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L'ARN, clé de la coordination de l'expression génique

RNA: a key to coordination of gene expression

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Rapport de la Conférence

Conference report

RESUME DU RAPPORT

La conférence Jacques Monod « l'ARN : clé de la coordination de l'expression génique » s'est tenue à Roscoff (Bretagne) du 7 au 11 novembre 2012. Le principal objectif de ce colloque a été de couvrir les développements les plus récents et les résultats les plus excitants dans le domaine des ARNs non codants, qui sont actuellement reconnus comme des acteurs cruciaux du contrôle de l'expression génique. Le travail présenté et discuté par les conférenciers invités a porté à la fois sur les rôles biologiques et sur les mécanismes d'action des processus de contrôle gouvernés par l'ARN. Cette conférence a mis en lumière les nouvelles découvertes qui ont émergé ces dernières années sur les réseaux de régulation par l'ARN chez les eucaryotes (animaux et plantes) ainsi que chez les procaryotes.

Les thèmes sélectionnés sont de grand intérêt pour la communauté scientifique internationale, comme en témoigne la diversité d'origine des participants, un total de 73 issus de 14 pays différents (Allemagne, Argentine, Belgique, Canada, Danemark, Finlande, France, Israël, Italie, Pays-Bas, Royaume Uni, Russie, Suisse, USA). Cette conférence a réuni les spécialistes les plus renommés dans les champs couverts. L'échelle relativement petite de ce colloque, l'atmosphère conviviale et paisible du lieu d'accueil, les excellentes installations du CNRS à Roscoff et la bonne organisation logistique, tous ces éléments ont permis de stimuler des discussions scientifiques approfondies et l'initiation de futures collaborations.

Un aspect original de cette conférence a été de réunir des scientifiques de culture et de formation scientifiques très différentes. Notamment les spécialistes des systèmes biologiques eucaryotes et procaryotes ont pu se côtoyer. En organisant cette conférence, nous avons favorisé la diversité et les approches interdisciplinaires, ce qui a constitué sans nul doute une valeur ajoutée à ce colloque. Nous avons pris soin d'équilibrer le mieux possible les contributions des systèmes procaryotes avec les systèmes eucaryotes animaux et plantes, qui ont été réparties en 11 sessions : - ARNnc procaryotes - Architecture de l'ARN - ARNnc et transcription - ARNnc longs - Epissage et polyadénylation de l'ARNm - Contrôle de la traduction – piARNs – siARNs – miARNs - Coordination de l'expression génique.

Un total de 26 conférenciers invités ont fait des présentations de 30 minutes. Parmi eux, 11 venaient de laboratoires français, 10 de laboratoires européens et 5 du « reste du monde » (USA, Argentine, Israël). De plus, 23 présentations orales de 15 minutes ont été sélectionnées à partir des résumés soumis, en se basant sur l'originalité et la nouveauté des résultats. Au total 18 présentations on été faites par des femmes. Une session d'affiches de 2h45 pour 26 affiches a complété le programme scientifique. Du temps a été prévu pour les questions et discussions dans les sessions de présentation orales et dans la session d'affiche, ainsi que durant les temps de pauses, déjeuners et dîners. Les présentations orales et les affiches ont été d'excellente qualité et, malgré le programme chargé, les réponses reçues nous ont indiqué l'enthousiasme des participants. Ceci nous a convaincus de l'importance de renouveler la conférence d'ici deux ou trois ans.

CONFERENCE REPORT

Summary

The CNRS-Jacques Monod conference “RNA : a key to coordination of gene expression” was held in Roscoff, in Brittany, Novembre 7-11, 2012. The main objective of this meeting was aimed at covering the most recent developments and exciting results in the field of non-coding RNAs, as such RNAs now are known to be ubiquitously present elements in the control of gene expression. The work presented and discussed by the selected speakers addressed both biological roles and mechanisms of action on RNA-mediated control processes. This conference highlighted new features that have emerged over the last few years on the RNA-based regulatory networks in eukaryotes – animals and plants – and in prokaryotes.

The selected topics were of high interest to the scientific community, indicated by turnout of participants, a total of 73 from fourteen different countries (Argentina, Belgium, Canada, Denmark, Finland, France, Germany, Israël, Italy, Russia, Switzerland, The Netherlands, USA, United Kingdom). This conference featured many of the most highly recognized specialists in the fields covered. The relatively small scale of the meeting, the intimate and peaceful atmosphere, and the excellent facilities provided by the CNRS in Roscoff, stimulated many in-depth discussions and most likely initiated future collaborations. Much of this must be credited to Mrs Dominique Lidoreau, Nathalie Babic and the personnel of the Roscoff center who took care of the practical organization (administration, lodging, poster room, computer facilities). We also want to emphasize the very good quality of housing and the excellent food. On one of the afternoons, two parallel excursions were organized, left to the choice of the participants : either to the Onion Johnny museum, or to the St-Pol-de-Leon cathedral. 9 participants chose to visit the museum, whereas 40 participants chose to visit the cathedral.

A particularly valuable aspect of the meeting was that it brought together scientists from widely different cultures and scientific backgrounds, and that specialists in both eukaryotic and prokaryotic biological systems were communicating vividly. In planning this conference, we favored diversity and interdisciplinary approaches, and such a broad coverage was certainly appreciated and considered to be an 'added value' to this conference. Along these lines, we took care to balance contributions dealing with eukaryotic and prokaryotic systems and dispatched them into 11 sessions :

- Prokaryotic ncRNAs
- RNA architecture
- NcRNAs and transcription
- Long ncRNAs
- mRNA splicing and polyadenylation
- Translational control
- piRNAs
- siRNAs

- miRNAs
- Coordination of gene expression

A total of 26 speakers were invited to give 30 min talks. Of these, 11 came from French laboratories, 10 from other European laboratories and 5 from the "rest of the world" (USA, Argentina, Israel). In addition, 23 applicants were selected to give oral presentation (15 min talks), based on originality and novelty presented in their abstracts. In total 18 talks were given by women. One poster sessions of 2h45 (for 26 posters) completed the scientific program. There was time and opportunity for questions and discussions in both platform talks and poster sessions, as well as during breaks and over lunch and dinner. The oral and poster presentations were of outstanding quality and, although the schedule was rather tight, the responses received by us indicated the enthusiasm of the participants for having attended this meeting. This convinces us that it would be important to cover this topic, with a timely focus, again in two or three years.

Scientific report.

Although RNA was initially considered to be a passive intermediate in the flow of information from DNA to protein, the regulatory capacity of RNA is now well established. As regards the role of non-coding RNA (ncRNA), a key event occured in 1998 with the discovery of RNA interference (RNAi) showing that small ncRNAs have a high regulatory capacity. The Nobel Prize of Medicine has been awarded in 2006 to Fire and Mello for this discovery, definitively showing the importance of ncRNA in the control of gene expression. This, and previous years' recognition of the roles of RNA in regulation of gene expression in pro- and eukaryotes in disease, has resulted in a soaring interest and fascinating and groundbreaking discoveries in this already strong field.

Regulatory elements present in RNA are often, at least in eukaryotes, binding sites for key proteins that mediate activation or inhibition of translation, or affect decay. Much of our thinking about how gene expression is regulated has moved from cataloguing of RNAs to, on the one hand, in-depth mechanistic studies, and, on the other, global "system biology" studies. Messenger-ribonucleoprotein (mRNP) often organize and regulate subpopulations of functionally related mRNAs.

An emerging concept is the coordination of the different levels of regulation of gene expression in eukaryotes. Transcription, as well as post-transcriptional processes such as mRNA splicing, polyadenylation, degradation and translation, require a wide range of multi-component cellular machines in order to finely control protein production. For a long time, these steps have been considered to be a simple, linear assembly line. However, it has become apparent that gene expression, including steps such as transcription, capping, splicing, polyadenylation, RNA export and degradation, is coordinated in a complex and extensively coupled network.

This conference has emphasized the roles of regulatory non-coding RNAs, as well as regulatory cis-elements of mRNAs in the regulation of gene expression, across organisms. As can be seen from the list of invited and selected speakers, we have taken much effort in selecting some of the newest emerging topics.

PRINCIPAL THEMES

We have divided the conference into eleven thematic sessions. Each session included from three to six talks. The selected talks were dispatched into these sessions. A detailed scheme of session contents is presented below.

Session 1 - Prokaryotic ncRNAs (chairperson P. COSSART)
B. FELDEN reported the case of RNA SprG1, produced from pathogenicity island of many *S. aureus* clinical isolates, that expresses two peptides from two functional translation initiation codons whose expression induces *S. aureus* death. The level of SprG1 is regulated in bacteria by an antisense RNA, SprF1. J. VAN DER OOST focused to RNA guided RNA interference involving the key enzyme (prokaryotic) AGO, an endonuclease that uses small RNA guide molecules, CRISPR, to target RNA transcripts. He showed that the CRISPR defense mechanism also plays a role in host defense against plasmids and viruses, by a mechanism of DNA interference. B. WIEDENHEFT showed that CRISPR RNA guided surveillance is required for adaptive immunity in bacteria. P. ROMBY presented data on the coordinated regulation of transcriptional repressors of toxins, and virulence factors by RNAIII and RNAse III in *S. aureus*. She also showed the existence of novel non-coding RNAs in *S. aureus* that play a role in the quorum-sensing system of this pathogen. The complex interplay between small RNAs and the transcriptional regulatory networks in bacteria was addressed by M. GUILLIER who identified sRNAs as actors of translational repression of bacterial two-components systems, in particular PhoQ/PhoP involved in magnesium homeostasis and pathogenicity of several bacterial species.

Session 2 - RNA architecture (chairperson E. WESTHOF)
RNA architecture can be viewed as the hierarchical assembly of double-stranded helices defined by Watson-Crick base pairs and RNA modules maintained by non Watson-Crick base pairs. E. WESTHOF presented a computational pipeline designed to identify 3D structural modules in single and multiple RNA sequences. P. COSSART explored the landscape of RNA worlds in bacteria *L. monocytogenes* and revealed a new concept in bacterial regulation : long antisense transcripts exhibit a dual role in inhibiting gene expression while serving as 5'UTR for the adjacent divergent gene, which results in gene activation. This new process was named the « excludon ». C. TISNE presented the bioengineering of small molecules able to modulate RNA structure and function. A ligand-based binding competition NMR screening was performed using fluorinated ligands to investigate RNA-ligands interactions.

Session 3 -NcRNAs and transcription (chairperson Y. LIU)
J. CAVAILLE focused onto the regulation of miRNA expression by genomic imprinting, in particular to the Dlk1-Dio3 domain containing the miR-379/miR-410 gene cluster whose expression is restricted to the maternal chromosome. He showed that the genetic ablation of the locus in mouse does not affect viability but affects perinatal lethality. M. GIRARDOT also addressed genomic imprinting, and reported data on the MADAM-ncRNAs located in the Dlk1-Dio3 domain. He showed that the allelic expression of these ncRNAs prevents DNA methylation of the maternal chromosome whereas MADAM ncRNAs expression is linked to early replication of the Dlk1-Dio3 domain. Y LIU discovered in *N. crassa* a new class of small RNAs, qiRNAs, that are induced by DNA damage under the control of RdRP QDE-1 and helicase QDE-2. A. MORILLON presented pervasive transcription in yeast. He reported that large regions of the genome are transcribed, producing

a large variety of ncRNAs that exhibit an important regulatory potential through epigenetic modifications, in particular by interplaying with histone methyl transferase and deacetylase.

Session 4 - Long ncRNAs (chairperson A. MORILLON)

In some cases, it appears that simply the act of ncRNA transcription is sufficient to positively or negatively affect the expression of nearby genes. However, in many cases, the long ncRNAs themselves serve key regulatory roles that were assumed previously to be reserved for proteins. T. CSORBA presented data on the role of long antisense ncRNAs in plant flowering (*Arabidopsis*) whose central regulator, FLC, encodes a transcriptional repressor. Acceleration of flowering results from FLC repression by prolonged cold. Such repression involves the antisense RNA COOLAIR, whose alternative 3' processing and splicing triggers transcriptional down-regulation by forming a RNA-DNA hybrid in the promoter region. B. SAVILLE reported data on natural long antisense transcripts (NAT) in the pathogenic plant fungus *Ustilago maydis*, suggesting that control of NAT expression is required for full virulence of *U. maydis*. The session was closed by S. PLAZA who revealed the role of short open reading frames (ORFs) coded by ncRNAs. An evolutionary conserved sORF, was recently identified in Drosophila polycistronic transcript *pri* that encodes four similar small peptides controlling a developmental process through the post-translational processing of the transcriptional regulator Shavenbaby.

Session 5 - mRNA splicing and polyadenylation (chairperson C. DE MOOR)

It has been established for more than a decade that post-transcriptional regulations play a fundamental role in the control of gene expression. C. GIRARD addressed the global extent of co-transcriptional versus post-transcriptional splicing. Data indicated that 85% of the splicing events occur co-transcriptionally. However immunofluorescence experiments showed that active spliceosomes containing polyadenylated mRNAs accumulate in speckles and that splicing completion triggers the release of newly spliced mRNA from speckles and export to cytoplasm. S. MILLEVOI demonstrated pre-mRNA splicing and polyadenylation is regulated by G-quadruplexes, non-canonical structures present in G-rich mRNAs. Furthermore G-quadruplexes are also involved in translational regulation, as such structures are present in about 3000 human mRNA 5'UTRs. C. DE MOOR showed the role of poly(A) tail metabolism in the regulation of transcription : the deadenylation delay changes the kinetics of transcription. In addition she reported that not all mRNAs start out with the same size poly(A)tail, and this influences the deadenylation delay. A. BÖTTGER described a new oxygen-dependent splice regulator, Jmjd6, involved in the transcriptional regulation of the cellular hypoxic response at the level of pre-mRNA processing. Finally, J. RODOR focused to the role of RBM-10, a protein whose mutation results in a syndromic form of cleft palate, the TARP syndrome. She showed, by an iCLIP approach, a direct role of RBM10 in splicing regulation.

Session 6 – Translational control (chairperson A. TREMBLEAU)

C. ECKMANN addressed poly(A) tail-mediated translational control during *C. elegans* development and pointed to the role of global RNA regulatory networks in the coordination of germ cell development. He identified an intricate RNA regulatory web built on four RNA-associated factors, the CEBPs interfacing with two cytoplasmic poly(A) polymerases, GLD-2 and GLD-4. This control network operates predominantly in male rather than in female germ cells. A.E. WILLIS focused to translational regulations in mammals following genotoxic stress, by an approach of cDNA microarrays on polysome profiling. She identified an increase in translational efficiency of DNA repair enzymes ERCC1 and ERCC5 mRNAs, and found a polymorphism in an uORF in the 5'UTR of CCR5 mRNA that determines its sensitivity to

cisplatin sensitivity. D. WEIL showed data on translational repression by the P-body protein Rck/p54 which is recruited on mRNA 3'UTRs by sequence specific translational repressors resulting in mRNA masking, unwinding and recruitment to P-bodies. N. STANDART reported a study of the role of human 4E-T(ransporter), a nucleocytoplasmic shuttling eIF4E-binding protein enriched in P-bodies, demonstrating that 4E-T represses global translation by sequestering eIF4E and enhances silencing of micro-RNA-target mRNAs. B. COSSON presented the characterization of a new 4E-interacting partner, 4E-IP1, using an original combinatorial approach. 4E-IP1, called Angel 1, is a member of the CCR4 family and displays a tissue-specific expression pattern, but its role on translational regulation remains to be elucidated.

Session 7 - RNA Metabolism, turnover and transport (chairperson A. EPHRUSSI)

The path of RNA from transcription through processing, association with partner proteins, transport, to its designated function and ultimately decay, is an exquisitely controlled process. A. EPHRUSSI presented the mechanism of assembly of endogenous *oskar* mRNA particles for motor-dependent transport in the drosophila oocyte and showed the crucial role of splicing and Exon Junction Complex (EJC) in the transport of *oskar* mRNPs in Drosophila. Splicing of intron 1 is required for assembly of a novel posterior targeting element, the Oskar Localization Signal (OLS). D. NIESSING focused to the ASH-1 complex involved in active transport of ASH1 mRNAs during asymmetric cell division of yeast. He reconstituted the ASH1 mRNA-transport complex and identified the protein Shep-2, interacting with RNA as a tetramer, as sufficient to promote motor oligomerization and activation of motility. H. LANGE studied the MTR-4 helicases in *Arabidopsis thaliana*. Yeast and human have a single MTR4 helicase required for all nuclear functions of the exosome. In contrast, *A. thaliana* has two MTR4-like helicases, AtMTR4 and HEN2. Both function as exosome co-factors, but each in a different compartment and targeting a distinct subset of RNA substrates. HEN-2 is a plant-specific protein. H. LE HIR reported a CLIP-seq of the DEAD box RNA helicase eIF4AIII, a component of the EJC, resulting in an RNA binding signature of eIF4AIII. Peaks mark most exons, indicating that a large proportion of spliced junctions are associated to eIF4III, mostly 24 nt upstream of exon junctions.

Session 8 – piRNAs (chairperson M. SIMONELIG)

Germline and the early embryo appear to be stages where small ncRNAs are playing essential roles in cell type specification and maintenance. This topic has been first addressed by M. SIMONELIG, who recently showed that component of the piRNA pathway are required for deadenylation of Drosophila *nanos* mRNA, including piRNAs complementary to the *nanos* mRNA 3'UTR. As these piRNAs are produced by transposable elements, these data reveal a direct developmental function of transposable elements in the regulation of gene expression. The generality of gene regulation by the piRNA pathway was addressed by CLIP experiments which allowed identification of several hundred of maternal mRNAs directly interacting with Aubergine (Aub), the Argonaute protein specific of the piRNA pathway. P. RANGAN focused on transcriptional repression in Drosophila primordial germ cells PGCs). He found repressive marks (H3K9me3, H4K20me3) consistent with heterochromatin in the nuclei of differentiating germ line stem cells (GSC) progeny, correlated with the location of piRNA precursors production, major components of the transposable elements defense mechanism in the germ line. He proposed that heterochromatin protects the germline by activating the piRNA pathway. Small RNA silencing pathways were also addressed by R. KETTING who studied the piRNA pathway in zebrafish germ cells. He presented the role of zebrafish piwi proteins, Ziwi and Zili, in the ping pong circle leading to accumulation of piRNAs responsible for retrotransposon silencing. M. AMEYAR-ZAZOUA described a role of Argonaute proteins

in splicing, in the CD44 gene model of alternative splicing. She showed that AGO proteins facilitate the spliceosome recruitment and modulate the elongation rate of RNA polymerase II, demonstrating for the first time that endogenous RNAi pathway is involved in alternative splicing decisions.

Session 9 – siRNAs (chairperson A. Nielsen)

A. MOLNAR presented data on RNA silencing in flowering plants (*Arabidopsis*). He showed it involves a signal that can spread from the site of initiation to neighbouring cells or systematically over long distance. Three ncRNAs of 21, 22 and 24 nt were identified in this mobile RNA silencing signal, responsible either for post-transcriptional silencing (PTGS) that involves mRNA destabilization or translational inhibition or for transcriptional silencing (TGS) by RNA-dependent gene methylation. E. MISKA worked on antiviral RNA interference in *C. elegans*. He identified a 157 nt-long sequence in *C. elegans* genome, encoding a RIG-I-like helicase, DRH-1, essential for antiviral response. M. POOGGIN focused on the role of primary and seconday siRNAs in geminivirus-induced gene-silencing. Massive production of siRNAs was observed in geminivirus-infected *Arabidopsis*, but it does not require RNA-dependent-RNA polymerase (RDR) usually involved in generation of secondary siRNAs. These are primary viral siRNAs generated by RNA PolII-mediated bidirectional readthrough on the circular viral DNA. Thus the virus have developed an RDR-independent system to amplify large amounts of siRNAs. K. FÖSTERMANN described the generation of a small RNA response at DNA ends of transfected plasmids in Drosophila. Double-stranded siRNA precursors form with an antisense transcript that initiates at the DNA break. This response is specific to double strand breaks and siRNAs are generated independently of the exact end structure (blunt, 3'- or 5'-overhang). Such a process has also a role in quality control by clearing potentially truncated messages from genes in the vicinity of the break. F. DAUTRY addressed the issue of the microRNA limited efficiency due to RISC complex saturation by competing substrates. He showed that the efficiency of silencing of an exogenous mRNA target is robust and independent of the mRNA/miRNA ratio, in contrast to the limites efficiency of miRNAs exhibiting numerous cellular endogenous targets. Single cell analysis indicated that miRNA silencing can be as efficient as siRNA silencing but does not take place in all the cells. He also showed that RNA interferenc on perfect or inperfect targets is more efficient on the most abundant target and almost inactive on the less abundant ones.

Session 10 – miRNAs (chairperson B. MARI)

H. GROSSHANS focused on recent discoveries about the biogenesis of miRNAs in *C. elegans*. His data revealed that individual miRNA targets differ in their response to individual miRNA family members as well as their spatial patterns of repression. He also showed that active miRNA degradation is used as a regulatory mechanism to control miRNA levels during *C. elegans* development. Plants miRNAs and siRNAs pathways were dealt by H. VAUCHERET. In particular, he studied the crosstalk between small RNA pathways and RNA quality control (RQC) that targets endogenous aberrant RNA for degradation. He identified the demethylase JMJ14 as a key in posttranscriptional gene silencing mediated by sense transgenes (S-PTGS). D. GILOT studied the role of the tyrosine-related protein 1 (TYRP1) in melanoma. He showed that the silencing of TYRP1 mRNA (by RNAi) leads to the release of several miRNAs, which are thus able to target accessible binding sites on other mRNAs whose down-regulation may explain the loss of aggressiveness of melanoma in response to TYRP1 knock-down. Thus TYRP1 indirectly controls melanoma aggressiveness via miRNA sesquestration. This illustrates the concept of miRNA sponge. R. ATANASSOVA presented data on miR393, an miRNA involved in water and biotic stress

response. She showed that miR393 overexpression induces resistance to water stress in *Arabidopsis thaliana*, and sensitivity to the necrotrophic fungus *B. cinerea*. At the mechanistic level, Mir393 overexpression impacts on hormonal and metabolic signals resulting in modification of sugar transporters. L. BALLY-CUIF addressed the involvement of miR-9 in neurogenesis progression in the embryonic zebrafish mid- and hindbrain. MiR-9 concomitantly inhibits the expression of progenitor maintenance genes and neurogenesis commitment genes. The data suggest that miR-9 expression is associated with the quiescent NSC state and that this association depends upon Notch signalling, a major pathway controlling neural progenitor cell fate.

Session 11 - Coordination of gene expression (chairpersons M. CHODER, T.H. JENSEN)

It has become apparent that the regulation of gene expression, including steps such as transcription, capping, splicing, polyadenylation, RNA export and degradation, is coordinated in a complex and extensively coupled network. M. DUTERTRE focused on the importance of splicing programs in gene expression alteration during cancer initiation and progression. He identified the ddx5 and ddx17 RNA helicases as controlling splicing events contributing to cancer cell aggressiveness. As these helicases regulate the splicing of transcription factors such as c-fos and NFAT5, this creates a strong impact of splicing programs on transcription programs. M. CHODER presented the concept regulation of gene expression as a circular system based on observations that 1) RNA pol II controls mRNA translation and decay via Rpb4/7, 2) mRNA imprinting which corresponds to co-transcriptional mRNA tagging with factors that will later regulate their localization, translation and decay, 3) Cytoplasmic mRNA « decaysome », involving Rpb4/7, functions as a transcription activator by associating with chromatin. These findings demonstrate that gene expression is a circular process in which hitherto first and late stages are interconnected. TH JENSEN focused to the RNA exosome degradation machinery. Depletion of human Trf4p/Air2p/Mtr4p polyadenylation (TRAMP) complex led to identification of short-lived promoter upstream transcripts (PROMPTs equivalent to CUTs in yeast), about 100 nt length. PROMPTs degradation requires the trimeric nuclear exosome targeting (NEXT) complex. PROMPTs function remains to be elucidated. M. MUNOZ addressed the impact of UV irradiation and DNA damage on the transcriptional regulation and alternative splicing. He showed that UV irradiation causes hyperphosphorylation of the carboxyterminal domain (CTD) of RNA pol II, which slows transcriptional elongation rate and affects alternative splicing. Data obtained from keratinocyte treatment by UVC and UVB showed that hundreds of genes are affected, mostly by transcription downregulation and higher exon inclusion. AC PRATS presented a mechanism of coupling between transcription and IRES-dependent translation controlling fibroblast growth factor 1 induction during myoblast differentiation. Two regulatory factors were identified, hnRNPM-p54nrb/NONO, that are able to activate the FGF1 promoter as well as the FGF1 IRES. Furthermore, the data show that a transcriptional event is required for IRES activation by these two proteins, indicating that the recruitment of IRES-transacting factor sis transcription-dependent. B. JOLLES concluded the meeting by showing that translation termination efficiency modulates mTOR signaling pathway through the activation of the transcriptional activator ATF4: depletion of termination factor eRF3 led to upregulation of ATF4 (by mRNA stabilization) and of its transcriptional targets, concomitantly with hypophosphorylation of S6K1 and 4E-BP1, two direct targets of the mTOR kinase activity. She demonstrated that inhibition of mTOR signaling pathway involves REDD1, a target of ATF4, revealing a link between translation termination and initiation mediated by a transcriptional factor.

Conclusion and recommendations

This conference has been really exciting and showed again that the field of RNA in gene regulation remains a growing field. The thematic sessions have shown the increasing importance of small ncRNAs, with identification of new species of such ncRNAs and of their multiple mechanisms of action to regulate gene expression post-transcriptionally as well as transcriptionally. The importance of small ncRNAs in bacteria has been demonstrated. Also, the long non-coding RNAs more and more appear as crucial actors of the regulation of gene expression, and this is worth in animal as well vegetal kingdom. This conclusion is confirmed by the numerous publications of high level articles focusing on ncRNAs.

In addition, this conference has shown the importance of the network existing between all steps of gene regulation, including mRNA transcription, processing and translation. The concept of gene expression as a circular process in which all the stages of regulation are interconnected has appeared as obvious during this conference. Such a concept of coordinated gene regulation really revolutionizes our idea of gene expression.

The participants were overall happy with the content and the stimulating atmosphere of this conference. We heard several comments that indicated strong support for the perspective of pursuing a future Jacques Monod conference on RNA and regulation. The format of the conference was highly appreciated, and the mix between pro- and eukaryotic model systems was considered very fruitful. As regards the participants, the future organizers should try to be more attractive for students (only 4 students applied to the conference). Another piece of advice for the future organizers, based on recommendations from participants concerns the poster session that was found too short. It would be better to organize two poster sessions to provide more time to the participants to look the posters. We obtained a strong approval of the participants for the designated next president, Dr R. Ketting, and the newly elected vice-president, Dr A. Morillon, and feel confident that they will be able to put together a very strong, exciting program.