2016

A YEAR IN REVIEW

IFOM
FIRC INSTITUTE OF MOLECULAR ONCOLOGY

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About IFOM Review

The idea of publishing an annual report for the institute has been in the air for a very long time. However, we did not like producing every year a cold document highlighting our own results with plain scientific data.

Thus, we came to the conclusion that it would have been better to receive a sincere and frank opinion on our work from external colleagues and collect these commentaries in an editorial product.

Therefore, we consider the IFOM Review a chance for reflection on the progress of knowledge, moving from IFOM activities and results.

A special thanks goes to the authors who generously spent their time and energy to share their views on the progress and perspectives of our research.

Marco Foiani

Francesco Blasi

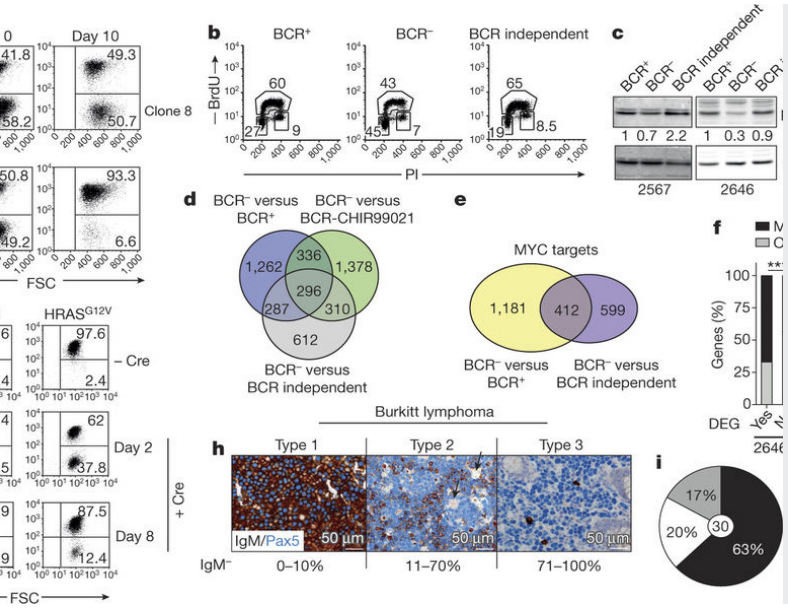
The authors:

Marco Foiani
Scientific Director

Prof. Foiani has a Ph.D. in Molecular Biology from the University of Milan (Italy).
Since 2002, Prof. Foiani, who is also Head of the Genome Integrity Laboratory at IFOM since its establishment, is Full Professor in Molecular Biology at the University of Milan.
His research interest focuses on the regulatory mechanisms that control genome integrity. Particularly, his work has contributed to elucidate the cellular mechanisms causing genome instability in cancer cells and chromosome abnormalities in certain human syndromes leading to cancer predisposition. Prof. Foiani has more than 80 papers published in international scientific journals.
Since 2008 Prof. Marco Foiani is the Scientific Director of IFOM.
Prof. Foiani was honored with internationally recognized memberships and awards, such as: the European Molecular Biology Organization membership; the Academia Europaea membership; the New York Academy of Sciences membership; the Italian Society of Genetics (AGI) membership; the Italian Society of Biophisics and Molecular Biology (SIBBM) membership; the Award from the Italian Society for Biophysics and Molecular Biology (SIBBM); the Biotec Award promoted by Amgen and Dompé; the "Chiara D'Onofrio" Prize from the Italian Federation of Life Sciences.
He was the founder in 2009 of the European Nanomedicine Foundation (CEN) and vice-president up to 2011.
He is also member of the Scientific Advisory Board of AIRC, the Italian Cancer Research Association, member of the editorial board of Cell and editor and reviewer for top impact factor scientific journals.

Francesco Blasi
IFOM Deputy Director

Francesco Blasi born in Naples, October 19, 1937.
MD from Naples University Medical School, then two post-Docs at the Max Planck Institut fuer Biophysik (Frankfurt, Germany) and NIH (National Institute of Arthritis and Metabolic Diseases) Bethesda, MD (U.S.A.).
In 1970 back in Italy at the CNR Research Center in the Naples University Medical School, then in 1980 Full Professor at the II Faculty of Medicine of the University of Naples.
Subsequently, Professor at the University of Copenhagen, Denmark and finally in Milano since 1992.
Is at IFOM since 2004, Director of research program Transcriptional Regulation in Development and Cancer.
From 2007 to 2011 coordinates the Molecular Oncology PhD program of SEMM. In 2011 becomes Deputy Director for Science of IFOM.
Has previously been Director of the International Institute of Genetics and Biophysics of CNR in Naples (1980-1983), of the Molecular and Cellular Biology Center in Copenhagen (Denmark), (1988- 1992), and of the Department of Cellular Biology and Functional Genomics (1998-2006) at DIBIT, Ospedale San Raffaele.
In 1979 is elected member of EMBO, the prestigious European Molecular Biology Organization, and 1991-1993 of its Council. Since 1992 is a member of Academia Europaea.
Has received national and international prizes and is Author of over 270 research articles in prestigious international Journals, including Nature and Cell.
Has been a member of the Advisory Board of AIRC, Associazione Italiana per la Ricerca sul Cancro, and of the Board of EMBO Journal.



Lymphomas: the backstage of the research that highlights their complexity and recommends the use of combined therapies

Commentary on Varano et al. "The B-cell receptor controls fitness of MYC-driven lymphoma cells via GSK3β inhibition", Nature 2017, 546:302-6.

by Klaus Rajewsky

Habent sua fata libelli - that's what came to my mind when I was asked to comment on the Varano et al. paper. In this case the special fatum is time scale and initial misfortune. The work started fifteen years ago, in 2002, in my laboratory at Harvard Medical School in Boston. A senior postdoc, Stefano Casola, and Simon Raffel, a German MD student, set out to explore whether what we had found for mature B cells in normal physiology also holds true for malignant B cells, namely that cellular survival depends on the expression of the B cell antigen receptor (BCR; Ref. 1). This was an important and therapeutically relevant question, and a clear answer came within a year or so, in the affirmative: In our mouse model of a MYC-driven B cell lymphoma complete cure was achieved when we inducibly deleted the BCR on the surface of the tumor cells in vivo! Fortunately we managed to stop publication of this spectacular result in a (very) high-ranking journal in the last minute: We had fallen into the trap of a technical artifact (2). And thus began the long and windy road towards the resolution of the problem. Still in Boston, Simon and Stefano showed that, surprisingly, in isolation BCR-negative lymphoma cells proliferated nearly as well as their BCR-positive counterparts; and that BCR-positive cells outcompeted BCR-negative cells in a variety of conditions. At that point Simon had to leave for his home university in Heidelberg, and in 2006 Stefano accepted a PI position at the IFOM in Milano. He built up his lab, hired students, wrote grants and embarked on numerous projects – but never gave up on studying the BCR dependency of B cell lymphomas, about which we continued to discuss. In the meantime the subject became popular and gained practical relevance, because B cell lymphoma therapies targeting the BCR signaling cascade were on the rise. They were not only in line with evidence from mouse models, but also directly supported, indeed suggested, by genetic experiments addressing the "Achilles heel" of human lymphoma cells in vitro (3).

The painstaking experiments carried out in the Casola lab (Varano et al.) on the competition of BCR-positive and –negative MYC-driven lymphoma cells in mice add a new perspective to

the multiple roles that BCR signaling presumably plays in transformed B cells. They suggest scenarios like that of human Burkitt lymphoma, where BCR expression impacts the fitness of the tumor cells in their competition with tumor cells that have lost the BCR. However, while the competitive advantage of the BCR-positive cells is indeed dramatic, variants of BCR-negative cells arise spontaneously and rapidly, often through RAS-mediated MAP kinase activation. The amazing efficiency of this process may be due to the surprising finding that BCR-mediated competitive fitness seems to critically depend on a single signaling pathway, namely PI3K/AKT dependent GSK3b inactivation, promoting MYC activity. Thus, therapeutic strategies targeting the BCR signaling cascade in B cell lymphomas may profit from complementary drugs targeting BCR loss variants. Note in this context that B cells are always in danger of losing BCR expression, given the mechanism of somatic hypermutation operating in these cells on antibody variable region genes to increase antibody affinity during antibody responses.

Beyond these translational considerations, the work of Varano et al. exemplifies the fundamental role of cellular competition in multicellular organisms in general and in our immune system in particular. To which extent and how wild type cells outcompete or actively eliminate spontaneously arising unwanted mutants, and whether such processes mainly apply to cancer pathogenesis or also operate in normal physiology remains a vast area for future research. Indeed, in the case of the B cell system it is striking that the central pathway controlling BCR-dependent lymphoma cell competitive fitness, namely PI3K signaling, has also been shown to control the survival and proliferation of normal B cells at various developmental stages, including that of the mature resting B cell (4).

Acknowledgements: I am grateful to Christine Kocks for critical reading.

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The B-cell receptor controls fitness of MYC-driven lymphoma cells via GSK3β inhibition

Similar to resting mature B cells, where the B-cell antigen receptor (BCR) controls cellular survival, surface BCR expression is conserved in most mature B-cell lymphomas. The identification of activating BCR mutations and the growth disadvantage upon BCR knockdown of cells of certain lymphoma entities has led to the view that BCR signalling is required for tumour cell survival. Consequently, the BCR signalling machinery has become an established target in the therapy of B-cell malignancies. Here we study the effects of BCR ablation on MYC-driven mouse B-cell lymphomas and compare them with observations in human Burkitt lymphoma. Whereas BCR ablation does not, per se, significantly affect lymphoma growth, BCR-negative (BCR-) tumour cells rapidly disappear in the presence of their BCR-expressing (BCR+) counterparts in vitro and in vivo. This requires neither cellular contact nor factors released by BCR+ tumour cells. Instead, BCR loss induces the rewiring of central carbon metabolism, increasing the sensitivity of receptor-less lymphoma cells to nutrient restriction. The BCR attenuates glycogen synthase kinase 3 beta (GSK3β) activity to support MYC-controlled gene expression. BCR- tumour cells exhibit increased GSK3β activity and are rescued from their competitive growth disadvantage by GSK3β inhibition. BCR- lymphoma variants that restore competitive fitness normalize GSK3β activity after constitutive activation of the MAPK pathway, commonly through Ras mutations. Similarly, in Burkitt lymphoma, activating RAS mutations may propagate immunoglobulin-crippled tumour cells, which usually represent a minority of the tumour bulk. Thus, while BCR expression enhances lymphoma cell fitness, BCR-targeted therapies may profit from combinations with drugs targeting BCR- tumour cells.
[PMID 28562582]

Genetics of B Cells and Lymphomas
Stefano Casola

Lymphomas: the backstage of the research that highlights their complexity and recommends the use of combined therapies

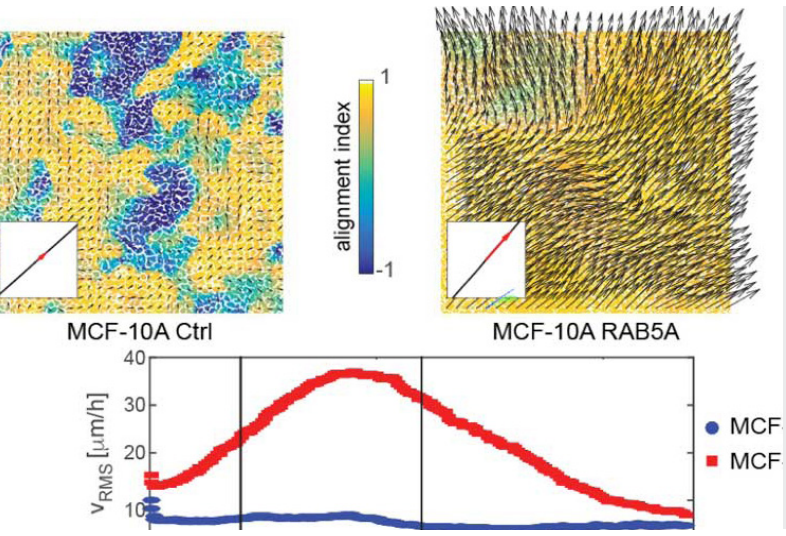
The author:

Klaus Rajewsky
Max-Delbrück-Center for Molecular Medicine, Berlin

Klaus Rajewsky developed a general method of targeted mutagenesis in mouse embryonic stem cells by introducing bacteriophage- and yeast-derived recombination systems, which opened the way for conditional gene targeting. Using this and other methods in his immunological work, he developed, together with N. A. Mitchison and N. K. Jerne, the antigen-bridge model of T-B cell cooperation, identified germinal centers as the sites of antibody somatic hypermutation, the B cell antigen receptor as a survival determinant of B cells, and the germinal center as a major site of human B cell lymphomagenesis, including Hodgkin lymphoma. Over the last years the work of his group has focused on mechanisms of microRNA control and the development of mouse models of human B cell lymphomas.

After postdoctoral work at the Institut Pasteur in Paris he built an immunology department at the Institute for Genetics at the University of Cologne, where he stayed for 38 years, was the founding Program Coordinator of the EMBL Mouse Biology Program at Monterotondo near Rome, worked for 10 years at Harvard Medical School in Boston, and is since 2012 at the Max-Delbrück-Center for Molecular Medicine in Berlin, Germany.

Klaus Rajewsky won numerous scientific awards and is a member of several learned societies including the National Academy of Sciences of the USA and the American Academy of Arts and Sciences.



Be still like a mountain and flow like a river: The role of endocytosis in the control of collective epithelial movements

Commentary on Giorgio Scita paper's published in Nature Material

by Aldo Ferrari

For several years biologists have studied the migration of mammalian cells as individual entities placed at the centre of a microscope spotlight. These fundamental investigations led to the establishment of a universally-accepted model for mesenchymal migration valid for all cells adhering to a substrate. Cells advance through repeated cycles of polarized membrane protrusion, new focal adhesion assembly, actomyosin contraction, translocation of the nucleus, and old adhesion disassembly1. This model provided a platform to reveal the signalling pathways involved in the regulation of motility and a reference to detect alternative migration schemes such as those appearing in cancer or immune cells. Yet, as much as they tend to be refractory to any stereotyped model, mammalian cells rarely find themselves isolated in the body. In particular, epithelial cells provide a beautiful example of a functional community, that is an ensemble working for a common purpose.

Single epithelial cells behave and migrate according to the mesenchymal scheme. However, as soon as they attain a sufficient density, their dynamics starts to change, migration velocity decreases and coherent, multicellular movements appear. Cells now reach confluency, which literally means 'flowing together', a prerequisite for the generation of differentiated, functional epithelia. The phase transition from a gas-like moving group of individual cells to a liquid-like flowing collective is enabled by the establishment of connections between cells, the cell-to-cell junctions, which form supra-cellular mechanical structures. As cell density further increases, collective movements become restricted by the crowding and the monolayer experiences a further transition to a solid-like, jammed phase identifying a quiescent monolayer. This final transition is however reversible, as in various cases epithelial monolayers reactivate collective motility, in order to heal a wound, to execute development, or to descend the path of neoplastic transformation2. This entire complexity goes far beyond what we have learnt for single cell motility. To study this exciting phenomena a new access is needed.

The work led by Prof. Scita, to which I had the pleasure to collaborate, introduces a novel approach which exploits synergies from the fields of biology, engineering, and physics, to provide a multiscale comprehension of epithelial un-jamming3. It all started from the observation that the upregulation of RAB5A, a master regulator of endocytosis, is alone sufficient to reactivate collective motility in quiescent epithelia. At this point the reader should watch the truly amazing

videos accompanying the publication. But how to link a boost in endocytosis to the reactivation of multicellular dynamics?

Overexpression of RAB5A has no impact on the motility of isolated MCF-10A cells. RAB5A-mediated un-jamming is therefore a typical emerging trait of epithelial collectives. On the other hand, the upregulation of endomembrane trafficking in an epithelial monolayer increases the intensity of traction forces transmitted to the substrate and the related junctional tensions. This translates into more motile cells, which in a crowded environment can rapidly align membrane protrusions and propelling forces to generate actual movements. In these flowing monolayers, cell-generated forces are efficiently converted into collective motion over large areas whereas in the jammed counterpart, cells are stuck in a thug of war which allows for little movement despite the applied force.

With the support of physical modelling, this entire new set of information could be implemented to an in silico representation setting the minimal parameters required to describe the observed phase transitions in epithelial dynamics. Cell density and shape, together with the efficiency to align force and motion, provide a predictive environment that captures un-jamming as well as other multicellular phase transitions altogether forming a typical phase diagram for an active material. This work provides evidence that endocytosis can drive one of such phase changes by perturbing critical parameters and thus impinging in the dynamic control of multicellular motility.

Improved wound healing efficiency and faster accomplishment of morphogenetic movements in the zebrafish embryo are among the biological consequences of RAB5A-mediated epithelial un-jamming. Endocytic reawakening of motility also supports behaviours typically observed in cancers, without the requirement of more complex genetic changes subtending epithelial to mesenchymal transition.

Endocytic reawakening of motility in jammed epithelia.
Dynamics of epithelial monolayers has recently been interpreted in terms of a jamming or rigidity transition. How cells control such phase transitions is, however, unknown. Here we show that RAB5A, a key endocytic protein, is sufficient to induce large-scale, coordinated motility over tens of cells, and ballistic motion in otherwise kinetically arrested monolayers. This is linked to increased traction forces and to the extension of cell protrusions, which align with local velocity. Molecularly, impairing endocytosis, macropinocytosis or increasing fluid efflux abrogates RAB5A-induced collective motility. A simple model based on mechanical junctional tension and an active cell reorientation mechanism for the velocity of self-propelled cells identifies regimes of monolayer dynamics that explain endocytic reawakening of locomotion in terms of a combination of large-scale directed migration and local unjamming. These changes in multicellular dynamics enable collectives to migrate under physical constraints and may be exploited by tumours for interstitial dissemination.
[PMID 28135264]

Altogether this paper introduces several conceptual and methodological innovations, beyond the definition of a novel biological role for RAB5A and endocytosis. From now on we shall consider epithelial monolayers as active materials which are to be studied with a combination of methods from engineering, physics, biology and medicine.

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Be still like a mountain and flow like a river: The role of endocytosis in the control of collective epithelial movements

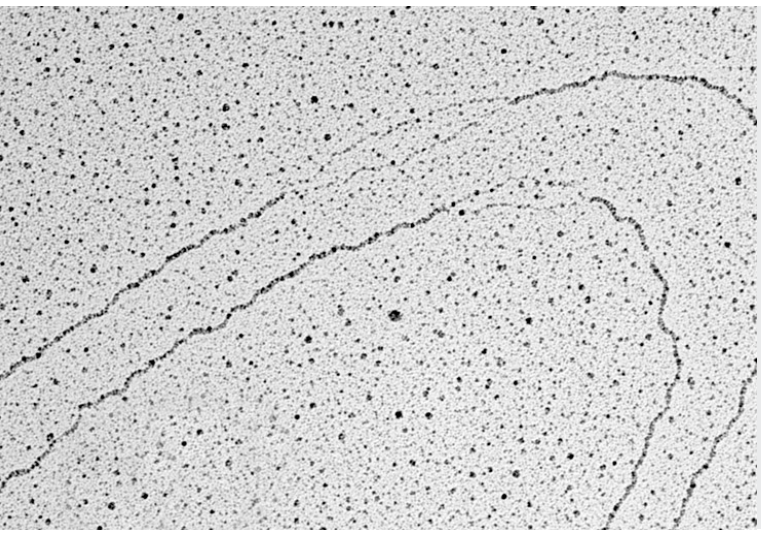
The author:

Aldo Ferrari

Aldo Ferrari studied biology at the University and Scuola Normale Superiore of Pisa. He was then selected for a PhD in Physics at the Scuola Normale Superiore in the laboratory of Prof. Fabio Beltram, where he developed mutants of the green fluorescent protein (GFP) for single molecule applications in cell biology and virology. In 2004 he moved to ETH Zurich for a PostDoc in Biochemistry where he applied a combination of physical modelling and live cell fluorescent analysis to investigate lumen formation during epithelial morphogenesis.

In 2007 he went back to Scuola Normale Superiore as research scientist in mechanobiology and material interfaces. During this period he acquired knowledge in material science and engineering fabrication and their application to the study of fundamental biological questions in physiology and development. Since 2009 he is back to ETH Zurich, where he is currently leading a group of Biothermofluidics in the department of Mechanical Engineering. The main activities of the group are in the development of active interfaces supporting the establishment and maintenance of endothelial monolayers, the investigation of interstitial migration of cancer cell using nanofabricated obstacles, and the definition of new protocols for traction force microscopy. In addition, since 2014 he is CTO and head of R&D of the ETH start-up company HYLOMORPH AG commercializing a platform technology to protect body implants from fibrotic encapsulation.

At ETH, Aldo is organizing yearly classes in ‘Mechanobiology’ and ‘Energy Conversion and Transfer in BioSystems’ and serves as editor for Scientific Reports and Frontiers in Biomaterials. He co-organises the international symposium ‘NanoEngineering for Mechanobiology’ which will see its third edition in 2018.



Replicating repeats: the checkpoint turns a blind eye

Commentary on Vincenzo Costanzo paper's published in Nature Cell Biology

by Óscar Fernández-Capetillo

We humans have a difficult time reading through texts with complicated character sequences and frequently stutter. A similar problem is faced by DNA Polymerases when they try to make a copy of DNA. Anyone with a bit of experience in Molecular Biology is well aware of this problem as amplifying repeated sequences by PCR is often problematic and leads to either failure of the reaction or to the presence of errors in the amplified copy. These problems observed in vitro, are nothing else but a recapitulation of the same problem that cells experience every S phase when trying to duplicate repetitive DNA.

While the key to cellular functions lies in genes, only 5-10% of our genome is made of genes or functional elements. The rest, frequently called as "dark-matter", is to a large extent filled with repetitive sequences including leftovers of viral integrations, transposable elements and alike. Recent estimates indicate that up to two-thirds of the human genome may be present in the human genome. Interestingly, even if repeated sequences comprise most of our genome, they are often neglected in biomedical research studies, in part due to the technical difficulties in working with them. A paradigmatic example are most Next Generation Sequencing datasets, where the analysis starts by excluding repeated sequences since they cannot be mapped to a defined position in the human genome.

While the majority of the repetitive sequences might be non-functional and simply represent scars of past integrations of exogenous DNA, some of them play central roles in cellular biology such as telomeres, centromeres or ribosomal DNA. Consistent with the difficulties that DNA polymerases face during the replication of repetitive sequences, many of them are actually considered "fragile sites". The instability of ribosomal DNA is well known particularly from yeast studies, and has been even associated to the process of ageing. Telomeres have also recently been found to be fragile, and they contain a unique dedicated pathway to complete their replication. To what extent the replication of other repeats, including centromeres or rDNA, also demands ad-hoc machinery, remains unknown.

To tackle this problem, the group of Vincenzo Costanzo took an original approach that exploited the usefulness of frog oocyte extracts to replicate exogenous DNA. Antoine Aze and colleagues explored how Bacterial Artificial Chromosomes (BACs) containing repeats from human centromeric alpha-satellite sequences were replicated in these extracts, and compared it to the replication of BACs containing a similar GC base content but free of repeats. Their strategy proved to very useful as it yielded important insights into the replication or centromeric DNA.

The first cool observation was that human BACs added to Xenopus extracts form a nucleus, similar to the endogenous one. The BAC containing centromeric repeats (cenBAC) was then replicated, albeit more slowly than the control BAC (cBAC). Subsequent proteomic analysis identified proteins that were enriched (or depleted) from the replicating BACs. These analyses revealed that cenBACs presented a higher presence of DNA repair factors, which might be there as a consequence of DNA breaks arising during DNA replication, or perhaps are already there in a preemptive position "just in case" breaks do happen. Particularly enriched were components of the Mismatch Repair machinery, which would make sense since these factors travel with the replisome to correct mistakes placed by DNA polymerases. It is also possible, however, that the increase in MMR proteins simply reflects a higher amount of replisomes in the cenBACs, which could be due to the more frequent stalling of the replication forks. Other factors enriched in replicating cenBACs were proteins involved in chromosome architecture and topology such as Topoisomerases or components of SMC complexes, likely due to the particular topology of centromeric chromatin.

A surprise, however, was to find that several components from the replication checkpoint were depleted from cenBACs. In vertebrates, the S phase checkpoint is coordinated by the ATR kinase. The activation of ATR is mediated by the ssDNA-binding factor RPA, which together with the recruitment of additional factors such as the allosteric activator TOPBP1, trigger the kinase activity of ATR. In other words, what

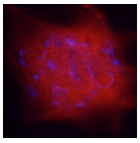
Centromeric DNA replication reconstitution reveals DNA loops and ATR checkpoint suppression.
Half of the human genome is made up of repetitive DNA. However, mechanisms underlying replication of chromosome regions containing repetitive DNA are poorly understood. We reconstituted replication of defined human chromosome segments using bacterial artificial chromosomes in Xenopus laevis egg extract. Using this approach we characterized the chromatin assembly and replication dynamics of centromeric alpha-satellite DNA. Proteomic analysis of centromeric chromatin revealed replication-dependent enrichment of a network of DNA repair factors including the MSH2-6 complex, which was required for efficient centromeric DNA replication. However, contrary to expectations, the ATR-dependent checkpoint monitoring DNA replication fork arrest could not be activated on highly repetitive DNA due to the inability of the single-stranded DNA binding protein RPA to accumulate on chromatin. Electron microscopy of centromeric DNA and supercoil mapping revealed the presence of topoisomerase I-dependent DNA loops embedded in a protein matrix enriched for SMC2-4 proteins. This arrangement suppressed ATR signalling by preventing RPA hyper-loading, facilitating replication of centromeric DNA. These findings have important implications for our understanding of repetitive DNA metabolism and centromere organization under normal and stressful conditions.
[PMID 27111843]

the checkpoint first “smells” is actually the accumulation of ssDNA at stalled replication forks. In this context, and as readily imagined by the Costanzo team, one mechanism to explain why checkpoint factors could be depleted from centromeric DNA is that the abundance of ssDNA is somewhat limited at these sequences. And this is exactly what they found.

Using another technique mastered by their team, Electron Microscopy, Aze and colleagues found that replicating cenBACs were full of looped sequences. The most parsimonious interpretation is that when the double helix opens up during DNA replication, the repetitive nature of the sequences will lead to their spontaneous formation of loops and other sort of secondary structures, thus occluding the presence of ssDNA and the activation of the checkpoint. In support of this, the use of Topoisomerase I inhibitors reduced the presence of supercoils and restored checkpoint activation in centromeric DNA.

The story is round and provides one of the first examples and initial insights as to how centromeric DNA is replicated. The discovery that the checkpoint is somewhat silenced at this region is surprising, but makes sense from an evolutionary point of view. ATR activates the alarm when DNA replication problems occur, leading to cellular consequences that can include the activation of apoptosis. Since repetitive sequences will always face problems during their replication, one could envision that the bar to activate the checkpoint should be a bit higher at these regions. In other words, the checkpoint needs to turn a blind eye at repetitive regions.

Finally, as any important study, this work also brings to mind many new questions that could be now tackled. For instance, what about the new and uncharacterized factors that were found in the proteomic studies as enriched in replicating cenBACs? Is it possible that, like in telomeres, the replication of centromeres also uses specialized machinery? Additionally, the group could also exploit this system to address additional questions about centromere replication. I am a good friend of Vincenzo, who I consider one of the most original scientists from our field. I still remember one of our conversations where he told me that he believes that Homologous Recombination factors are not essential in yeast, but yes in mammals, due to the higher presence of repeats in the mammalian genome. I have always liked the idea! They now have the opportunity to address this experimentally. To start with, they could simply explore how the depletion of HR proteins affects the replication of repetitive DNA. Anyway, from what I know of the team, I am sure that I cannot really predict what will be next from their lab. What I do know is that it will help all of us to understand a bit more how life works.



DNA Metabolism
Vincenzo Costanzo

Replicating repeats: the checkpoint turns a blind eye

The author:

Óscar Fernández-Capetillo
Department of Biological Regulation

Óscar Fernández-Capetillo (Bilbao,1974) obtained his PhD from the Universidad del País Vasco working on the role of E2F transcription factors on the development of the immune system with A. Zubiaga.He then joined the laboratory of A. Nussenzweig at the National Cancer Institute, USA, where he started to work on the cellular response to DNA damage (DDR), focusing particularly on the role of the histone variant H2AX and other chromatin-related aspects. After three years at the NCI he joined the CNIO to lead the Genomic Instability Group where his work has continued to focus on chromatin but now mainly concentrates on developing cellular and animal tools for studying the role of the ATR/Chk1 signalling cascade in the protection against cancer and ageing. Since 2016 Oscar is also a Professor of Cancer Therapy at the Karolinska Institute in Sweden.

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Corporate profile

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