

Preface

Since their discovery in 1993 by the Ambros lab there has been a phenomenal increase in research into microRNAs. There are now thousands of peer-reviewed publications describing all aspects of their biogenesis and function, and indeed the resulting diseases when they dysfunction. Yet considerable gaps remain in our understanding of how these tiny regulators of gene expression are borne, live and die. What is overwhelmingly obvious is that they play a critical role in many if not all important cellular processes. Their regulatory niche within the cell lies at the interface between the mRNA transcript and its translation into a functional protein providing the cell or organism with yet another mechanism to fine-tune gene expression. Like transcription factors, individual miRNAs also possess the ability to interact with and influence the expression of tens to hundreds of target genes providing a mechanism to rapidly influence entire cellular pathways or processes. Importantly, this intervention can be deployed quickly (and at a cheaper metabolic cost) due to the absence of a translational step—they are functional without the need to build a protein.

It is these two properties in particular that make them of potential interest to those involved in the production of recombinant proteins by mammalian cells. The desire to improve efficiencies in the biosynthesis of Biopharmaceutical products, including monoclonal antibodies, blood factors, fusion proteins and other exotic polypeptides continues to motivate research into improving culture medium, bioreactor design, vector design and process control. In the last decade there have been a number of research groups in both industry and academia that have focused on what many believe to be the source of the next major improvements in process efficiencies—genetically engineering the producer (usually CHO) cell. The goal is typically to bestow improved phenotypic characteristics, such as rapid proliferation to high density, prolonged viability in the challenging environmental conditions in late stage culture, reduced reliance on particular substrates or reduced sensitivity to waste metabolites, and high specific secretion rates of an active, intact protein product with the most desirable post-translational modifications. The search for key molecules responsible for these cellular properties has resulted in numerous publications describing genes and proteins whose expression changes in CHO cells under different culture conditions or in cells with different phenotypic characteristics. There have been several

examples of exogenous dysregulation of particular genes leading to improvement in these traits though it is less clear how many of these have made their way into actual industrial processes. One of the challenges associated with this approach is the fact that complex traits, such as proliferation, are necessarily controlled by multiple genetic interactions meaning that frequently, engineering the expression of a single gene may not be sufficient to influence the phenotype. On the other hand, exogenous overexpression of multiple protein-coding genes places a metabolic burden on cells whose main role is to generate large quantities of the product, hence causing intracellular competition for biosynthetic resources. miRNAs, therefore, could provide an alternative means to influence the expression of multiple genes simultaneously in order to modify the pathways and processes underpinning particular phenotypes without competing with product protein synthesis.

This volume aims to provide those interested in the potential utility of miRNAs in the bioprocessing field with a succinct overview of what is known about these fascinating molecules—their biogenesis, mode of action, known functions in the cell, how they can be detected, measured and modified—with a particular focus on relevance to recombinant protein production in CHO cells.

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