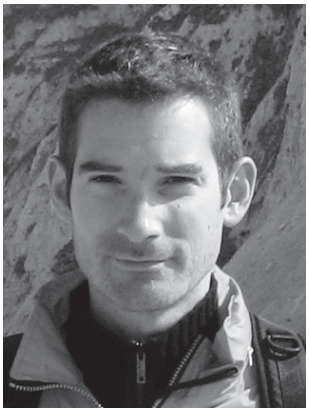

2000 - 2006	Ph.D. – BZH
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2007 - 2008	Lab head – Novartis Pharma AG, Basel, Switzerland
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Julien Béthune

Posttranscriptional regulation of mRNA expression and localization

Goal

We are interested in the mechanisms of post-transcriptional gene silencing, notably by miRNAs, as well as in the interplay between membrane trafficking and mRNA regulation and localization.

Background

While protein-coding transcripts represent a tiny fraction of the transcriptome of human cells, many non-coding RNAs play a very important role in regulating gene expression. Among them, miRNAs have emerged as key regulators of most cellular functions by post-transcriptionally repressing at least 50% of expressed mRNAs. Not surprisingly, misregulation of miRNAs leads to diseases including cancer. While most mRNA targets of miRNAs end up being degraded, others are kept stable in a silent state until an appropriate stimulus triggers reversal of miRNA-mediated silencing. The latter implies that the action of miRNAs may be used as a temporary process, and suggests that miRNAs may play a role in mRNA transport and localized translation. Membrane-enclosed transport vesicles mediate protein and lipid transport within the secretory pathway, from the ER to the plasma membrane. A surprising and largely unexplored link between mRNA and vesicular transport has been suggested by several studies. Indeed, protein complexes involved in vesicle formation and capture of protein cargo were suggested to bind to mRNAs and regulate their translation. In addition, some mRNAs, and components of the miRNA machinery, were found to associate with purified vesicles. An emerging picture is that vesicular carriers may also transport and help localizing silenced-mRNAs, and thus add another layer of regulation to gene expression.

Research Highlights

While it is has been known that miRNA-mediated silencing results from the combination of translational repression and mRNA decay, we and others have recently shown that there is a temporal order of silencing. Indeed, targets of miRNAs first undergo a translational repression step that is followed by a stimulated deadenylation step, which then leads to mRNA decay. Such a mechanism involving successive and potentially reversible steps is compatible with a role of miRNA in mRNA transport or storage. However, it is still not clear how certain miRNA targets escape degradation while staying in a silent state. To address this, we are investigating the dynamics of miRNA-mediated repression, both temporally and spatially,

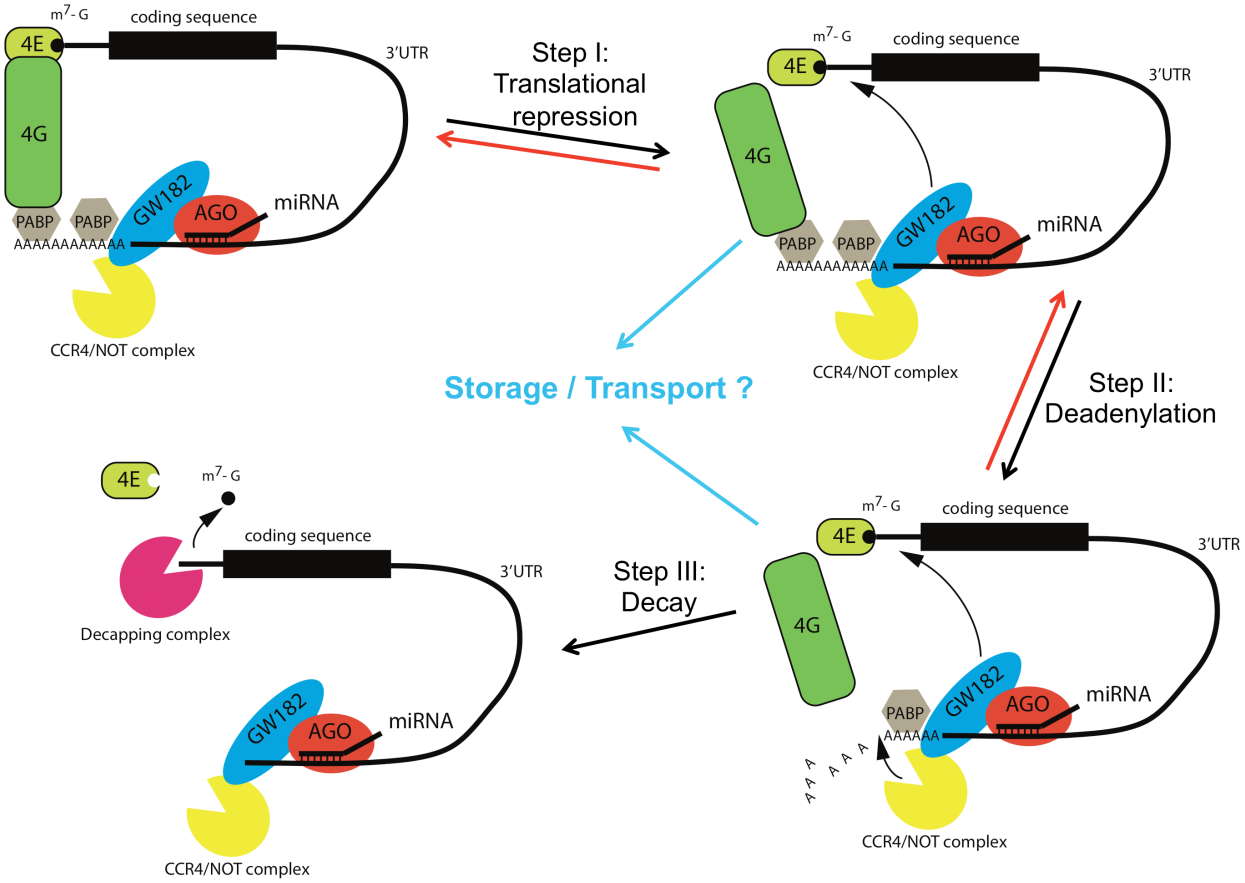

Fig. 1: The temporal order of miRNA-mediated silencing. *The mechanism of action of miRNAs, consisting of three successive major steps, is compatible with a role of miRNAs in mRNA transport or storage.*

and we aim at identifying trans acting factors that modulate silencing on specific mRNAs.

Proper localization of mRNAs is critical for establishing and maintaining cell polarity. As several reports and observations suggest that transport vesicles may help localizing certain mRNAs, we are characterizing the populations of RNAs that are found on different types of intracellular transport vesicles. This is the first step to systematically define an atlas of vesicle-associated RNAs, and will serve as the basis to characterize how specific RNAs are recruited to specific transport vesicles as well as the significance of such an interaction.

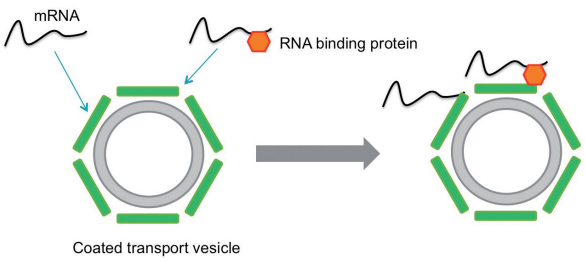

Fig. 2: A working model for vesicle-mediated mRNA transport. *Certain mRNAs may directly, or through a bridging interaction mediated by an RNA binding protein, bind to coat protein complexes found on intracellular transport vesicles. Hence, these mRNAs may hitchhike on the transport vesicles to reach their final destination.*

Selected Publications

Béthune, J., Artus-Revel, C.G., and Filipowicz, W. (2012). Kinetic analysis reveals successive steps leading to miRNA-mediated silencing in mammalian cells. EMBO Rep 13, 716-723.

Beck, R., Sun, Z., Adolf, F., Rutz, C., Bassler, J., Wild, K., Sinning, I., Hurt, E., Brugger, B., Béthune, J., and Wieland, F. (2008). Membrane curvature induced by Arf1-GTP is essential for vesicle formation. Proc Natl Acad Sci U S A 105, 11731-11736.

Sun, Z., Anderl, F., Frohlich, K., Zhao, L., Hanke, S., Brugger, B., Wieland, F., and Béthune, J. (2007). Multiple and stepwise interactions between coatomer and ADP-ribosylation factor-1 (Arf1)-GTP. Traffic 8, 582-593.

Béthune, J., Kol, M., Hoffmann, J., Reckmann, I., Brugger, B., and Wieland, F. (2006). Coatomer, the coat protein of COPI transport vesicles, discriminates endoplasmic reticulum residents from p24 proteins. Mol Cell Biol 26, 8011-8021.

Béthune, J., Wieland, F., and Moelleken, J. (2006). COPI-mediated transport. J Membr Biol 211, 65-79.

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