CONFÉRENCES JACQUES-MONOD

MOLECULAR MACHINES IN CELL DIVISION

LES MACHINES MOLÉCULAIRES DE LA DIVISION CELLULAIRE

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Administrative report

The Jacques Monod conference on the Cell Cycle: Molecular machines in Cell Division took place in Roscoff from September 11th to 14th with the participation of 104 scientists from 15 countries:

- Austria (5)
- Belgium (2)
- France (24)
- Germany (9)
- Holland (1)
- Israel (1)
- Italy (4)
- Japan (3)
- Portugal (1)
- Spain (7)
- Sweden (1)
- Switzerland (6)
- Taiwan (1)
- United Kingdom (23)
- USA (16)

The total number of invited speakers was 28. From the abstracts submitted to the Conference, 9 additional speakers were selected for shorter oral presentations. Unfortunately one of them had to cancel his trip at the last minute because of VISA problems with the US. In summary the total number of oral presentations was 36.
All the other participants (68) presented their work in the format of posters that were on display during two afternoon sessions of 1h 45min and 34 posters each.
Among the participants, 15 PhD students (representing almost 15% of the participants) were present during the whole conference.

The conference was highly appreciated by all participants. Many of them expressed their satisfaction to the organizers and pointed out that they particularly enjoyed the small size of the conference and the focused theme because it allowed them to meet

with many colleagues working in the same field and have enough time to discuss at length and in some cases to establish collaborations. Therefore both the focus and the size of the conference seemed good.

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 the overwhelming support from the participants for organizing another meeting in 3 years time. Jon Pines (vice-president of this conference and president of the next) accepted to present an application for the next conference. Since the first Cell Cycle Conference was organized in 1988, it seemed a good idea to aim at organizing the next Cell Cycle Conference in 2008 to celebrate the 20th anniversary of this very successful series.

Yves Barral was elected unanimously on the last evening of the Conference as the next vice-president and he accepted the charge. He will assist Jon Pines for the organization of the next Conference.

Finally, we want to point out that the successful organization of the Conference was largely due to the very good practical skills of Mme Lidoreau. We thank her warmly for her diligent advice, help and work in all the matters relating to the practical organization of the Conference.

Scientific summary of the Conference

The conference "Molecular machines in Cell Division" more than lived up to the high standards set by previous meetings. The quality of the talks was excellent and the poster sessions were very lively and overflowing with participants.

This theme of the conference - Molecular Machines - brought together sets of researchers from the cell division, chromosome and cytoskeletal fields, who have overlapping interests but who normally do not tend to attend the same meetings. This led to unusual insights and the realization of common themes in different fields.

Five supra-molecular machines were addressed at the conference: the mechanics of chromosome condensation, the centrosome, the kinetochore, the mitotic spindle, and the cytokinetic apparatus. Topics ranged from the structure of these machines, to their assembly and disassembly, and their interactions with the enzymes – notably protein kinases and ubiquitin ligases - controlling cell division. Of these enzymes the cyclin-dependent kinases are probably the most well known and Tim Hunt (LRI, Clare Hall) gave the opening presentation in which he put our knowledge of exactly how cyclin-dependent kinases orchestrate the assembly and disassembly of the structures required for cell division in context.

1) Chromosome condensation

For daughter cells to inherit identical copies of the genome it is important for newly replicated DNA to remain attached to its sister chromatid until mitosis, and, in most cells with large genomes, for the chromosomes to condense to be manipulated by the mitotic apparatus. This is achieved by related macro-molecular complexes forming the cohesin and condensing complexes. Mitsuhiro Yanagida (Kyoto University, Japan) showed that condensing subunits in both fission yeast and mammalian cells play an important part in forming the correct centromeres structure required for proper chromosome attachment to the spindle and sister chromatid separation. Claudio Sunkel (University of Porto, Portugal) showed that condensins are also important for centromeres structure and for sister chromatids to separate in invertebrate cells. Rebecca Heald (University of California, Berkeley) demonstrated that Histone H1 and condensing both play critical roles in sister chromatid segregation in Xenopus eggs. Jan-Michael peters (IMP, Vienna) showed that the initial establishment of cohesion between sister chromatids is dependent on the Scc4 protein that loads cohesin complexes onto DNA during replication. He further showed that the Wap1 protein is required for cohesin to be removed in prophase.

2) The centrosome

The centrosome in animal cells, and its equivalent the spindle pole body in yeast, is responsible for nucleating the microtubules that form the mitotic spindle. Both organelles duplicate only once per cell cycle and subsequently need to mature before they can properly function in mitosis. At its core the centrosome consists of two centrioles that have the remarkable property of acting as templates in what

appears to be a form of conservative replication. Eric Nigg (MPI Martinsreid) and David Glover (University of Cambridge) presented their recent finding that Plk4/SAK, a member of the Polo kinase family controls centriole duplication and restricts it to once per cell cycle, and this is conserved in vertebrate and invertebrate animal cells. Complementing this Pierre Gönczy (ISREC, Lausanne) showed how specific components that make up the mature centrosome are subsequently recruited in C. elegans, and Phong Tran (University of Pennsylvania, USA) showed how fission yeast spindle poles recruit components required to nucleate microtubules. Iain Hagan (Paterson Institute, Manchester) showed that the fission yeast spindle pole body has a crucial role to play in controlling the timing of entry to mitosis, especially in response to environmental stress.

3) The mitotic spindle

Centrosomes usually play a crucial role in nucleating the mitotic spindle in animal cells but there is a centrosome independent pathway that is particularly prominent in eggs and early embryos. This pathway uses Ran, the small GTPase that regulates nuclear import and export in interphase cells. Isabelle Vernos (CRG, Barcelona) showed that the Aurora A protein kinase previously shown to affect centrosome maturation – also has an important role in regulating the centrosome-independent pathway in frog eggs where it acts through maskin, a TACC family member, to stabilize microtubules. Marie-Hélène Verlhac showed that the Ran-dependent pathway also has a crucial role in assembling the meiotic spindle in mouse oocytes. Eric Karsenti (EMBL, Heidelberg) showed that our current knowledge of the Ran-dependent spindle assembly pathway is sufficiently detailed to be able to generate a model for Ran behaviour during spindle assembly from the biophysical characteristics of the known components that substantially agrees with the Ran gradient measured by a bio-sensor.

In somatic cells the centrosome-dependent pathway for spindle assembly assumes more importance, and perturbing the number or function of centrosomes have been suggested to contribute to cancer by disrupting proper spindle assembly and thus chromosome segregation. Bill Saunders (University of Pittsburgh, USA) contributed a further parameter to this debate by showing that the spindle poles of transformed cells may also be disrupted by changes in the level of the protein NuMA through its effect on cytoplasmic dynein. Sandrine Grava (ETH, Zurich) showed that

dynein in mitotic budding yeast is asymmetrically distributed on the mitotic spindle and that this depends on the major mitotic cyclin-dependent kinase. Recently, attention has focused on importance of asymmetric cell division to regulate the proper differentiation of particular cell lineages and in particular the possibility that defects in spindle orientation can also contribute to cancer. Michel Bornens (Institut Curie, Paris) showed remarkable data where he used micropatterned slides to direct the orientation of the cell division axis, demonstrating that the cortical actin cytoskeleton and its focal contacts determines the subsequent axis of cell division. Cayetano Gonzalez (CRG, Barcelona) presented data that made a direct link between cancer and the controls on the orientation of the mitotic spindle. He showed that mutations in many of the genes that control asymmetric cell division in the neuroblasts of Drosophila cause these cells to form tumours if they are transplanted from the brains of larvae to the abdomen, which has obvious implications for metastatic growth. Jurgen Knoblich (IMP, Vienna) also linked asymmetric cell division in Drosophila neuroblasts to cancer by showing that the polarity genes that control asymmetry act on proteins that are known tumour suppressors.

4) The kinetochore

Clearly, the proper segregation of chromosomes also depends crucially on their attachment to the mitotic spindle in a bi-polar fashion to ensure that the two sister chromatids move to opposite poles. Attachment to the spindle microtubules is the function of the kinetochore and a number of speakers addressed the question of how the kinetochore functions, and how it transduces a signal to block mitosis should chromosomes be improperly attached. Tomoyuki Tanaka (University of Dundee, Scotland) used time-lapse fluorescence microscopy to show the process by which individual kinetochores capture a microtubule in a budding yeast cell, and used this assay to identify proteins required for capture and for bi-orientation. Jason Swedlow (University of Dundee, Scotland) had also identified proteins required for attachment but through a proteomics approach using isolated Xenopus chromosomes. Valérie Doye (Institut Curie, Paris) described a new, unexpected kinetochore component. She showed that proteins that form part of the nuclear pore complex in interphase cells are recruited to kinetochores in mitosis where they may be required for proper chromosome attachment and congression. Conversely, Claude Antony (EMBL, Heidelberg), demonstrated that a kinetochore component could have a second

function at the spindle pole, because a 3-D electron microscopy reconstruction of the mitotic spindle in a yeast cell with a mutation in the Ndc10 kinetochore protein showed defects in spindle pole body maturation and ability to nucleate microtubules.

Peter Sorger (MIT, USA) addressed the question of how defective chromosome attachment is able to trigger a checkpoint and block further progress through mitosis. He used time-lapse microscopy of mammalian cells to show that some defects could trigger a checkpoint but others, including those caused by removing the APC protein implicated as a tumour suppressor, were not sensed. Andrea Musacchio (EIO, Milan) complemented this with his data on how the checkpoint proteins interact at the molecular level using a combination of structural and biophysical studies. Jonathon Pines (University of Cambridge, UK) showed how these checkpoint proteins controlled progress through mitosis by influencing the timing of when specific mitotic regulators were inactivated by proteolysis. These regulators include the securin protein that blocks sister chromatid separation, and the major mitotic cyclin, cyclin B1, and Takeo Kishimoto (Tokyo Institute of Technology, Japan) showed that securin and cyclin B1 had to be degraded in meiosis I for homologous chromosomes to segregate. Katja Wassmann (University of Paris) showed that these proteins were prematurely degraded in meiosis I in mouse oocytes with only one copy of one of the checkpoint gene, Mad2. The Emi1 and Emi2/Xerp1 proteins have been implicated in preventing securin and cyclin B1 degradation in the Meiosis II arrest of vertebrate eggs and Thomas Mayer (MPI, Martinsreid) showed how Emi2/Xerp2 is finally removed by proteolysis when the egg is fertilised.

5) The last event in cell division is the formation of the 2 daughter cells – cytokinesis. Michael Glotzer (University of Chicago, USA) showed how the Cyk4 RhoGAP and the Zen4 motor protein assembly in the central anaphase spindle of C. elegans cells to form an important signaling complex for cytokinesis, and how the Ect2 GTP-exchange factor interacts with Cyk4 and regulates assembly of the contractile ring through Rho A and myosin, and is itself regulated by cyclin-Cdk activity. The Zen4 motor protein has an orthologue in mammalian cells called Cho1 and Ryoko Kuriyama (University of Minnesota, USA) showed that disrupting this protein disrupted the final separation of the 2 daughter cells (abscission). Unexpectedly, Yves Barral (ETH, Zurich) found that there is a mechanism in yeast cells that detects when formation of the central spindle has been perturbed and prevents abscission, and that

this pathway uses the Aurora B kinase that plays an important role in the spindle checkpoint detecting whether kinetochores are properly attached to the spindle.

Concluding remarks

The Jacques Monod conference on the Cell Cycle: Molecular machines in Cell Division held in Roscoff from September 11th to 14th was therefore a highly successful meeting in the line of previous conferences in the now classical Cell Cycle series.

It goes beyond doubt that the success of the next conference planned for 2008 is granted. In fact it should be a highlight in this series since it will mark the 20th anniversary of the first Cell Cycle conference organized by the CNRS in the context of the Jacques Monod Conferences series.