Preface

Despite centuries filled with biological discoveries that shaped our fundamental view and understanding of nature and that refined our approaches to distinguish and treat human diseases, few findings made such a pivotal dual impact as the one that RNA interference (RNAi)—an evolutionarily conserved cellular means of specific and potent gene silencing—is active in mammals. Indeed, what we have witnessed over the past decade since RNAi's initial description in a nematode is nothing short of a revolution in our awareness of the amazing intricacy underlying gene regulation in higher organisms, and yet we are probably only beginning to appreciate the inherent beauty and complex diversity of the numerous relevant mechanisms. Concurrently, we are experiencing constant shifts in our perception of the molecular processes governing human diseases that offer a myriad of exciting and promising novel avenues to expand our repertoire of diagnostic and prognostic tools and to further enlarge our clinical arsenal of potent intervention strategies.

In this issue of *Progress in Molecular Biology and Translational Sciences*, a collection of six chapters provides an insight into the amazing sophistication and versatility underlying "cellular RNAi mechanisms" in healthy or diseased humans, hoping to leave the reader with an impression of the sometimes breathtaking speed at which the entire field is moving and incessantly pushing the boundaries of biology and medicine like no other before.

Starting off the issue is a chapter by Stuart Knowling and Kevin V. Morris, which reviews one of the latest and most unanticipated discoveries in our area, namely the fact that small RNAs not only regulate gene expression on the posttranscriptional level (the canonical RNAi pathway) but also exert their control at the stage of transcription. Even more, we are just now starting to realize that small RNAs not only suppress but can also activate gene expression, by means that still escape our current understanding but will certainly provide intriguing research topics for years to come. As is typical for this review series as well as for the field of RNAi, Knowling and Morris finally round up their chapter by highlighting the promises to translate these new discoveries into novel future biomedical concepts ideally allowing us to control human gene expression at yet another important level.

Following up on this introductory overview is a second complementing chapter by Victoria Green and Marc Weinberg, which delves even deeper into the astonishingly large variety of molecular mechanisms that potentially govern

these noncanonical epigenetic RNAi-related regulatory processes in human cells. While today we can hardly fully appreciate the surprisingly vast array of noncoding RNA-based networks acting at this fundamental level of gene expression, Green and Weinberg already present their insightful vision of the significant possible implications of these new findings for our basic understanding of the function of human cells as well as for the implementation of entirely novel biomedical strategies in future drug and gene therapy development.

Leaving the cellular nucleus and entering gene regulation in the cytoplasm, Roberto Fiore, Sharof Khudayberdiev, Reuben Saba, and Gerhard Schratt next review another flourishing and exciting area of current RNAi research which is posttranscriptional gene silencing by miRNAs in the central nervous system. Also here, our understanding of how RNAi shapes and controls central cellular processes such as neuronal differentiation, synaptogenesis and plasticity is in its infancy at best, as are our insights into how RNAi is involved in higher cognitive functions and the etiology of neurological diseases. All these are utmost fascinating and captivating questions that the authors will address and whose answers will continue in the following years to revolutionize and overthrow our current picture of cellular RNAi mechanisms in the human nervous system in health and disease.

Complementing these three reviews of endogenous RNAi processes in human cells, two consecutive chapters then enter the thrilling field of pathogenic viruses and assess their relationship with cellular RNAi mechanisms from the molecular biology and translational sciences standpoints. In the first, Ashley P.E. Roberts, Andrew P. Lewis, and Catherine L. Jopling will initially provide a broad and comprehensive overview over virus structure and function, in general, before moving into the incredible intricacies of virus–host interactions involving miRNAs and human RNAi machinery. One special example that will then be discussed in particular detail is the interplay of human hepatitis C virus (HCV) with a liver-specific miRNA the unconventionality of which has consistently amazed the RNAi and virus communities over the past few years and will hopefully excite the readers of this chapter as well.

Taking over from this overview over how viruses exploit and modulate the human RNAi machinery, Julia Eekels and Ben Berkhout next highlight how one can turn this cellular mechanism against the intruder and develop clinical RNAi-based strategies that not only aim to battle and eradicate the AIDS virus HIV-1 but concurrently also rob it of any chance to ever escape from therapy by natural mutation. Therefore, the authors first thoroughly review the plethora of strategies and tools that have recently been discussed, developed, and validated to achieve these goals, before they describe combinatorial RNAi targeting of multiple essential viral and cellular genes as the latest and most promising therapeutic approach to tackle and forever eliminate the HIV pathogen from infected patients.

Finishing off this issue is a chapter from our own group that once again documents the remarkably tight affiliation of basic and applied RNAi research by reviewing our emerging picture of cellular RNAi mechanisms potentially dysregulated in human cancers and other devastating diseases, and by concomitantly discussing the novel therapeutic concepts and translational avenues that fortuitously continue to surface and materialize with each new report. Extending the preceding chapters, special focus will also be put on viruses not only because they represent beautiful authentic examples for molecular means to perturb, hijack, and reprogram cellular processes but because viruses are also being engineered as RNAi-expressing tools to treat human diseases that can occasionally turn into our worst enemy and unintentionally overthrow the human RNAi machinery. The related recent observations and vital lessons learned will be discussed, before Stefan Mockenhaupt, Nina Schürmann, and Dirk Grimm round up the chapter and issue with an outlook into what may be the next important steps to even further advance our understanding and utilization of cellular RNAi mechanisms and to ensure that the whole field will positively continue to prosper and thrive for many more years to come.

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