncRNAs are the focus of three reviews in this Special Issue. A central feature of many small ncRNA pathways, including microRNA (miRNA) (Lee et al. 1993), small interfering RNA (siRNA) (Fire et al. 1998; Hamilton and Baulcombe 1999), and Piwi-interacting RNA (piRNA) (Aravin et al. 2006; Girard et al. 2006; Watanabe et al. 2006), is the *trans*-acting effector protein, Argonaute. Blake Billmyre and colleagues focus on the various RNAi-dependent silencing mechanisms reported throughout the fungal kingdom. The authors also consider the independent loss of RNAi pathways in diverse fungal lineages and speculate on potential evolutionary forces that may drive RNAi loss. Christopher Wedeles, Monica Wu, and Julie Claycomb discuss the many functional properties of the *Caenorhabditis elegans*-specific Argonaute protein, CSR-1, including involvement in chromatin and chromosome organization, histone RNA processing, and silencing of exogenous DNA in the germ line. The authors also discuss an ncRNA-independent function of CSR-1, raising the intriguing possibility that other ncRNA effector molecules could function in pathways that are distinct from their roles in ncRNA biology. Small ncRNAs are central players in the biology of transposable elements and transposon defense systems employed by the host genome. Bayly Wheeler discusses the interdependent relationship between transposon control and host response in a variety of organisms, from fungi to mammals. She highlights the critical functions of small ncRNAs, acting in both *cis* and *trans*, in the response to environmental stresses.

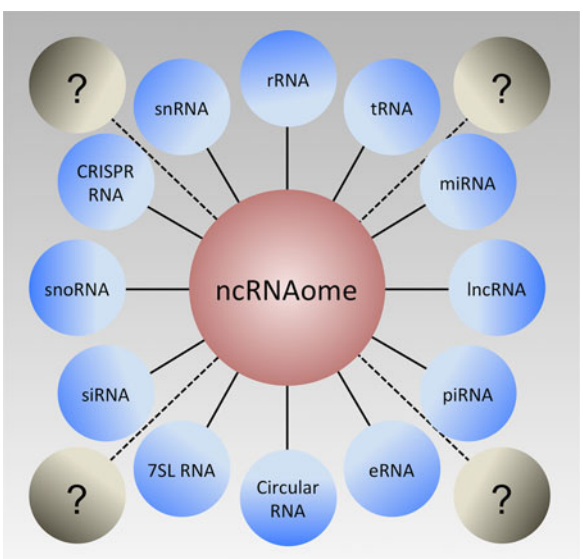

Fig. 1 Image indicating the many different types of known and to-be-discovered ncRNAs that constitute the ncRNAome

In addition to these small ncRNA species, the 1990s also witnessed the discovery of a novel class of transcript now collectively known as the long ncRNAs (lncRNA). These RNAs closely resemble mRNA in that they are transcribed by RNA polymerase II, are typically composed of exons and introns, are capped at the 5′ end, and generally polyadenylated. lncRNAs are diverse in size, origin, and function, and we include many examples of lncRNAs having critical roles across numerous biological pathways, in a wide variety of eukaryotes. One of the earliest identified and widely studied lncRNA is the X-inactive specific transcript (XIST/Xist). Xist is a central component in the mammalian form of dosage compensation: X-chromosome inactivation (Brockdorff et al. 1992; Brown et al. 1992). In this issue, Sundeep Kalantry and colleagues bring us up to date with a review of the multitude of lncRNAs that function in concert with Xist to mediate mammalian dosage compensation.

Two articles highlight recent progress in our understanding of how ncRNAs regulate chromatin structure and the maintenance of epigenetic states. Tanmoy Mondal and Chandrasekhar Kanduri discuss functional links between ncRNA and DNA methylation in mammals. The authors propose a model that incorporates two functionally distinct classes of ncRNAs: namely those specifically required for only the establishment of chromatin states and those that are continuously required for both the establishment and maintenance of such states. Claudia Keller and Marc Büehler review how work in the fission yeast *Schizosaccharomyces pombe* has contributed to the current mechanistic understanding of ncRNAs functioning as guide, effector, and tethering molecules in the establishment and maintenance of chromatin structure. Intriguingly, they highlight work (Keller et al. 2012, 2013) demonstrating that protein-bound ncRNAs can induce a conformational change in protein structure and feature similar studies in mammals (Sun et al. 2013) and Tetrahymena (Couvillion et al. 2012). Chromatin structure can also influence genome stability. Kristin Scott explores the role of centromeric transcription and the resulting ncRNAs in establishing a

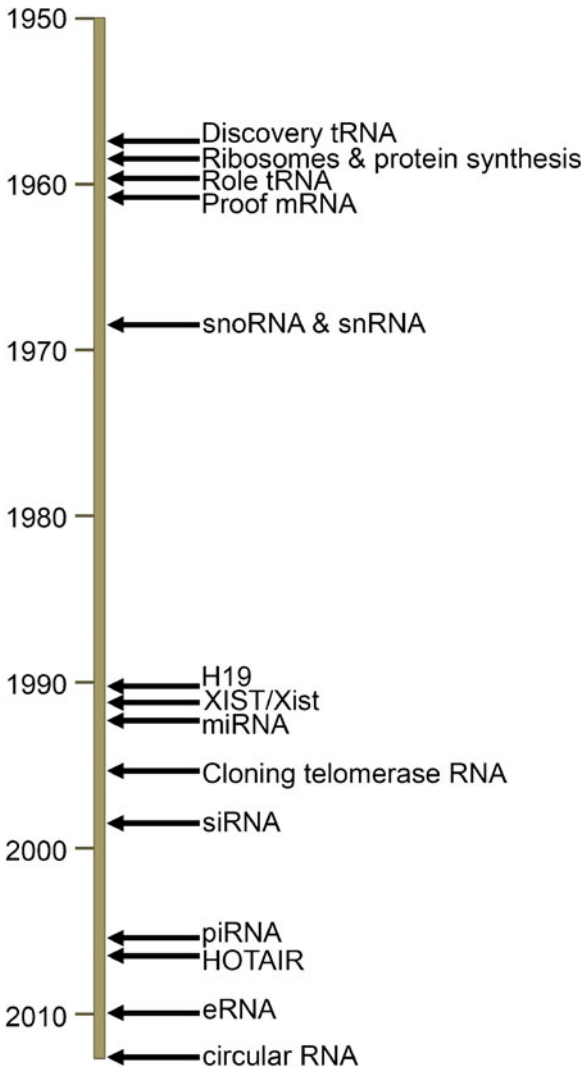

Fig. 2 Timeline highlighting key events in RNA discovery, including tRNA discovery (Ogata and Nohara 1957; Hoagland et al. 1958) and function (Hecht et al. 1959), ribosome role in protein synthesis (Littlefield et al. 1955; Siekevitz and Palade 1959), proof of mRNA (Brenner et al. 1961; Gros et al. 1961), discovery of small nuclear RNA (snRNA) (Hodnett and Busch 1968) and snoRNA (Weinberg and Penman 1968, Prestayko et al. 1970), the long noncoding RNAs H19 (Bartolomei et al. 1991; Leibovitch et al. 1991), XIST/Xist (Brockdorff et al. 1992; Brown et al. 1992) and HOTAIR (Rinn et al. 2007), the small RNAs miRNA (Lee et al. 1993), siRNAs (Fire et al. 1998; Hamilton and Baulcombe 1999) and piRNA (Aravin et al. 2006; Girard et al. 2006; Watanabe et al. 2006), cloning of telomerase (Feng et al. 1995), and the reporting of circular RNAs (Jeck et al. 2013) and eRNA (Kim et al. 2010)

chromatin environment that ensures proper centromere function. Also considered are the various known functions of the resulting ncRNAs in the assembly and stability of the multiprotein kinetochore.

In concert with regulating changes in chromatin structure, numerous lncRNAs regulate gene expression, differentiation, and development. Edwige Hiriart and André Verdel compare and contrast the key functions of lncRNAs during sporulation in the highly diverged yeasts *Saccharomyces cerevisiae* and *S. pombe*. Although both yeasts use ncRNAs to control germ cell differentiation, the functional and temporal involvement of key ncRNA molecules differs significantly. Da-Qiao Ding, Tokuko Haraguchi, and Yasushi Hiraoka continue the theme of ncRNAs during meiosis in their discussion of meiotic ncRNAs (meiRNAs) as key molecules that both regulate a cell's entry into meiosis and coordinate meiotic chromosome dynamics. The authors also present a model for homologous chromosome pairing in meiosis that is mediated by local ncRNA accumulation, or meiRNA bodies.

Several authors describe recent studies documenting ncRNA involvement in developmental biology. Jamila Horabin discusses the key features and emerging mechanisms of lncRNAs involved in homeotic gene expression and dosage compensation in *Drosophila melanogaster*. Plant species also respond to developmental cues, often originating from the environment. Sibum Sung and colleagues review the process of vernalization in *Arabidopsis*, focusing on the properties of lncRNAs COOLAIR and COLDAIR. The authors draw functional parallels between plant ncRNAs and mammalian Xist. Deepak Singh and Kannanganttu Pransanth summarize various roles of lncRNAs in

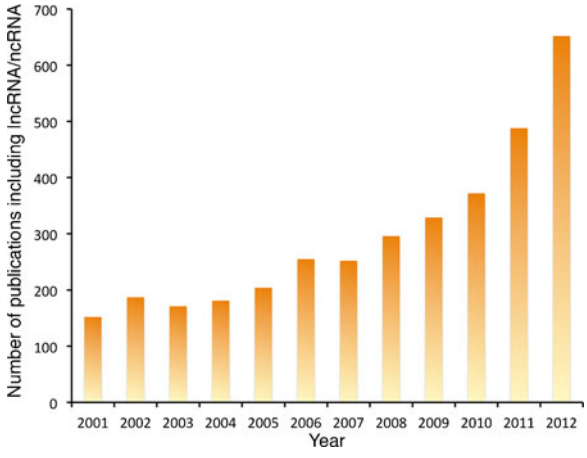

Fig. 3 Graph showing the number of publications in PubMed returned per year when searching for the terms lncRNA and ncRNA

mammalian gene expression, focusing on nuclear functions including transcription, pre-mRNA processing, and nuclear organization. The authors also discuss the consequences of aberrant ncRNA regulation, which is linked to the development of many types of cancer in humans. Finally, Emily Darrow and Brian Chadwick describe the mounting experimental evidence for the importance of enhancer transcription in order for these distal regulatory elements to modulate transcriptional programs in response to signaling, development, and differentiation.

So far this millennium, the number of publications per year recorded in PubMed that involve lncRNA or ncRNA has increased more than fourfold and shows a trajectory that suggests that this trend is set to continue for years to come (Fig. 3). Clearly, this is an exciting period in molecular biology with major advances in pluripotency biology, genome engineering, and high-throughput sequencing technologies. As these approaches continue to improve and their application and analysis become as common in molecular labs as gel electrophoresis or PCR, our understanding of ncRNA function will almost certainly move forward at a staggering pace. Who can predict how many more ncRNA types will be discovered over the next decade is unclear, but one thing is certain, it promises to be an exhilarating era.

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