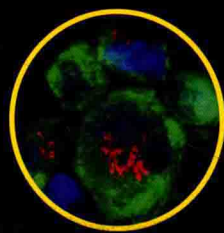


# MicroRNAs in Medicine



Edited by  
*Charles H. Lawrie*

WILEY Blackwell

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# MICRORNAs IN MEDICINE

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# MICRORNAs IN MEDICINE



# FOREWORD

The history of microRNA (miRNA) starts with an elegant genetic analysis by Ambros and Ruvkun that led to the discovery of a small non-coding RNA regulator of developmental timing. Eventually these two collaborators realised, during a late night phone conversation, that their RNA regulator binds, by Watson-Crick base pairing, to its target mRNA. Later work in the 1990s identified a second similar regulatory RNA, but I do not think that anyone would have predicted at that time that these RNA regulators would be the pioneers of a large class of RNA—the miRNAs—that affects the expression of a very large number of mRNAs.

In my laboratory, we work on plants and, in 1997, we tried to make a connection with the work of Ambros and Ruvkun. We had discovered small RNA that has a role in post-transcriptional gene silencing of transgenic and virus-infected plants. Like most biologists, we are always keen to make connections between different branches of the tree of life, and we hoped that our plant RNA would be similar to the regulatory RNA of worms. However, our silencing phenomena clearly operated at the level of RNA turnover, whereas the Ambros and Ruvkun RNAs mediated translational suppression. Our initial reluctant conclusion was that the worm RNAs and transgene silencing are separate phenomena.

Two later developments caused us, and others, to change our minds. First, there was use of sequencing to characterize the small RNA populations in several animals. This analysis revealed that the original Ambros and Ruvkun miRNAs are highly conserved from worms to man and that there are many similar RNAs that also bind to the 3'-UTR of their target RNA. Second, from genetic analyses, it was clear that the enzymes involved in the biogenesis and the effector activity of these regulatory RNAs—Dicer and Slicer—are implicated in many regulatory processes throughout development, as well as with gene silencing in transgenic and virus-infected plants. It was clear that the RNAs of Ambros and Ruvkun do not represent a specialized regulatory mechanism of early development in worms: they are part of a large family of silencing RNAs that includes the short RNAs that we had seen in plants. RNA silencing is common to both animal and plant kingdoms, and it can have many different biological effects.

The diversity of RNA silencing is indicated by the multiplicity of effector mechanisms involving RNA turnover and chromatin modification in addition to translational effects. This diversification is manifested even among miRNAs. They can act on target RNA stability, as well as on translation and they can both block and activate translation. Adding to the complexity of miRNA regulation there are “sponge” RNAs that are decoys of the natural miRNA target and miRNAs feature in regulatory systems with negative feedback loops. Some miRNAs are found in circulating blood, and they may act both outside and inside the cell. Clearly, there is the potential for great diversity and complexity in miRNA-mediated regulation.

Given this diversity and complexity, it is not surprising that there is great interest in clinical application of miRNAs. There is a good prospect that, even with the present level of understanding, miRNAs will feature in novel diagnostic tools, and that they will help



identify targets for pharmaceutical and other inventions. Key areas for research include the targeting specificity of miRNAs and their place in networks of genetic regulation. New analytic methods based on next-generation sequencing will accelerate this research, and computational approaches for data analysis and systems modeling will be important drivers of progress.

The other, as yet relatively underexplored potential of miRNA, is as a therapeutic agent. A set of artificial miRNAs could be designed that would target one or more motifs in disease genes, and these RNAs could then be delivered so that they are taken up and have an effect in cells. In plants, the use of artificial miRNAs is a routine tool, although the targeting mechanism is simpler than in animals and delivery can be via transgenes rather than through uptake of RNA molecules into cells. Delivery is the major challenge for this therapeutic application of miRNAs, but there are early indications that it can be overcome for liver and possibly superficial tissues.

The translation pathway from basic research to the clinic and patient care is always complicated. Practical requirements often thwart the good intentions or clever ideas of the researchers. However, in the case of miRNAs, as with other applications related to RNA silencing, we can be more than usually optimistic for two reasons. The first reason is because a single set of miRNA mechanisms are involved in many aspects of growth, development, and responses to external stimuli. There is, therefore, a good prospect that miRNA research findings will have general relevance to many clinical applications. The second reason follows from the finding that miRNAs interact with their target through Watson-Crick base pairing. Such interactions are more predictable and computable than processes involving, for example, proteins or lipids or small molecules. Over the next decade, I anticipate that miRNAs will feature in many different clinical applications.

PROF. SIR DAVID BAULCOMBE

*University of Cambridge*

*Corecipient (along with Victor Ambros and Gary Ruvkun)  
of the 2008 Lasker Award for work on siRNA and miRNA*

# PREFACE

Since their formal recognition just over 10 years ago, microRNAs (miRNAs) have become one of the hottest topics in biology, not least of all because during this short time they have been found to act as crucial regulators of many, if not all, physiological and pathological processes. Nowhere has this increasing interest in miRNAs been more pronounced than within the medical field. Yet surprisingly, until now, there has been no book that attempts to cover this subject in any significant depth. Therefore, the primary aim of this project was to fill this gap by putting together a comprehensive collection of reviews from some of the leading lights in the miRNA world; for the first time, combining areas of medicine as diverse as stem cells, immunology, aging, infectious disease, cancer, psychiatric disease, and hereditary disorders are united by the central theme of miRNA involvement.

A criticism often leveled at a project like this is that it covers such a fast-moving subject that the book is out of date before it even hits the shelf. Had the aim of the book been solely to provide a collection of up-to-date reviews, then this criticism would indeed have been well founded; instead, we have tried to highlight general concepts of miRNA involvement as applied to well-established areas within medicine. While the specific roles for miRNAs described within these chapters will surely change and expand in the future, it is believed that the field is now sufficiently mature that these central concepts will stand the test of time and consequently this book will provide an invaluable resource for many years to come. Moreover, although specialist scientific journals can provide the reader with the very latest developments in the miRNA arena, in general, these texts are presented within a very narrow context and are not readily accessible to non-experts. A central goal of this endeavor was to provide each chapter with sufficient background context in order to open it up to readers outside of their specialist field, and in doing so, allow the reader to draw comparisons of the role of miRNAs between differing disciplines. For example, the hematologist may recognize the central role of *miR-181* in lymphoid differentiation and malignancy, but may not yet realize its importance to other pathologies, such as breast cancer, colorectal carcinoma, or even schizophrenia. This book attempts to offer a “one-stop shop” for information related to miRNA involvement in differing areas of medicine, and it is hoped that this cross-fertilization of ideas will stimulate novel research directions as a consequence. Another important role for this book was to serve as a preparatory text to the world of miRNAs for the uninitiated. With this in mind, an introductory chapter that aims to cover the FAQs of miRNAs has been included in order to provide a general framework for appreciating the subsequent chapters.

In summary, *MicroRNAs in Medicine* aspires to provide experts and non-experts alike with an understanding of the excitement, importance, breadth, and potential of miRNAs to modern medicine, and is aimed to appeal to clinicians, researchers, students, and journalists, as well as the interested public. It is hoped that this book marks the beginning (or continuation) of the readers journey into the miRNA world, and although comprehensive, the book makes no claim to be an exhaustive authority on the subject; rather, it is intended to serve as a foundation for further investigation.

I am indebted to the many contributing authors who have given so much of their valuable time to make this project a success. The involvement of such a high caliber of contributors, including some of the true pioneers of the field, have made the editorial role a pleasure, and it has been a great honor to work alongside many of the people that inspired my original foray into the miRNA world.

Special thanks should be given to Dr. Chris Hatton (Director of Clinical Medicine at the John Radcliffe Hospital, Oxford) for his inspiration and continual support over the years. This book is dedicated to my two beautiful children, Julia and Carlos, and my wonderful and understanding wife, María.

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