Roscoff (France), 11-15 septembre 2010

Cycle de division : dans le temps et l'espace

Cell division: time and space

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Conférence Jacques Monod intitulée : Cycle de division : dans le temps et l'espace

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Au cours de la division cellulaire, une cellule duplique son génome et le sépare entre deux cellules filles. Il est crucial que chaque étape soit coordonnée avec la précédente afin d'assurer qu'une, et une seule copie de chaque chromosome soit transmise aux cellules fille. La coordination de ces événements a tout d'abord été comprise comme un contrôle temporel s'assurant que chaque étape se produise de façon ordonnée. Cependant, au cours des dix dernières années, il est devenu de plus en plus évident que certaines étapes du cycle cellulaire ont plus besoin d'être spatialement que temporellement coordonnées. En effet, la division cellulaire est un processus morphogénétique qui requiert que la cellule résolve un certain nombre de problèmes géométriques. Par exemple, la géométrie du fuseau bipolaire et l'attachement précis des chromosomes sur cette structure sont absolument essentiels à la ségrégation équitable des chromatides sœurs entre les deux cellules filles. Au cours de ce congrès, nous avons cherché à comprendre comment la coordination de ces différents événements est assurée avec une grande fidélité, en tenant compte des différentes contraintes, notamment spatiales et temporelles.

Pour saisir l'entière complexité de ce sujet, 10 thèmes ont été abordés et combinés lors de cette conférence :

- Division cellulaire asymétrique
- Réplication de l'ADN et cohésion chromosomique
- Modèles numériques du contrôle du cycle cellulaire
- Le contrôle de la sortie de mitose et du clivage cellulaire
- Assemblage du fuseau mitotique
- Dynamique du fuseau mitotique et ségrégation des chromosomes
- Le contrôle de la dynamique des organelles et leur ségrégation pendant la mitose
- Dynamique du noyau
- Le contrôle de la progression mitotique
- Le « Checkpoint » de l'assemblage du fuseau mitotique

CONFERENCE REPORT

Final report from the Jacques-Monod Conference entitled: Cell division: time and space

Roscoff, September 11-15, 2010

The recent Jacques Monod conference on the Cell Cycle: "Space and Time" was the 11th edition of this conference series and aimed at opening the field to a new generation, carrying new questions, yet in continuing the high standards set by the previous meetings. The quality of the talks was outstanding, and the discussions after each talks were numerous and lead to very stimulating discussions. Both poster sessions were very lively and extremely well attended. Once again the unique venue at Roscoff generated a remarkable atmosphere at the conference, which was marked by constructive, friendly and productive discussions. The success of the conference can be judged by it being largely oversubscribed. A strong request to organise another meeting in the next 2 years was clearly and strongly voiced by many participants.

During cell division a cell duplicates its genome and segregates it into the two future daughter cells. It is crucial that every event is coordinated with the precedent at to ensure that one copy of each chromosome but only one is transmitted to each daughter. Co-ordination of cell cycle events have been first understood as a temporal control ensuring that each step occurs in a well ordered fashion. However, over the last decade it has become more and more clear that cell cycle processes do not all need as much to be temporally coordinated as to be spatially controlled. Indeed, cell division is morphogenetic process and as such proper division requires that the cell appropriately solves a number of geometrical problems. For example, the precise geometry of the bipolar spindle and the precise attachment of chromosomes to this structure are absolutely paramount for the proper segregation of sister-chromatids to opposite daughter cells. Therefore, the meeting has put a strong emphasis on discussing and trying to understand how the complex coordination of the different events involved in the cell cycle is achieved with high fidelity with respect to the spatial and temporal constraints and requirements of cell division.

To grasp the entire complexity of this topic, 10 themes were addressed and combined at the conference:

- Asymmetric cell division
- DNA replication and chromosome cohesion
- Computer modelling of cell cycle control
- The control of mitotic exit and cell cleavage
- Spindle assembly
- Spindle dynamics and chromosome segregation
- The control of organelle dynamics and segregation during mitosis
- Nuclear dynamics
- The control of mitotic progression
- The spindle assembly checkpoint

The first evening was dedicated to a keynote lecture by Kim Nasmyth (Biochemistry, University of Oxford, UK), who gave a broad and sharp overview of our understanding of how chromosomes are cohesed, oriented and segregated during mitosis and meiosis. His lecture was illustrated with the latest finding of his group on the behaviour of cohesin during early embryonic states. Using mice whose kleisin subunits are able to be cleaved by the protease TEV and looking at the effect of Rec8 and Scc1 have on meiosis I and II, he concluded that cohesin turnover does not, or to a small extend, happen during the growing phase of oocytes.

1) Asymmetric cell division

The process during which mitotic events are controlled with the highest level of precision is probably during asymmetric cell division, one of the major process for the generation of cellular diversity in eukaryotes. **Monica Gotta** (University of Geneva, Switzerland, EMBO Young Investigator Lecture) used a genome-wide RNAi screen in *C. elegans* to identify genes coordinating cell polarity and mitotic progression. This screen identified SPAT-1, the homologue of Bora in *Drosophila*, and showed it controls both cell polarity and cell cycle progression through Plk1. **Nathan Goehring** (Hyman lab, Dresden, Germany) presented recent work on the establishment of cortical polarity during the first division of the *C. elegans* oocyte, and particularly on the role of the emergent properties of the cortex in this process. **Shahragim Tajbakhsh** (Institut Pasteur, Paris, France) talked about stem cell identity and DNA strand segregation in satellite cells of the skeletal muscle. **Yves Barral** (ETH Zurich, Switzerland) proposed a mechanism for asymmetric inheritance of prion-based memory in *S. cerevisiae*. Altogether, the model presented proposed an explanation for how cellular identity can be established and asymmetrically segregated over time. **Jürgen Knoblich** (IMBA, Vienna, Austria) presented his work on the MBT (malignant brain tumour) gene in Drosophila and mouse, and its role in the control of cell proliferation coupled with asymmetric cell division. **Eric Weiss** (Evanston, USA) described how the transcription factor Ace2 is asymmetrically segregated in yeast, and how this controls late cytokinetic events. **Sylvie Tournier** (Toulouse, France) described biophysical and modelling approach to characterize spindle dynamics in the presence of merotelic chromosome attachments.

2) DNA replication and chromosome cohesion

Philippe Pasero (CNRS, Montpellier, France, EMBO YIP lecture) focused on the regulation and timing of DNA replication in budding yeast, showing that checkpoint kinases are able to detect and regulate ongoing DNA replication by controlling the timing of origin firing in every mitosis to avoid replication stress. **Prasad Jallepalli** (New York, USA) explained how acetylation of cohesin speeds up the replication fork by promoting replication fork progression, and providing ideas about how establishment of cohesion and DNA replication might be coordinated. **Jan-Michael Peters** (IMP, Vienna, Austria) spoke about the role of Wapl in the control of cohesin loading on DNA, and the consequence of cohesion for interphase chromatin. **Etienne Schwob** (CNRS, Montpellier, France) on his side focused on the coordination of DNA replication with spindle assembly in budding yeast. His data demonstrated the importance of this coupling for the proper assembly of a bipolar spindle, and underlined the importance of the proteins Bub1 and Bub3 in this process.

3) Modelling the cell cycle

Our understanding of individual biochemical processes and of their importance in cell cycle control has greatly increased over the years, yet understanding how these processes function together to coordinate cell cycle events requires that we are able to model and interrogate cell cycle regulatory networks in silico. **Béla Novák** (University of Oxford, UK) reported about his work on the mechanisms ensuring the irreversibility of cell cycle transitions, taking the interplay between Cdk1 activity and APC/C as an example. A radical conclusion of his analysis is that irreversibility does not come from protein degradation, as frequently assumed, but emerges from the architecture of the regulatory network. **Andrea Ciliberto** (Milano, Italy) demonstrated that the cell cycle is not coordinated by a single oscillator, but by several ones that entrain each others.

4) Late mitosis and cytokinesis

This session was dedicated to the investigation of the signals that determine the end of mitosis and the onset of cytokinesis. Investigating how cells exit mitosis in an orderly fashion, **Frank Uhlmann** (Cancer research UK, London, UK) provided a biochemical model for how Cdk1 substrate dephosphorylation is organized as mitosis progresses, demonstrating that substrate affinities for the phosphatase Cdc14 correlates with the time at which these substrates are dephosphorylated during mitosis. **Simonetta Piatti** (Montpellier, France) talked about a novel role for the GTPase Rho1, the yeast counterpart of metazoan RhoA, in regulation of septin dynamics at the bud neck and in controlling the reorganization of septin structures at cytokinesis onset. **Tarun Kapoor** (New York) addressed the mechanisms contributing to cleavage-plane determination in higher eukaryotes and suggested a two steps model where an Aurora-kinase dependent phosphorylation gradient first provides spatial information to guide furrowing, while the microtubule crosslinker PRC1 marks in a second step the spindle midzone and define positional cues for proper cell cleavage. **Mohan Balasubramanian** (TILL, Singapore) presented his work using fission yeast to study the mechanisms of cleavage plane positioning. **Arnaud Echard** (Paris, France) described recent findings about the molecular mechanism underlying abscission in metazoans, and particularly about the role of Rab35 in septin recruitment and stabilization of the intercellular bridge between the daughter cells, and in removal of F-actin prior to abscission. **Daniel Gerlich** (Zurich, Switzerland) talked about the process of abscission in animal cells and described the involvement of the microtubule-severing factor spastin and of the ESCRT III complex. Finally, both **Anne Royou** (CNRS, Paris, France) and **Manuel Mendoza** (CRG, Barcelona, Spain) provided evidence for the existence of compensatory mechanisms that ensure clearing of extra long chromosomes from the cleavage plane in *Drosophila* and budding yeast. While in the insect system the experiments demonstrate the existence of a mechanism to promote the elongation of the dividing cell, the experiments reported the existence in budding yeast of control mechanisms able to detect the presence of one extra-long chromosome and promote its hyper-condensation.

5) Spindle assembly

The complex and dynamic morphology of the mitotic spindle, together with its ability to self-assemble, have fascinated cell biologists for over a century already. With the help of computer simulations, **Francois Nedelec** (EMBL, Heidelberg, Germany) explored the molecular principles and rules underlying the self-assembly and dynamics of the spindle observed in *Xenopus* egg extracts. **Helder Maiato** (IBMC, Porto, Portugal) provided

evidence that the protein Megator forms a matrix within the area of the mitotic spindle to control spindle assembly and confine signaling of the spindle assembly checkpoint. **Renata Basto** (Institut Curie, Paris, France) reported on her analysis of the effect that centriole over-duplication has in *Drosophila* and particularly its transforming effect.

6) Spindle dynamics and chromosome segregation

Stephen Doxsey (Worcester, USA) showed that the intraflagellar transport protein IFT88 interacts with EB1 and dynein and suggested that these interactions ensure their proper transport to the spindle poles, astral microtubule nucleation and proper spindle orientation. **Stefan Westermann** (IMP, Vienna, Austria) focused on the molecular mechanisms ensuring that kinetochores remain associated with the end of microtubules transiting between growth and shrinkage phases, focusing especially on the biochemistry of Dam1 and Ndc80 complexes. The talk of **Sue Biggins** (FHCR, Seattle, USA) focused on the development of an efficient method for purifying and characterizing the biophysical properties and behaviour of yeast kinetochores. These studies particularly demonstrate that even in the absence of aurora B the strength with which kinetochores bind microtubules increases with the pulling force applied on them. **Patrick Meraldi** (ETH Zurich, Switzerland) presented his work about the role of early centrosome separation during spindle assembly.

7) Organelles in mitosis

While this topic is frequently under investigated and we know little about it, it is clear that mitosis is also about ensuring the proper segregation of vital organelles between daughters. Remarkably, **Liza Pon** (Columbia University, USA) demonstrated the existence of a cell cycle checkpoint delaying cytokinesis as long as the yeast bud has not inherited a mitochondrion. Unexpectedly, this checkpoint impinges upon the regulation of the MEN network. **Marina Barac** (CHUV, Lausanne, Switzerland) showed that securin and separase unexpectedly associate with internal cell membranes in mammalian cells and that their depletion perturbed the golgi apparatus and endosome function. **Snezhana Oliferenko** (TILL, Singapore) showed that division site positioning in fission yeast is strongly influenced by the organization of the cortical endoplasmic reticulum.

7) Mitotic progression

Ariane Abrieu (CNRS, Montpellier, France) reported on her findings that the master cell cycle regulator Cdk1 controls the spindle assembly checkpoint, through phosphorylation of the Mps1 kinase. **Thierry Lorca** (CNRS, Montpellier, France) focused on the function of the mitotic regulator Greatwall (GW) in inhibiting the kinase PP2A during mitosis. The results indicate that mitotic entry is not solely dependent on Cdk1 activation but also on PP2A inhibition. **Izabela Sumara** (Zurich, Switzerland) talk showed that E3-ligases could have different function during cell division than targeting substrate for proteolysis. For example, Cul3-based E3-ligases interact and monoubiquitinate the Polo-like kinase 1 (PLK1) to promote its dissociation from kinetochores.

9) Nuclear dynamics and meiosis

Valérie Doye (Institut Jacques Monod, Paris, France) introduced the function of the transmembrane nucleoporin Pom33 in nuclear pore complex (NPC) distribution and assembly. **Ulrike Kutay** (ETH Zurich, Switzerland) described how NPC disassembly and

nuclear envelope breakdown are controlled by phosphorylation of the nucleoporin Nup98. **Katja Wassmann** (Université Pierre et Marie Curie, Paris, France) uses mouse and ascidian oocytes to understand how chromosome cohesion and disjunction is controlled during meiosis. **Michael Knop** (EMBL, Heidelberg, Germany) discussed his labs studies on the yeast *Saccharomycodes ludwigii*, which performs meiosis without any crossing over occurring.

10) Spindle assembly checkpoint

Jonathon Pines (Gordon Institute, Cambridge, UK) presented his work on the role of the Anaphase promoting Complex/Cyclosome (APC/C) in regulating the right timing of substrate degradation during mitosis using life cell assay in human cells. His data indicate that substrates are recognised by different subunits of the APC/C, providing an important clue about how the APC/C differently targets checkpoint-dependent and checkpoint-independent substrates. **Andrea Musacchio** (IFMO, Milan, Italy) provided biochemical and structural data about how the KMN (Knl1-Mis12-Ndc80) complex is essential for the feed back mechanism linking the error correction and the spindle assembly checkpoint. **Geert Kops** (Utrecht, Netherlands) presented the work of his laboratory about how the kinase Mps1 controls the activity of the spindle assembly checkpoint, and how checkpoint silencing is achieved.

Conclusions, remarks and suggestions for the next editions of the conference

Globally, the participants expressed a high level of satisfaction, and even enthusiasm, about the conference. 98% of the participants found that the presentations were excellent (76%) or good (22%), and fully subscribed to the decision of the organizers to diversify the topics addressed by the conference (in fact that the session that represented more novel topics: asymmetric cell division, and late mitosis/cytokinesis ranked first and second in the category of most impressive sessions in the evaluation of the attendees). The decision to focus on younger generations has also been a very interesting experience. While at the beginning the attendees were still shy, and discussion started mainly under the impulsion of the senior attendee, the group dynamics evolved fairly rapidly such as to become much more vivid and authentic at the end. This contributed greatly to the establishment of a highly stimulating atmosphere. Accordingly, the discussions after the lectures emerged as a highlight in the evaluation sheets. These developments will no doubt play an important role in establishing a new generation in the cell cycle field. An overwhelming majority of the attendees (96% of the 72 evaluation sheets that were returned) pronounced themselves in favor of repeating this conference.

This being said, there were a few things that could be improved. Particularly, the rooms for the poster sessions were too small. As a consequence, it was very noisy and it was difficult to have discussions around the data. Also, the temperature became rapidly unbearable. Many participants recommended that a bigger room be chosen, preferably in the same building as the meals. Likewise, a larger venue for the coffee breaks would be very welcome.

To be noted for the next organizers, the organization of the free evening on the Monday was a mistake, because many restaurants were closed. Altogether, some participants expressed the wish of having more free time for informal discussions, and to avoid sessions in the evenings.

Finally, some participants expressed the wish that more attention being brought to introduce technical breakthroughs and innovations.

To finish on a very positive note, though, wireless access has been greatly improved – Thank you very much!