Introduction
Our research interest is focused on regulatory non coding (nc)RNAs. In high eukaryotes, regulatory ncRNAs have been shown to regulate gene expression, chromatin domains and genome stability. There are a growing number of evidence suggesting that they play central roles on cancer formation and cellular differentiation. Regulatory ncRNA can be classified in two categories depending on their size. Short interfering (si)RNAs, also known to be part of the RNA interference pathway, have been extensively studied and control gene expression and chromosome segregation. Large ncRNAs participate also in gene silencing and are key players in cell differentiation and development but, in contrast to siRNAs, their mode(s) of action remain poorly characterized. Our lab was one of the first to describe large ncRNA-mediated epigenetic regulation in the budding yeast that control transposon proliferation and gene expression, providing powerful genetic and large scale tools to uncover their regulatory mechanisms in this classic model organism.

Methods
Indeed, focusing our experimental strategies on S. cerevisiae allows multiple complementary technical approaches. On single genes, we perform routinely in vivo analyses at the level of chromatin or RNA, followed by phenotype studies of a combination of mutants involved in RNA decay or chromatin regulation. At the level of the genome, we perform RNA-SEQ and ChIP-SEQ experiments to draw global transcriptome and epigenetic landscape.

Results
Since the beginning of our research project in 2005, we obtained 2 main results showing the existence of a trans-acting ncRNA controlling the Ty1 transposon in yeast (Figure 1).
In addition, we provided evidence that cryptic transcription mediates the deposition of histone marks controlling inducible genes (Figure 2).

Figure 2.
We addressed the existence of an RNA-dependent gene regulation mechanism in S. cerevisiae by analogy with transposon regulation in higher eukaryotes. Indeed, we hypothesized that regulatory RNAs might provide the silencing signal for Ty1 expression. Following our pioneer work on ncRNA mediating gene silencing in S. cerevisiae, our recent results show that cryptic transcripts initiate the deposition of H3 lysine 4 di and trimethylation (H3K4me2/3) in promoter proximal regions on GAL10-GAL1 and SUC2 genes.

Conclusion and future directions

Our works show that yeast is indeed an excellent organism to study regulatory lncRNAs that are involved in chromatin regulation. So far, original high-throughput sequencing and bioinformatics approaches developed in the lab allowed us to reveal the existence of novel classes of lncRNAs (XUTs, antisense ncRNAs, others) associated with housekeeping genes, subtelomeric regions and telomeres, but also adaptation and stress response genes. Preliminary results point to a conservation of these non-coding transcripts not only within the yeast kingdom but also within human cells supporting chromosomal destabilization, suggesting their universal role as key regulators of normal and pathological development of a cell. Our main current research activities in the lab are: I. Comprehensive yeast non-coding transcriptome and its role in gene expression regulation. We aim to pursue our study of non-coding transcriptome in different yeast species and further characterize large ncRNAs and their protein partners implicated in gene expression regulation through histone modifications at both euchromatin and heterochromatin domains. This ongoing work will set up a fundamental basis for future studies in humans. II. Catalog of antisense human lncRNAs. In parallel, we are performing an exhaustive analysis of human non-coding transcriptome with a particular interest to yet poorly characterized antisense ncRNAs. A plethora of large ncRNAs has been already annotated with increasing number of examples demonstrating their fundamental genomic functions, cancer, hereditary and acquired diseases. However, given the extremely dynamic and specific character of lncRNAs’ expression, not all of the dark matter of the non-coding genome is yet elucidated. To prove biological and clinical relevance of non-coding transcriptome we aim to draw an exhaustive map of ncRNAs in primary, immortalized and cancer cell lines. III. Large ncRNAs in aging and disease. Some of ncRNAs have been proved to regulate genes involved in cellular growth and proliferation thus navigating the balance between cellular self-renewal, differentiation, senescence and aging. In our lab, we have shown a subfamily of large ncRNAs which expression is naturally activated from telomeric and subtelomeric regions when cells enter senescence in yeast. Cellular senescence marks the onset of cellular degradation that is often seen as a cellular parallel to aging of organisms. Cellular
senescence can also be induced prematurely by certain oncogenes, DNA damage, oxydative stress, etc...; and is considered as a barrier to the cancer spread in pre-malignant tumors. To apprehend a functional link between large ncRNAs, aging and cancer transformations, we currently explore human non-coding transcriptome in the context of chromosomai instability and cancer progression (telomerase reactivated and ALT cell lines, solid tumors). Studies in both, yeast and human cells, will allow us to address the fundamental question of how large ncRNAs are implicated in telomere homeostasis and genome fluidity.

Publications clés

Année de publication : 2019

(2019 Nov 15)
Reference-free transcriptome exploration reveals novel RNAs for prostate cancer diagnosis.
*Life Sci Alliance*: DOI : 10.26508/lsa.201900449

Ugo Szachnowski, Sara Andus, Dominika Foretek, Antonin Morillon, Maxime Wery (2019 Aug 30)
Endogenous RNAi pathway evolutionarily shapes the destiny of the antisense IncRNAs transcriptome.
*Life science alliance*: DOI : e201900407

(2019 May 1)
Long non-coding RNAs: towards urinary diagnosis for prostate cancer
*Bulletin de l'Académie Nationale de Médecine*: DOI : https://doi.org/10.1016/j.banm.2018.03.001

Aria Ronsmans, Maxime Wery, Ugo Szachnowski, Camille Gautier, Marc Descrimes, Evelyne Dubois, Antonin Morillon, Isabelle Georis (2019 Mar 1)
Transcription-dependent spreading of the Dal80 yeast GATA factor across the body of highly expressed genes.
*PLoS genetics*: e1007999 : DOI : 10.1371/journal.pgen.1007999

Bingning Xie, Emmanuelle Becker, Igor Stuparevic, Maxime Wery, Ugo Szachnowski, Antonin Morillon, Michael Primig (2019 Feb 15)
The anti-cancer drug 5-fluorouracil affects cell cycle regulators and potential regulatory long non-coding RNAs in yeast.

Blind exploration of the unreferenced transcriptome reveals novel RNAs for prostate cancer diagnosis

*bioRxiv*: DOI: [10.1101/644104](https://doi.org/10.1101/644104)