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The Role of Non-Coding RNAs in Biology

Edited by Mark A. Lindsay and Sam Griffiths-Jones

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PREFACE

It has been known for many years that some genes in both eukaryotes and prokaryotes are transcribed to produce RNA, but are not translated into proteins. The advent of high-throughput sequencing technology has led to an explosion in the discovery of these 'non-coding RNA' genes, and functional analysis has indicated their diverse biological roles, including the regulation of transcription and translation, catalysis, chromatin structure, RNA processing and transposon silencing. In this volume of *Essays in Biochemistry*, we have attempted to produce an accessible introduction to this rapidly developing area by inviting leading experts to review some of the most important and interesting families of non-coding RNAs. Non-coding RNAs are often subdivided into 'short' and 'long' families, and we have organized the chapters accordingly.

In Chapter 1, Michael Clark, Anupma Choudhary, Martin Smith, Ryan Taft and John Mattick provide a concise overview of non-coding RNAs in both eukaryotic and prokaryotic organisms. The small non-coding RNAs section begins with two chapters on the most extensively investigated family, the microRNAs. In Chapter 2, Nham Tran and Gyorgy Hutvagner examine the mechanism of microRNA biogenesis, whereas Chapter 3, by Tamas Dalmay, discusses the mechanisms by which microRNAs regulate the translation of protein-coding genes via the RNA interference pathway. Subsequent chapters examine the biogenesis and role of other important families of small RNAs. In Chapter 4, Kauro Sato and Mikiko Siomi assess the importance of piwi-interacting RNAs in maintaining germline integrity through the silencing of transposable elements. In Chapter 5, Lauren Lui and Todd Lowe examine the role of small nucleolar RNAs in guiding the post–transcriptional modification of other non-coding RNAs, as well as recent studies that implicate these RNAs in RNA silencing, telomerase maintenance, alternative splicing and human cancer. The small RNA section is completed by Saba Valadkhan and Lalith Gunawardane, who survey the role of small nuclear RNAs in splicing as well as other aspects of RNA biogenesis, including polyadenylation and RNA stability (Chapter 6).

In general, much less is known about the evolution and function of long non-coding RNAs. These sequences are therefore commonly classified based on their origin and/or genomic context: for example, natural antisense (Chapter 7), pseudogenes (Chapter 8) and long intergenic non-coding RNAs (Chapter 9). The chapter on natural antisense by Megan Wight and Andreas Werner (Chapter 7) considers the evidence that the pairing of antisense with sense transcripts can regulate gene expression, and the potential importance of this mechanism in disease. Although pseudogenes are no longer able to produce proteins, there is increasing evidence that many are transcribed, and that this might have an impact on protein expression from other loci. In Chapter 8, Ryan Pink and David Carter assess the evidence to support this contention, the possible mechanisms and their potential biological

function. The section on long non-coding RNAs is finished by Robert Young and Chris Ponting (Chapter 9), who discuss the various approaches that have been employed to identify long intergenic non-coding RNAs and their biological functions. Finally, Chapter 10, by Thomas Roberts and Matthew Woods, considers the potential of targeting non–coding RNAs as a novel therapeutic approach.

We thank the *Essays in Biochemistry* Editorial Advisory Panel and all members of the Portland Press staff for their work on producing this volume. We particularly thank Clare Curtis for her efficient management of the entire process. We also thank the authors for their efforts in producing high-quality reviews in a timely manner, and the anonymous reviewers for their comments and suggestions.

Mark Lindsay and Sam Griffiths-Jones
March 2013

AUTHORS

Mark Lindsay obtained a degree in Natural Sciences from Cambridge University in 1986 and a Ph.D. investigating the mechanism of insulin release from Nottingham in 1991. In the intervening years he has held positions at Imperial College London, AstraZeneca Pharmaceuticals and the University of Manchester. In 2011, he moved to the position of Chair in Molecular Pharmacology at the University of Bath. Dr Lindsay has spent the last 10 years examining the role of non–coding RNAs in inflammation and respiratory diseases such as asthma, chronic obstructive pulmonary disease and cancer.

Sam Griffiths-Jones is a Senior Lecturer in the Faculty of Life Sciences, University of Manchester. Dr Griffiths-Jones has research interests in the computational analysis of non-coding RNA biology. In particular, his group work on the evolution, annotation and function of microRNAs, including management and production of the miRBase database of microRNA sequences. From 2001 to 2006, Dr Griffiths-Jones worked at the Wellcome Trust Sanger Institute, where he founded miRBase and the Rfam database of RNA families, and worked on the Pfam and Interpro protein family resources. Prior to that he obtained a degree in Biochemistry and Biological Chemistry (1997) and a Ph.D. in Chemistry (2001) from the University of Nottingham.

Michael B. Clark is a research officer at the Institute for Molecular Bioscience at the University of Queensland. His research focuses on transcriptomics, long non-coding RNAs and how RNA-based regulation underlies human traits and diseases.

Anupma Choudhary is a Ph.D. student in the Taft Laboratory at the Institute for Molecular Bioscience, University of Queensland. She has a Bachelor of Science with Honours in Microbiology and a Master's degree in Genetics from the University of Delhi, India. Her research interests lie in understanding novel features and functions of small non-coding RNAs, with particular focus on deciphering the regulatory roles of nuclear microRNAs.

Martin Smith completed a B.Sc. in Biological Sciences at the Université de Montréal, where he also obtained an M.Sc. in Bioinformatics in collaboration with the Infectious Disease Research Center of the Centre Hospitalier de l'Université Laval and the McGill Center for Bioinformatics. Dr Smith investigated the impact of a class of short interspersed degenerated retroposons on gene expression and genome organization in the parasitic protozoan *Leishmania*. He then obtained a Ph.D. from the University of Queensland in genomics and computational biology at the Institute for Molecular Bioscience. His Ph.D. thesis is entitled '*Widespread purifying selection on RNA structure in mammals*'. Dr Smith is currently a research officer at the Garvan Institute of Medical Research in the RNA Biology and Plasticity group in Sydney.

Ryan Taft is a Laboratory Head and Australian Research Council Discovery Early Career Research fellow at the Institute for Molecular Bioscience at the

University of Queensland. His work is focused on the cryptic genomics that underlies the RNA regulatory world and rare inherited disease.

John Mattick is head of the RNA Biology and Plasticity Laboratory at the Garvan Institute of Medical Research. He is the executive director of the Garvan Institute, Conjoint Professor in the St Vincent's Clinical School and Visiting Professorial Fellow, School of Biotechnology and Biomolecular Science, University of New South Wales. His work focuses on the role of RNA regulatory systems in the evolution and development of complex multicellular organisms.

Nham Tran obtained his Ph.D. at Johnson & Johnson Research and the University of New South Wales, Australia. During this period, he studied with Dr Greg Arndt in designing a dual-promoter system for expressing small interfering RNAs in mammalian cells and using long double-stranded RNA to regulate genes. In 2005 he joined Professor Christopher O'Brien and Professor Barbara Rose at Sydney University to elucidate the role of small RNAs in head and neck cancer. This group was the first to perform a genome-wide screen of microRNAs in head and neck cancer. In 2010, Dr Tran was awarded the Chancellor's Fellowship at the University of Technology, Sydney, to further his work in small RNAs. During this period, he won the early career development award from the CDMRP–DoD (Congressionally Directed Medical Research Programs of the Department of Defense) to investigate the use of exosomal small RNA as biomarkers for early cancer detection. In 2013 he established his own independent laboratory with the aim of using small RNA biomarkers for the early detection of head and neck cancer. His laboratory is also focused on trying to understand the function of microRNAs in this disease.

Gyorgy Hutvagner obtained his Ph.D. at the Szent Istvan University in Hungary. He won several Hungarian and international short-term fellowships which allowed him to work in Sweden and in The Netherlands. In 2001, he joined Dr Phillip Zamore's laboratory at The University of Massachusetts Medical School as a postdoctoral fellow. As a postdoc, he studied the biochemical pathway of RNA interference and contributed to several key discoveries. In 2002, he won the postdoctoral fellowship of the Medical Foundation. In 2005, Dr Hutvagner joined the Division of Gene Regulation and Expression at the School of Life Sciences at the University of Dundee as a lecturer and an independent investigator. He is also the recipient of the prestigious Wellcome Trust Career Development Fellowship. In 2011 he took up a new post as an Associate Professor at the University of Technology, Sydney, and was awarded the Australian Research Council Future Fellowship. His laboratory continues to unveil the mechanism of microRNA-mediated gene silencing in human cells. Also his laboratory is involved in the identification and characterization of novel small regulatory RNAs.

Tamas Dalmay graduated in Budapest and did his Ph.D. in Molecular Plant Virology in Godollo, Hungary. He moved to Norwich in 1995 with an EMBO fellowship to work with Professor David Baulcombe on the genetics of gene silencing. He obtained a Lectureship in 2002 and became a Professor in 2012 at the University of East Anglia where his group has been working on the biology of small non-coding RNAs in animal and plant systems.

Kaoru Sato studied for a Ph.D. in Life Sciences at the Graduate School of Frontier Sciences, the University of Tokyo, and received his Ph.D. in 2009. He subsequently undertook postdoctoral training with Professor Haruhiko Siomi at Keio University School of Medicine, where he started ongoing studies on the molecular mechanisms of RNA silencing. In 2012, he became an Assistant Professor at Keio University School of Medicine. In 2013, he moved to the University of Tokyo as an Assistant Professor, where he works with Professor Mikiko C. Siomi.

Mikiko C. Siomi is a Professor in the Graduate School of Science in the University of Tokyo, Japan. She was awarded Ph.D.s from Kyoto University in 1994 and the University of Tokushima in 2003. In 1999, together with Haruhiko Siomi, she founded a laboratory at the University of Tokushima to study the molecular function of *Drosophila* FMR1 (dFMR1). Later, her research focused on small-RNA-mediated gene silencing pathways in *Drosophila*. In 2012, she moved to her present position at the University of Tokyo, where her study of small RNA-mediated gene silencing continues.

Lauren Lui is a graduate student in the Biomolecular Engineering and Bioinformatics program at the University of California, Santa Cruz. She received her B.S. from the University of California, Davis, as a Mathematical and Scientific Computation major.

Todd Lowe is an Associate Professor in the Department of Biomolecular Engineering, and member of the Center for Molecular Biology of RNA at the University of California, Santa Cruz.

Saba Valadkhan started her scientific career in Professor James Manley's laboratory in Columbia University as a graduate student, where she worked on elucidating the structure and function of U6 and U2 small nuclear RNAs. In 2004, she joined the Center for RNA Molecular Biology in Case Western Reserve University School of Medicine as an Assistant Professor and continued her work on the catalytic properties of the *in vitro* assembled protein-free complex of U6 and U2 snRNAs and their relationship to spliceosomal catalysis.

Lalith Gunawardane is currently a postdoctoral scientist in the Valadkhan laboratory in the Center for RNA Molecular Biology at Case Western Reserve University. As a graduate student in Professor Haruhiko Siomi's laboratory in Keio University School of Medicine in Tokyo, he worked on the small non-coding RNAs and their interactions with proteins. Since joining the Valadkhan laboratory, he has continued his work on analysis of function of nuclear non-coding RNAs in mammalian cells.

Megan Wight graduated from Newcastle University with an honours degree in Biomedical Sciences specializing in the genetics of complex disease. Her research project focuses on non-coding RNAs with particular emphasis on natural antisense transcripts.

Andreas Werner received his degree in Biochemistry and a Ph.D. in Physiology from the University of Zurich, Switzerland. He is now a Reader for Molecular Physiology at the Institute for Cell and Molecular Biosciences at Newcastle

University, U.K. The serendipitous discovery of a naturally occurring antisense transcript in 1995 prompted his interest in non-protein-coding RNAs. His research focuses on molecular mechanisms of gene regulation by antisense RNAs. The aim is to understand a bigger picture of antisense transcription in the context of evolution and organismal complexity.

Ryan Pink is a postdoctoral research fellow at Oxford Brookes University. He received his Ph.D. from Cranfield University in 2007 working on molecular links of diet and oesophageal cancer in South Africa. This was followed by his first postdoctoral position working on novel cancer nucleotide-based sensors. In 2009, Dr Pink moved to Oxford Brookes University to develop novel methods for RNA analysis in blood systems. He now works on the role of non-coding RNAs in the regulation of both cancer and blood disorders. Dr Pink also has awards for his prolific science engagement and arts–science cross-over projects.

David Carter received his Ph.D. from Cambridge University, U.K., in 2003, where he developed a novel technique to detect the physical interaction between the β-globin gene and its enhancer, the locus control region. He moved to Oxford University to pursue postdoctoral research in the structure of the nucleus and how this influences gene expression. He then spent 2 years as a lecturer at Cranfield University before taking up a senior lectureship at Oxford Brookes University where he spends most of his time getting very excited about non-coding RNAs.

Robert Young completed his D.Phil. entitled 'Evolution and Function of long non-coding RNAs in *Drosophila*' in Chris Ponting's laboratory in 2011. He is currently working as a postdoc at the MRC Human Genetics Unit, investigating transcribed enhancers and their mechanisms of action.

Chris Ponting is Deputy Director of the MRC Functional Genomics Unit, University of Oxford, and Associate Faculty member of the Wellcome Trust Sanger Institute. His ERC Advanced Grant has allowed his group to focus on the computational and experimental characterization of long non-coding RNAs in both vertebrate and invertebrate model systems.

Thomas Roberts is a doctoral candidate working in the Department of Physiology, Anatomy and Genetics at the University of Oxford. His research has focused on small-RNA-mediated epigenetic modulation of therapeutic target genes and the role of differential microRNA expression in the pathophysiology of Duchenne muscular dystrophy. His research interests include RNA biology, non-viral gene therapy and neuromuscular disorders.

Matthew Wood is Professor of Neuroscience at the University of Oxford, and Fellow and Tutor in Medicine at Somerville College, Oxford. He directs a research group investigating RNA biology and the development of RNA-based therapies for neurological and neuromuscular diseases.

ABBREVIATIONS

ABC	ATP-binding cassette
ADAR	adenosine deaminases that act on RNA
aHIF	antisense hypoxia-inducible factor
AMO	anti-miRNA oligonucleotide
ANRIL	CDKN2B antisense RNA 1
APC	antigen-presenting cell
BACE1	β-secretase 1
Bcd1	box C/D RNA 1
BDNF	brain-derived neurotrophic factor
BLV	bovine leukaemia virus
CLL	chronic lymphocytic leukaemia
CPSF	cleavage and polyadenylation stimulating factor
CRC	colorectal cancer
CRISPR	clustered regularly interspersed short palindromic repeat
crRNA	CRISPR RNA
cuff	*cutoff*
DGCR8	Di George Syndrome critical region gene 8
DHFR	dihydrofolate reductase
DMD	Duchenne muscular dystrophy
dsDNA	double-stranded DNA
dsRNA	double-stranded RNA
EBV	Epstein–Barr virus
eIF4G	eukaryotic translation-initiation factor 4G
EM	electron microscopy
eRNA	enhancer RNA
EST	expressed sequence tag
FasIII	*Fasciclin III*
flam	*flamenco*
FS(1)Yb	Female Sterile (1) Yb
GAR	glycine–arginine rich
Gas–5	growth arrest–specific 5
GFP	green fluorescent protein
GR	glucocorticoid receptor
H3K9me3	histone H3 Lys^{9} trimethylation
HCV	hepatitis C virus
HDAC1	histone deacetylase 1
HDE	histone downstream element
HMG	high-mobility group
HMGA1	high-mobility group A1
hnRNP	heterogeneous nuclear ribonucleoprotein

hnRNPA1	heterogeneous nuclear ribonucleoprotein A1
HP1	heterochromatin protein 1
Hsp	heat-shock protein
ICG	interchromatin granule
Igf2r	insulin-like growth factor 2 receptor
IRES	internal ribosome entry site
ISL	intramolecular stem-loop
KHSRP	KH-type splicing regulatory protein
KSHV	Kaposi's sarcoma-associated herpes virus
lincRNA	long/large intergenic ncRNA
LNA	locked nucleic acid
lncRNA	long ncRNAs
Mael	Maelstrom
MALAT–1	metastasis associated in lung adenocarcinoma transcript-1
MCPIP1	monocyte chemoattractant protein-1-induced protein 1
MDV	Marek's disease virus
miRISC	miRNA-induced silencing complex
miRLC	miRNA loading complex
miRNA	microRNA
MLE	Maleless
MOF	Males absent on the first
MSL	male-specific lethal
MTOC	microtubule-organizing centre
Naf1	nuclear assembly factor 1
NAT	natural antisense transcript
ncRNA	non-coding RNA
NFAT	nuclear factor of activated T-cells
nos	*nanos*
NSCLC	non-small cell lung cancer
ORF	open reading frame
PABC	cytoplasmic polyA-binding protein
PABP	polyA-binding protein
PAPI	Partner of PIWIs
PARE	parallel analysis of RNA ends
PASR	promoter-associated small RNA
piRISC	piRNA-induced silencing complex
piRNA	piwi-interacting RNA
PNA	peptide nucleic acid
PRC2	Polycomb Repressive Complex 2
pre-miRNA	precursor miRNA
pri-miRNA	primary miRNA
PRMT5	protein arginine N-methyltransferase 5
pRNA	promoter-associated RNA

PROMPT	promoter upstream transcripts
P-TEFb	positive transcription elongation factor
PTEN	phosphatase and tensin homologue deleted on chromosome 10
PUA	pseudouridine and archeosine transglycosylase
PWS	Prader–Willi syndrome
RdRP	RNA-dependent RNA polymerase
Rhi	*Rhino*
RISC	RNA–induced silencing complex
RITS	RNA-induced transcriptional silencing complex
RLC	RISC loading complex
RNA Pol II	RNA polymerase II
RNAa	RNA activation
RNAi	RNA interference
RNP	ribonucleoprotein
rRNA	ribosomal RNA
scaRNP	small Cajal body-specific RNA
sDMA	symmetric dimethylarginine residue
sdRNA	sno-derived RNA
SILAC	stable isotope labelling by amino acids in cell culture
siRNA	small interfering RNA
SL	spliced leader
sno-miRNA	snoRNA (small nucleolar RNA)-derived miRNA
snoRNA	small nucleolar RNA
snRNA	small nuclear RNA
snRNP	small nuclear ribonucleoprotein
SNV	single nucleotide variant
spliRNA	splice site RNA
sRNA	small RNA (prokaryote only)
sRNA	sno-like RNA
Ste	*Stellate*
stRNA	small temporal RNA
Su(*Ste*)	*Suppressor of Stellate*
TASR	gene termini-associated small RNA
TDRD	Tud domain-containing
TE	transposable element
TERT	telomerase reverse transcriptase
TFIIH	transcription factor II H
TGA	transcriptional gene activation
TGS	transcriptional gene silencing
TI	transcriptional interference
tiRNA	transcription initiation RNA
tj	*traffic jam*
TR	telomerase RNA

TRα2	thyroid hormone receptor α2
TRBP	*trans*-activation response RNA-binding protein
TSSa-RNA	transcription start-site-associated RNAs
TUTase	terminal uridyl transferase
UTR	untranslated region
VEGF	vascular endothelial growth factor
XCI	X chromosome inactivation
Xist	X-inactive specific transcript
Zuc	*Zucchini*