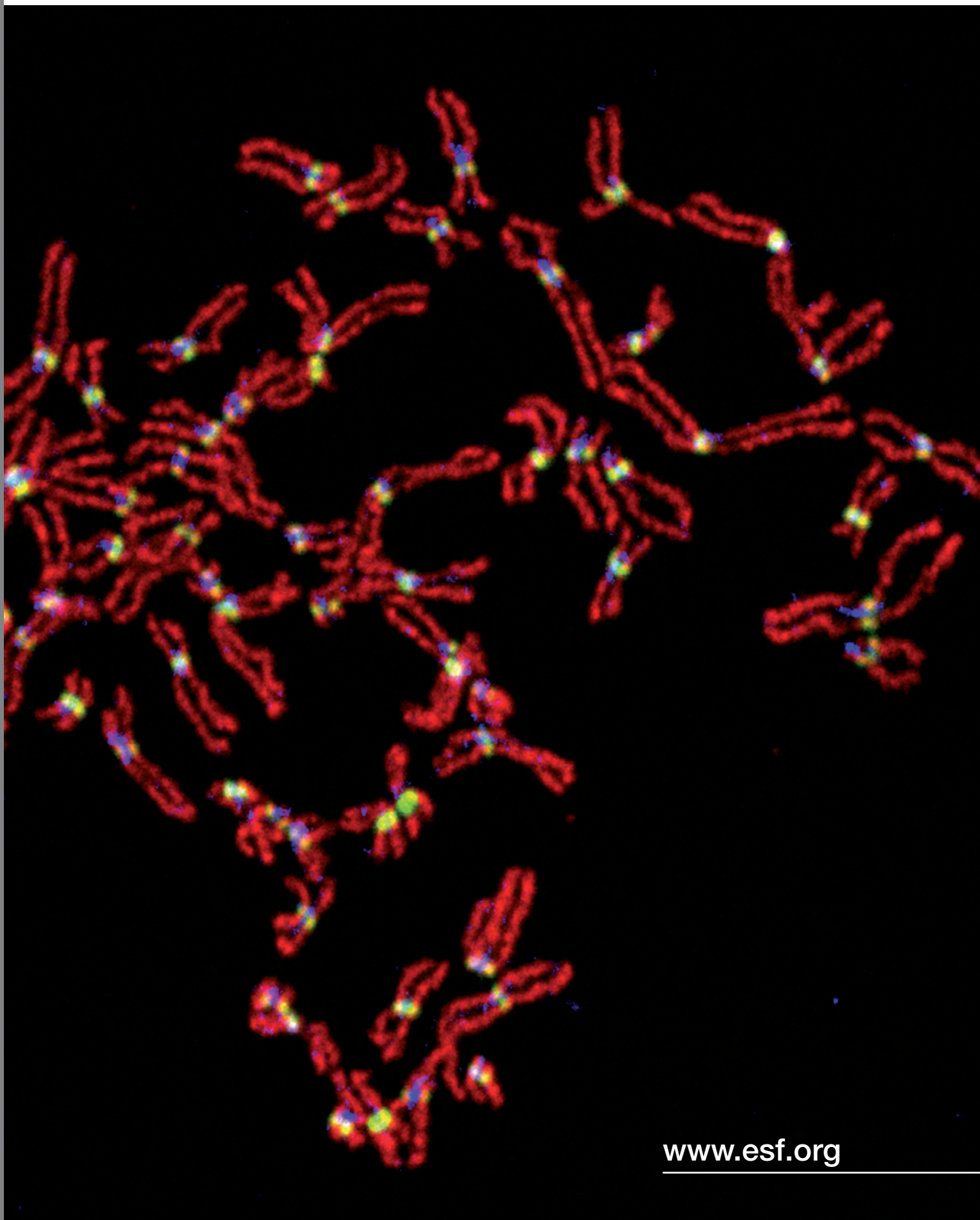
EUROPEAN SCIENCE FOUNDATION

SETTING SCIENCE AGENDAS FOR EUROPE

EUROCORES Programme

European Collaborative Research

EuroDYNA - Final Report



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General Information

What is EUROCORES?

The EUROCORES (European Collaborative Research) Scheme is a flexible framework that promotes excellence in collaborative research and networking. Offered by the European Science Foundation (ESF), EUROCORES tackles scientific questions in and across all disciplines by means of an integrated European or even global effort.

The Programmes encourage and foresee networking and collaboration of researchers to achieve synthesis of scientific results across the programme, to link to related programmes, and to disseminate results. EUROCORES Programmes allow national research funding organisations in Europe and beyond to support top class research in and across all scientific areas, by matching the needs articulated by the scientific community with their strategic priorities. Funding decisions on the projects and the research funding remain with the national research funding organisations, based on international peer review operated by ESF. ESF also provides support for networking the researchers and for the scientific synthesis of research results and their dissemination. Until December 2008 this is supported through a contract with the European Commission under the Sixth Framework Programme (EC Contract no. ERAS-CT-2003-980409). From January 2009 onwards this support will be provided by the national Funding Organisations participating in the Programmes. **www.esf.org/eurocores**

Programme Structure and Governing Bodies

A EUROCORES Programme is overseen by a *Management Committee* formed by one representative of each of the participating national funding agencies and the EUROCORES Programme Coordinator.

An international, independent *Review Panel* oversees the scientific aspects of the Programme. This includes assessment of outline proposals, selection of externally peer reviewed full proposals and the monitoring of the overall scientific progress of the Programme.

The *Scientific Committee* is formed by the Project Leaders of all funded Collaborative Research Projects (CRPs) and the EUROCORES Programme Coordinator. It is responsible for the networking and dissemination activities within the framework of the EUROCORES Programme.

Final Evaluation

Each EUROCORES Programme is subjected to a final evaluation by the Review Panel. The final evaluation concerns the overall achievements of the Programme as a whole and as such complements the evaluations of individual projects conducted at the national level. The merits of a Programme will be assessed on the basis of the scientific achievements highlighted by the Project Leaders as well as the usefulness and impact of the networking, training and dissemination activities undertaken. To this end, emphasis is placed on the activities which took place between the various CRPs with the aim to assess the added value of the Programme.

For the final evaluation of EuroDYNA, the Review Panel assessed the final reports of the CRPs and in addition attended the final EuroDYNA conference, during which the Project Leaders presented the highlights of their respective CRP. During a subsequent Review Panel meeting, the merits of the Programme and lessons to be learned were discussed.

This summary report is composed of three sections. The first one - EuroDYNA Recommendations - provides an overview of the Programme's achievements and recommendations for future research topics to scientists and funders; the second section highlights EuroDYNA's publications and in the last section, the Governing Bodies of EuroDYNA are presented.

Cover picture:
Spread of human mitotic chromosomes stained for the proteins condensin (red), cohesin (blue) and the centromere specific histone,CENPA (green). Micrograph by Peter Lenart, IMP, Vienna.

EUROPEAN SCIENCE FOUNDATION

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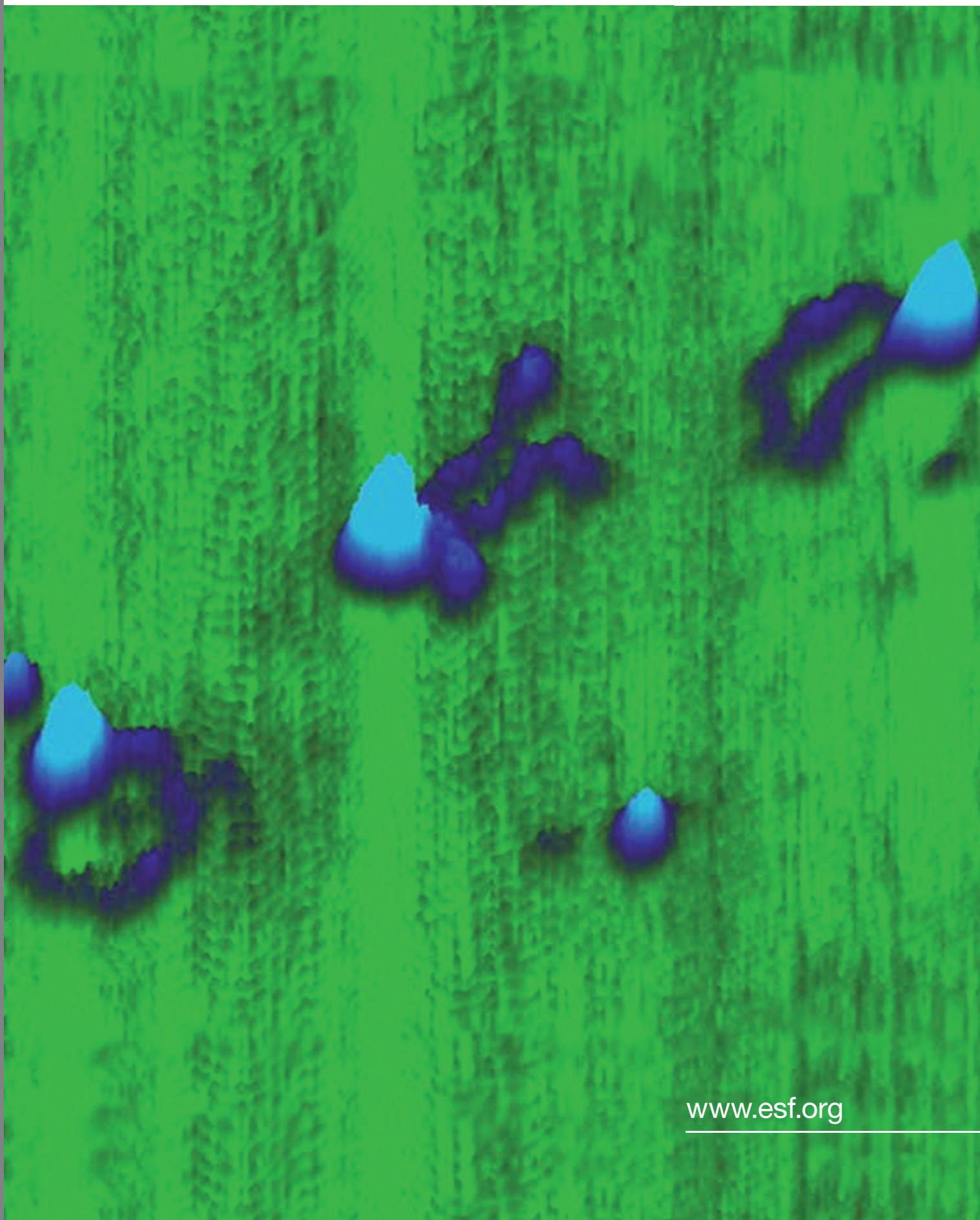
EUROCORES Programme
European Collaborative Research

Dynamic Nuclear Architecture and Chromatin Function (EuroDYNA)

EuroDYNA Recommendations



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Introduction

EuroDYNA[1], the European Collaborative Research (EUROCORES) Programme whose aim it was to shed light onto the functioning of the nucleus, the control centre of a cell, came to an end in 2008. Over a three-year period the Programme offered scientists the possibility of teaming up with peers and exploring new research directions in a flexible manner.

EuroDYNA accommodated nine thematic Collaborative Research Projects (CRPs), bringing together a total of 40 European research groups. Overall, the Programme combined expertise in different fields such as dynamic chromatin structure and nuclear architecture, regulation of gene expression, RNA processing and transport as well as genome surveillance. The latest technologies in molecular biology and biochemistry were employed together with advanced microscopy, structural analysis and computational approaches in order to gain a deeper insight into how the nucleus operates.

The Programme was funded by two sources: National funding agencies from eight European countries joined forces to provide a total of seven Million Euro to conduct research within the framework of EuroDYNA. This was complemented by a total of 170.000 Euro to support the networking and dissemination activities of funded scientists across CRPs, through the EU's Framework Programme 6.

The Programme's achievements

During its three-year life span, EuroDYNA offered its members a diverse array of networking opportunities, of which the annual conferences were particularly successful. This is illustrated by the fact that 17 new collaborations were formed between scientists across several thematic CRPs, a development that otherwise would not have happened. This is also where the added value of EuroDYNA kicked in as scientists with related yet slightly different research interests got together on a regular basis to present their data and have stimulating debates with the possibility of setting up new research initiatives. This interaction was further developed through short-term visits of students between the CRP labs.

EuroDYNA was also active beyond its boundaries, forging links with EU-networks and other EUROCORES Programmes within the same discipline and across scientific disciplines. For instance, in 2006 and 2007, two brain storming meetings took place involving members of EuroDYNA and SONS[2] (a EUROCORES Programme in the Physical Sciences) to facilitate cross-disciplinary exchange at the interface of molecular biology and material science/nanoscience. Within the Life Sciences, EuroDYNA members participated in a Mini-Symposium held by the EUROCORES RNAQuality in 2007 and the RNAQuality Training Workshop in 2008.

EuroDYNA held its last community event at The Wellcome Trust Conference Center in Hinxton, UK from 28-31 May 2008. This final conference highlighted the scientific achievements generated during the Programme's lifetime and provided a forum for discussion between EuroDYNA investigators and members of the EuroDYNA Review Panel. On the whole, EuroDYNA has produced numerous high-level publications, including articles in Nature and Cell, and the cross-CRP and cross-EUROCORES interactions have already successfully laid the foundation for joint publications and grant submissions.

Future prospects

EuroDYNA has yielded fruit and in order to build on the Programme's achievements, the EuroDYNA Review Panel and the EuroDYNA investigators discussed future opportunities in the field. Their recommendations, presented on the following pages, are meant to serve both the scientific community and funders alike; the scientific community for the development of new collaborative projects, the submission of a new EUROCORES theme proposal, etc.; the funders to raise awareness with regards to emerging topics to be supported on a national or transnational level across Europe.

Astrid Lunkes
EUROCORES Programme
Coordinator for EuroDYNA

[1] Dynamic Nuclear Architecture and Chromatin Function, [2] Self-Organised Nanostructures

EuroDYNA Review Panel - Consensus Report

The Programme is composed of nine Collaborative Research Projects (CRPs), with a fairly broad array of topics, focus and size. While the achievements vary between CRPs, the Panel was impressed by the overall output of papers produced during the Programme's 3-year lifetime. The integration of different disciplines was clearly considered an added value of the Programme as was the interaction between different CRPs. Most of these interactions were unforeseen and some have already led to joint CRP publications or grant submissions.

The Panel highlighted the added value of the networking activities, in particular the annual EuroDYNA conferences; these meetings proved to be an effective means to initiate new collaborations across CRPs and to generate new insights. The Panel was also very positive about the training possibilities the Programme offered to young scientists, be it within or across CRPs. They felt that it was important to expose the younger generation to the breadth and interdisciplinary character of the field.

The Panel indicated that the Programme did very well in terms of the dissemination of results to the scientific community at large. On the other hand, they felt that investigators should in general be more implicated in science communication with the lay public through open days/guided tours, newspaper interviews and articles, radio programmes etc..

On the whole, the Review Panel considered EuroDYNA a real success with all CRPs having been very productive in terms of publications, contributions to networking and training, as well as dissemination activities. While a lot of joint publications have already come out, more are to be expected in the future, especially those originating from recently started cross-CRP interactions.

The Panel recommended that EuroDYNA investigators build on the achievements of the Programme by:

1. Continuing to "create opportunities" through the organization of workshops/small conferences which could replace the annual EuroDYNA conference.

2. Linking up with other EUROCORES Programmes where possible (i.e. RNAQuality)

3. Submitting a new EUROCORES Theme proposal. A good concept for a Call today would be to focus on structural aspects, looking at different resolution ranges and encouraging the use of the latest technologies to address longstanding questions around the functioning of the nucleus.

Recommendations for Future Research Topics

When the EuroDYNA Call was published in 2003, the domain of nuclear dynamics was more difficult to study through lack of adequate equipment and technology. New developments and technological advances have since emerged and have opened new possibilities for future research in this domain.

Members of the EuroDYNA Review Panel and EuroDYNA investigators felt that a good concept for a Call in the near future would be to focus on structural aspects, looking at different resolution ranges and encouraging the use of the latest technologies to address longstanding questions around the functioning of the nucleus. Amongst others, investigation of the following subtopics could be envisaged:

- structure of higher order organisation of the nucleus and what controls it
- dynamics of nuclear structures and how these are controlled
- structural analysis of nuclear bodies
- regulation of nuclear processes in time
- three-dimensional control of gene expression: how gene/chromatin positioning affects expression capacity
- quantitative and theoretical approaches to analyse how molecules get together (molecular crowding)
- application of the use of new technologies to the study of chromatin conformation and function
- molecular mapping of gene contacts in the three dimensional nuclear space (using eg "chromosome conformation capture" (3C))
- organization of interphasic chromosomes
- intranuclear transport
- meiosis and oocyte maturation

  → could be developed into an own Call topic since it is highly relevant for research on fertility and genetic diseases.

Networking and Dissemination Activities

Annual Meetings

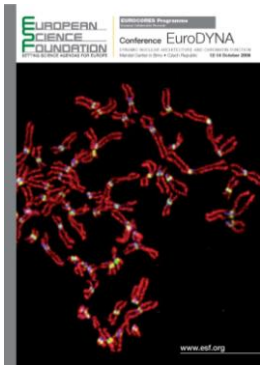
3rd EuroDYNA Meeting | 28 - 31 May 2008, The Wellcome Trust Conference Centre in Hinxton, UK

EuroDYNA takes lid off the genome
European researchers have made significant progress unravelling how genes are governed and why this sometimes goes wrong in disease. The key lies in the dynamic ever-changing structure of the chromatin, which...

EuroDYNA leaves healthy genomic research ecosystem as legacy
Europe's position as a major player in genome research has been boosted by the European Science Foundation's three-year EUROCORES Programme EuroDYNA. As it draws to a close, EuroDYNA is leaving behind a healthy European ecosystem of interacting...

read more at www.esf.org/eurodyna

2nd EuroDYNA Meeting | 12 - 14 October 2006, Gregor Mendel Center in Brno, CZ



EuroDYNA conference magnifies small components for big issues: finding the answer to human disease
At a recent EuroDYNA conference in Brno, Czech Republic, 60 scientists from nine European countries came together to present their research in the field of genetics and cell nucleus architecture...

Finding a cure for cancer: the holy grail of science
To find a cure for cancer, the modern-day plague of our society is synonymous to finding the holy grail of science...

read more at www.esf.org/eurodyna

Kick-off meeting | 22 - 24 September 2005, Thun, CH

The EuroDYNA community met for the first time to present their projects and to discuss the needs of the field and future activities; the importance of annual conferences was highlighted on this occasion.

Training

Fourth International Summer School on *DNA and Chromosomes* | 19 June - 1 July 2006, Corsica, FR

The Summer School aimed to integrate the various biological and physical approaches used to study DNA and chromosomes.

Short-term visits

EuroDYNA labs from different CRPs participated in the exchange of EuroDYNA students and postdocs.

Networking and Dissemination Activities

Topical Workshops

How we can benefit from each other

Impact of stress on the chromatin dynamics and global gene transcription in yeast and mammalian cells | 3 July 2006, Vienna, AU

Two of EuroDYNA's CRPs focusing on stress-induced global changes in gene expression in yeast and mammals respectively, came together to exchange techniques and reagents and to establish collaborations.

Establishing links with other European Projects

Chromatin-associated phosphorylation and dephorsphorylation | 18 - 20 January 2007, Vienna, AU

The workshop was dedicated to combine the systems biology experience of the EU-FP6 QUASI team with the experience of EuroDYNA groups for the development of novel approaches. This contributed to the submission of a joint article and joint grant proposal.

Activities across EUROCORES Programmes

Biologists meet physicists head on in 2006 and 2007

EuroDYNA – SONS brainstorming meetings | 4 December 2007, Lisbon, PT and 27 September 2006, Brussels, BE

ESF organised brainstorming meetings for investigators of the EUROCORES Programmes EuroDYNA and SONS (Self-organised Nanostructures) interested in, and working at the interface of molecular biology and physics. With biology becoming increasingly multidisciplinary ESF works to facilitate cross-disciplinary exchange. The meetings led to the introduction of short-term visits as networking activity for the EUROCORES Scheme at large and the submission of joint proposals.

RNAQuality establishes ties with EuroDYNA

Mini-Symposium on *RNA Biogenesis and Quality Control* | 18 September 2007, Aarhus, DK

The symposium was initiated to provide an efficient platform for establishing collaborations across CRPs within the RNAQuality Programme, as well as links to laboratories within the EuroDYNA Programme.

Workshop on *Structure and function of mRNP* | 4-8 August 2008, Aarhus, DK

This training workshop continued to foster links between RNAQuality and EuroDYNA. It involved PIs of both EUROCORES Programmes as lecturers. In addition, students from both the EuroDYNA and the RNAQuality network benefited from the event.

Networking and Dissemination Activities

Dissemination Events

International conference on *Telomeres and Genome Stability* | 30 August - 3 September 2006, Villars-sur-Ollon, CH

EuroDYNA was highlighted as sponsor of this international event. The visibility was further increased through the talk of EuroDYNA's Chair and poster presentations by EuroDYNA members.

Session on *Chromatin and Cell Cycle* at the ELSO meeting | 1 September 2007, Dresden, DE

Dissemination from the event:

- *At the ELSO meeting in Dresden in September 2007, members of the EuroDYNA community as well as invited speakers from the US and Canada came together for a EuroDYNA-organised session. On this occasion talks focused on the subject "Chromatin and the cell cycle" and the speakers covered everything from plant cells, via Drosophila cells to mammalian cells…*
- *Coling Logie, Chair of the EuroDYNA Scientific Committee, speaks about scientific achievements through the EUROCORES Programme EuroDYNA and his personal experience at the ELSO Conference, Dresden, Germany in September 2007…*

more at www.esf.org/eurodyna

A moment with Colin Logie

Colin Logie

A moment with Colin Logie

In a recent interview, Colin Logie, Chair of the EuroDYNA Scientific Committee, talks about organising the EuroDYNA session at ELSO and about future challenges for the cell biology field and for EuroDYNA.

Why did you choose the topic "Chromatin and the cell cycle" for the EuroDYNA session at ELSO?
Although we know a lot about the cell, DNA and chromatin, we still lack insight into how it functions. To understand how things function you have to put them into context. One thing about life is that it is cell based and one thing about cells is that they are always the product of the cell division of a previous cell. So, to really understand chromosomes we really have to understand how the chromosomes behave in the cell cycle. I think during the session we saw an example of very disparate talks ending up with conclusions about chromosomes which fitted together because they fit the context of the cell cycle as the common denominator.

What, in your opinion, are the challenges in your field?
One of the frontiers of this field is to really see what happens inside living cells. We have done many beautiful experiments in the recent past (by we, I mean the Scientific Community) but what we really need is multi-molecular assembly dynamics data. These things are very difficult to see at the moment and we really need to be able to see them to find out which factors are playing roles of messengers and which ones are playing more structural roles. Essentially it boils down to physically describing the isomerisations that take place in the cell, the DNA and also in the membranes. We also need to find ways of estimating the energetic code of each transaction and of integrating these types of data over multiple length scales from the nanometer to the micrometer. From this we should be able to formulate a mathematical description of biological systems.

What's also a big challenge is our ability to monitor things at the right timescale. We know that molecules function on the level of millions as well as thousands of a second and this spans six maybe even seven orders of magnitude. Right now we don't have good modelling systems to integrate all the data at those different time and length scales and I think that's a major challenge. It's not so complicated to address this. We need durable funding of scientific research; we need to maintain and sometimes also improve career opportunities, support institutes where innovation and originality are encouraged and promote communication amongst scientists. The latter is very important and something that ESF has been doing very well. We need communication between disciplines but also within disciplines.

What can the Scientific Community expect from EuroDYNA as a collaboration?
One field which is moving forward at the moment is nanoscience. By looking in great detail using biophysical methods on single molecules we are actually studying nanomotors which are driven by ATP. The exciting application for this is that maybe one day such motors can be harvested to produce DNA-based machines. EuroDYNA's contribution in this field involves what we are doing in defining the forces that are deployed by these motors. At the moment the physical description of biology is lagging behind but we are getting there now by finding forces, distances and time.

The full podcast with Colin Logie can be found on the EuroDYNA website at www.esf.org/eurodyna

The brains behind EuroDYNA

Niels Galjart

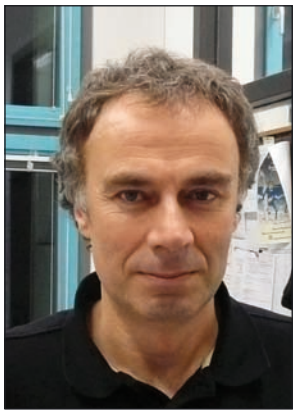
David Shore

EUROCORES is the European Science Foundation's flagship activity. It supports interdisciplinary research in non-traditional areas, thereby opening new horizons in science. With EuroDYNA, one of the EUROCORES Programmes, coming to an end, some of the Project Leaders have shared their experiences from the Programme with us.

"Thanks to EuroDYNA, nine research projects were funded that may otherwise not have been funded. Therefore, European research in the area of nuclear dynamics and architecture has been stimulated. Without EuroDYNA I would not have been able to perform the research I have carried out over the last three years. One aspect of EuroDYNA that I like a lot is the lack of bureaucratic burden compared to other research programmes. Another very important aspect is that the EUROCORES programmes are suggested by the scientists themselves (bottom-up approach). Finally, a great added value is the willingness at ESF to stimulate discussion among scientists, by organizing conferences, workshops and brainstorm meetings. As a EuroDYNA member I have benefited enormously from this valuable resource," said Niels Galjart, Department of Cell Biology and Genetics, Erasmus University, Rotterdam and the Project Leader of "Role of multi zinc finger proteins CTCF and BORIS in the dynamic change of the nuclear architecture and chromatin function during cell cycle and differentiation".

There is no doubt that EuroDYNA has achieved some great results and many of these results stem directly from the EUROCORES Programmes' focus on networking and collaboration. David Shore, University of Geneva and the Project Leader of "Environmental stress-induced dynamic modulation of chromatin structure, gene expression and nuclear architecture in yeast" commented, "My project recently entered into collaboration with a lab in Vienna. This wouldn't have happened if it weren't for EuroDYNA. The Vienna group is interested in understanding how arsenic affects cells and of course this has important global health implications. Arsenic is a pollutant in drinking water in many places in the world. Our collaboration began at a EuroDYNA meeting in Brno; we presented a gene we were working on that's involved in growth regulation in yeast cells and also in the cellular response to stress (which is what our project is aimed at understanding) when we were approached by a researcher from the Vienna group. The Vienna researcher noticed that this gene had also come up in his studies as a regulator of the cellular response to arsenic poisoning. As a result, we got together and did some more work which has now led to a manuscript ready for submission".

The brains behind EuroDYNA



Pavel Kovarik

René Ketting

EuroDYNA has been successful in generating new and exciting collaborations that have been hugely beneficial to the people involved. Now the scientists are focusing on what happens next. EuroDYNA is finishing but new collaborations have been set up.

"For me personally, the rather generous funding of the networking activities within EuroDYNA turned out to be very useful. Although I still maintain close links with the original members of my Collaborative Research Project (CRP), I have now made several links with members of other CRPs which are also relevant for my future research," said Pavel Kovarik, Vienna Biocenter Instititue of Microbiology and Genetics and the Project Leader of "Control of stress and interferon regulated gene expression by transcription factors, histone modification and nuclear compartmentalisation" during a recent interview.

This viewpoint is shared by René Ketting, Hubrecht Laboratory, Netherlands Institute for Developmental Biology and the Project Leader of "Nuclear actions of mRNAs". "I think scientific collaboration is essential. Many of my papers have resulted from collaborations that have been forged through meetings and exchange programmes. In my experience these collaborations are formed *de novo* on very different occasions, but a collective such as EuroDYNA is certainly a good catalyst for such interactions.

EuroDYNA is likely to have established new collaborations that will start to pay off in the future. I therefore think that the impact will not be limited to just the scientific progress that has been made during the funding period but will extend far beyond."

Find full profiles of these and other Project Leaders on the EuroDYNA website at www.esf.org/eurodyna

Cell biology of messenger RNA biogenesis

Abstract

Major events in the life cycle of a messenger RNA (mRNA) include transcription, splicing, 3' end processing, export from the nucleus to the cytoplasm, translation and degradation. These processes are intimately linked through proteins that bind to the mRNA in a specific and coordinated fashion. During the lifetime of an mRNA, the composition of associated protein complexes is under constant change. Through this Network the participating teams wish to study the dynamics of mRNA biogenesis making use of a wide range of multidisciplinary approaches. These include yeast genetics, molecular biology, structural biology, biochemical assays, proteomics, DNA microarrays, RNA interference, and live cell microscopy. The first Work Package of this proposal aims to dissect functional interactions between transcription initiation, RNA polymerase II, quality control and pre-mRNA processing events. The second Work Package is focused on the dynamics of pre-mRNA processing machines. The third Work Package aims to investigate the functional relevance of shuttling between the nucleus and the cytoplasm of proteins involved in mRNA biogenesis.

Partners

(FCT, FNU, SNF, NWO)

Prof Maria do Carmo-Fonseca (Project Leader)
University of Lisbon, Portugal

Dr Torben Heick Jensen
University of Aarhus, Denmark

Prof Walter Keller
University of Basel, Switzerland

Prof Jørgen Kjems
University of Aarhus, Denmark

Prof Angela Krämer-Bilbe
University of Geneva, Switzerland

Dr Ulrike Kutay
Swiss Federal Institute of Technology (ETH), Zurich, Switzerland

Dr Marc Timmers
University of Utrecht, The Netherlands

Role of multi zinc finger proteins CTCF and BORIS in the dynamic change of the nuclear architecture and chromatin function during cell cycle and differentiation

Abstract

The multi-zinc finger proteins BORIS and CTCF are unique and conserved factors with a role in transcriptional regulation, the organization of chromatin into distinct domains and imprinting. BORIS is expressed in the testis in cells that do not express CTCF. Abnormal upregulation of BORIS, on the other hand, may be linked to tumorigenesis. Thus, while binding to similar sites in the genome, these proteins could have distinct roles. We have generated inducible BORIS and CTCF knock out mice and are generating GFP- (or biotin)-tagged BORIS and CTCF knock in mice. From the inducible knock out mice cell lines have been isolated, which can be transfected with (mutant) multi-zinc finger proteins and/or DNA contructs with particular binding sites. Using these tools we will perform microscopic (live) imaging analysis (group Galjart), affinity purifications of biotin-tagged proteins (groups Galjart and Renkawitz) and structural analysis, like DNA loop formation (group Renkawitz) on the different types of mice, tissues and cells. This proposal aims at understanding the dynamic behaviour of both multi-zinc finger proteins during the cell cycle and the relevance of this behaviour and of these proteins for the maintenance of chromatin structure.

Partners

(DFG, NWO)

Dr Niels Galjart (Project Leader)
Erasmus University, Rotterdam, The Netherlands

Prof Rainer Renkawitz
Justus-Liebig-Universität, Giessen, Germany

Spatio-temporal organisation of genome surveillance in live cells

Abstract

Surveillance of the genome, which is vital for cellular function, cancer avoidance and many aspects of development, is comprised of a series of DNA repair and damage response pathways. Defects in damage surveillance result in severe genetic disorders. The mechanisms of these pathways are understood in varying degrees of detail, and the aim of this proposal is to understand the dynamics of the protein constituents within the cell nucleus before and after different DNA damaging treatments, as well as the inter-relationships between the different pathways. Normal and characterised mutant proteins tagged with GFP and its spectral variants, are either available from the participating laboratories or will be generated as part of the proposal. Motilities of the proteins are measured using variations of fluorescence recovery after photobleaching combined with whole cell or localised irradiation with either UV light or ionising radiation. The complementarity of the partners comes from their expertise in (1) different surveillance pathways and provision of tagged proteins; (2) advanced microscopic techniques; (3) delivery of different types of localised irradiation; (4) computer simulation. Through the integration of the different expertises, unique materials and reagents, and specialised equipment from the participating groups, the proposal forms a comprehensive and multidisciplinary approach to understanding the dynamics of genome surveillance in mammalian cells.

Partners

(DFG, FNU, MRC, NWO)

Dr Roland Kanaar (Project Leader)
Erasmus University, Rotterdam, The Netherlands

Prof Jiri Bartek
Institute of Cancer Biology, Copenhagen, Denmark

Prof Thomas Cremer
Ludwig-Maximilians Universität, Munich, Germany

Prof Günther Dollinger
Technische Universität Munich, Germany

Dr Anna A. Friedl
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Prof Jan H.J. Hoeijmakers
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Dr Adriaan Houtsmuller
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Prof Alan Robert Lehmann
University of Sussex, UK

Dr Jiri Lukas
Institute of Cancer Biology, Copenhagen, Denmark

Prof Leon H.F. Mullenders
University of Leiden, The Netherlands

Dr Wim Vermeulen
Erasmus University, Rotterdam, The Netherlands

Nuclear action of miRNAs

Abstract

Double stranded RNA (dsRNA) is potent inducer of gene silencing. The mechanism by which these molecules induce silencing is evolutionary conserved, and represents a very powerful and specific way of gene activity control. One of the intermediates of this silencing process is a short RNA(Srna) molecule that has been named short interfering RNA (siRNA) or micro RNA (miRNA). These molecules act as guides for either an RNA degradation enzyme that is active in the cytosol or a complex that targets translation inhibition. In addition to these cytosolic events, nuclear effects of dsRNA have also been observed. In plants, dsRNA leads to methylation of homologous DNA sequences, and induces transcriptional silencing when promoter DNA is targeted. In yeast, dsRNA mediated processes have been implicated in centromere function. In animals, evidence for such nuclear effects has been obtained as well. For example, phenotypes of C. elegans mutants defective in RNAi suggest an impaired centromere function, and partially overlap with phenotypes associated with defects in the maintenance of silent chromatin states. In this research proposal we aim at a better understanding of the nuclear effects of dsRNA. We will do this by analyzing nuclear dsRNA processing, by identifying nuclear sRNA, by analyzing proteins associating with the nuclear sRNA and by analyzing the effects of nuclear sRNA on chromatin modifications and transcriptional activity.

Partners

(NWO, FWF)

Dr René F. Ketting (Project Leader)
Netherlands Institute for Developmental Biology, Utrecht, The Netherlands

Dr Majori Matzke
Austrian Academy of Sciences, Vienna, Austria

Control of stress and interferon regulated gene expression by transcription factors, histone modification and nuclear compartmentalisation

Abstract

The precise regulation of gene expression in response to extracellular stimuli plays a key role in life and biological diversity. Specific transcription factors, general transcription machinery, histone modifying enzymes, chromatin remodeling complexes, as well as nuclear architecture all have roles in gene transcription. How these individual events are coordinated in time and space, and integrated into appropriate transcriptional responses is a challenging yet unresolved question. We will address this issue using as a model the transcription of stress and interferon regulated genes. Both signalling pathways can be activated by independent stimuli and may therefore be studied separately. However, under physiological conditions, the stress and interferon signalling cascades are often activated simultaneously resulting in enhanced transcriptional responses. This synergism is essential for defense against pathogens and in tumor surveillance. Our studies on the order, location and contribution of stress and interferon-induced changes in chromatin modification and nuclear architecture will improve our understanding of the regulation of gene expression and open up new possibilities to combat diseases, such as cancer and infections. The availability of cells and animals with specific genes of the stress and interferon pathways inactivated will enable us to test the working hypotheses under physiological conditions.

Partners

(FWF, GAČR)

Dr Pavel Kovarik (Project Leader)
Institute of Microbiology and Genetics, Vienna, Austria

Dr Pavel Hozák
Institute of Molecular Genetics, Prague, Czech Republic

The role of linker histone variants and their phosphorylation in chromatin structure and function

Abstract

The linker histones are known to contribute to the formation and maintenance of higher order chromatin structures but their physiological functions are still largely unknown. They display a complex pattern of variants and recent data suggest that they may have specific roles in epigenetic control of gene expression. The cell cycle dependent phosphorylation of certain serine and threonine residues in the charged tails of the linker histones is most probably of major importance in determining the architecture of chromatin during cell proliferation and differentiation, but the molecular details of this process are very unclear. Aberrant chromatin structure may contribute to malignant transformation and tumour formation. This project aims at elucidating these mechanisms by combining the expertise of Herbert Lindner's laboratory in Innsbruck and Jean Thomas' laboratory in Cambridge, in collaboration with Ingemar Rundquist's laboratory in Linköping. All three research groups have many years' experience in linker histone research and the laboratories complement each other well, offering a large range of methods and techniques in analytical chemistry, structural biology, biophysics, and cytochemistry. Together, these investigations should contribute to increased understanding of epigenetic mechanisms involved in chromatin architecture, regulation of cell growth and differentiation, and in malignant transformation and tumour progression.

Partners

(FWF, MRC)

Prof Herbert Lindner (Project Leader)
University of Innsbruck, Austria

Prof Jean O. Thomas
University of Cambridge, UK

Associated Partner:
Prof Ingemar Rundquist
University of Linköping, Sweden

Chromatin higher order dynamics: a single molecule approach

Abstract

Higher order structure of eukaryotic chromosomes is governed by protein/DNA interactions that mediate the folding of DNA into chromatin fibres. Chromatin fibre structure revolves around nucleosomes, the fundamental units of chromatin. SNF2 ATPases and histone modifying enzymes remodel nucleosomes and have been documented to play key roles in the generation, maintenance and alteration of the epigenetic code during the cell cycle and during ontogeny. We propose to study the influence of chromatin remodelling factors on the physical properties of chromatin fibres. To this end, fully recombinant model polynucleosomal arrays suited for physico-chemical characterisation will be generated. Second, defined prototypic chromatin remodelling activities will be purified in preparative quantities. Last, state-of-the-art single molecule magnetic tweezers and time-lapse Atomic Force Microscopy will be employed to rigorously investigate the physical properties and dynamics of chromatin higher order structural transitions catalysed by chromatin remodellers. With this combined multidisciplinary approach we expect to elucidate nucleosome mediated higher order chromatin structural transitions with an unsurpassed degree of resolution.

Partners

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The control of chromosome structure by cohesion/ condensin complexes

Abstract

All organisms possess sophisticated mechanisms to respond to environmental stress. The robust transcriptional response to osmostress in yeast works through a conserved MAP kinase signaling pathway that leads to a major reprogramming of the cell's transcriptional state. The MAPK Hog1 acts directly at a large number of promoters to induce expression of osmostress-reponse genes, while a less well understood mechanism(s) causes coordinate down-regulation of growth-related genes, such as those encoding ribosomal proteins. Our primary aim will be to characterize and elucidate mechanisms underlying the dynamic changes in chromatin structure and modification states that accompany both the induction and down-regulation of genes following osmostress, using chromatin immunoprecipitation as our standard experimental tool. We will also employ high throughput genetic screens and advanced biochemical methods to understand how the chromatin remodeling / modification machinery interacts with global and gene-specific transcription factors and how these interactions promote dramatic changes in transcription rates. Finally, advanced cell biological methods (e.g. FRAP) will be used to characterize the dynamic nuclear trafficking and chromatin association of specific transcription factors following osmostress. These studies should yield new and important insights into mechanisms by which chromatin modification is linked to highly dynamic changes in transcription and overall nuclear architecture.

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Environmental stress-induced dynamic modulation of chromatin structure, gene expression and nuclear architecture in yeast

Abstract

All organisms possess sophisticated mechanisms to respond to environmental stress. The robust transcriptional response to osmostress in yeast works through a conserved MAP kinase signaling pathway that leads to a major reprogramming of the cell's transcriptional state. The MAPK Hog1 acts directly at a large number of promoters to induce expression of osmostress-reponse genes, while a less well understood mechanism(s) causes coordinate down-regulation of growth-related genes, such as those encoding ribosomal proteins. Our primary aim will be to characterize and elucidate mechanisms underlying the dynamic changes in chromatin structure and modification states that accompany both the induction and down-regulation of genes following osmostress, using chromatin immunoprecipitation as our standard experimental tool. We will also employ high throughput genetic screens and advanced biochemical methods to understand how the chromatin remodeling / modification machinery interacts with global and gene-specific transcription factors and how these interactions promote dramatic changes in transcription rates. Finally, advanced cell biological methods (e.g. FRAP) will be used to characterize the dynamic nuclear trafficking and chromatin association of specific transcription factors following osmostress. These studies should yield new and important insights into mechanisms by which chromatin modification is linked to highly dynamic changes in transcription and overall nuclear architecture.

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University of Pompeu Fabra, Barcelona, Spain

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Scanning (Atomic) Force miscroscopy image of the SMClike protein complex RAD50/MRE11/NBS1, involved in the early cellular response to DNA double-strand breaks. The complex consists of a globular DNA binding domain and two protruding coiled-coil arms (50 nm in length) that are required to tether broken DNA molecules.

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