

2014

A YEAR IN REVIEW

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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





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 Biophysics

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.

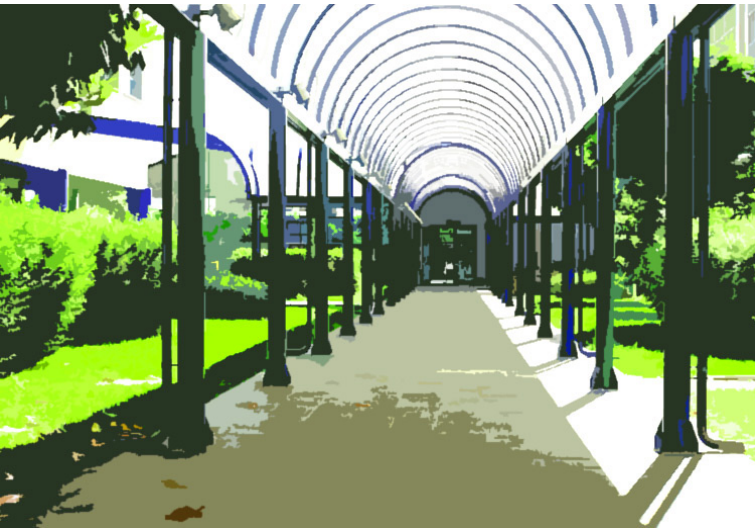
From 2007 to 2011 coordinates the Molecular Oncology PhD program of SEMM. In 2011 becomes Deputy Director for Science of IFOM.

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.



Interdisciplinarity, transnationality and competitiveness

Tomas Lindahl's commentary for IFOM Review 2014

by Tomas Lindahl

It was in 2010, ten years after they initiated their scientific program, that IFOM first asked me to organize and chair their Scientific Advisory Board. The institute had traced three lines of development: interdisciplinarity, transnationality and competitiveness.

The year 2014 has been a very representative year in terms of progress toward concrete implementation of these policy goals. After launching Joint Research Labs in Singapore with A*STAR in 2011 and in Bangalore, India with NCBS and inSTEM in 2012, indeed 2014 has seen the launch in May of a new international partnership with the Mechanobiology Institute (MBI) at the National University of Singapore in Singapore, resulting in a “Joint Research Laboratory” under the direction of Professor GV Shivashankar, Deputy Director of MBI. This project fully reflects the principle of interdisciplinarity: the collaboration aims to develop an approach to cancer research by augmenting molecular biology with technologies and methods developed in such fields as mathematics, physics, engineering,

and computational biology. The Joint Research Laboratory focuses on understanding the molecular mechanisms driving the formation and development of tumors.

As part of the institutional and scientific collaboration with NCBS-inSTEM in Bangalore, a pioneering training project launched by IFOM with the University of Milan has been consolidated in 2014. This program allowed outstanding students at the University of Milan to conduct thesis work in the Bangalore laboratories for a period of one year. Students have brought back to Italy this precious professional and social learning experience.

Periodic evaluation of IFOM scientific activities by our Scientific Advisory Board have revealed the overall high scientific quality of IFOM research groups, confirming the effectiveness of this monitoring methodology similar to that of international research centers comparable to IFOM. The triennial review on progress at the IFOM-A*STAR Joint Research Lab directed by Cheok Chit Fang was conducted on March 26,

2014 in Singapore. The review was successful and the collaboration with A*STAR has been confirmed for a further three years.

Promising and innovative new research programs were launched in 2014, each shared with prestigious international research institutions: one program focuses on the correlation between longevity and cancer and is led by Valter Longo, Biogerontology Professor and Director of the Institute on Aging at the University of Southern California (USC) - Davis School of Gerontology in Los Angeles, the world's foremost center for research in this field. Over the years, Longo's scientific approach has revealed several genetic mechanisms involved in aging, identified therapeutic and preventive strategies to counteract the development of cancer and other serious diseases and revealed the crucial role of caloric restriction in countering the effects of aging.

Another program initiated in 2014 is the IFOM-MBI Joint Research Laboratory led by G.V. Shivashankar, Deputy Director of the Mechanobiology Institute (MBI) at the National University of Singapore. As explained above, the collaboration aims to understand the effects of constraints to cell geometry on nuclear mechanisms and genome regulation in living cells. Using an interdisciplinary approach that combines mechanical experiments with high-resolution imaging of cells in vivo, the laboratory investigates the biophysical principles underlying the link between signals from cell geometry to the nucleus and their impact on gene regulation. In recent years, Shivashankar's laboratory has led the field by providing a quantitative framework for understanding the modular links between nuclear mechanisms and chromosomal organization in the regulation of genetic information.

The election of Giorgio Scita as Member scientist of the European Molecular Biology Organization (EMBO) brought much satisfaction. The EMBO made the announcement on May 2014, citing Scita's high-level scientific contributions in molecular oncology. He was elected along with 105 other scientists from 17 European and some non-European countries. Only five Italian scientists were nominated.

With this appointment, Giorgio Scita figures among the 1600 Scientists selected by EMBO in the international scientific community, including 100 operating in Italy. Among these, five scientists in addition to Scita conduct their research at IFOM: Francesco Blasi, Fabrizio d'Adda di Fagagna, Elisabetta Dejana, Pier Paolo Di Fiore and Marco Foiani.

In July 2014, the Italian Ministry of Health appointed Elisabetta Dejana to the High Council on Health, as President of the Second Section (Concerning requirements for health facility accreditation, quality, local health authorities and hospitals, health professions and training, blood, blood derivatives and transplants).

In November 2014, on the occasion of its 412th academic year, the Accademia Nazionale dei Lincei awarded Dejana the 2014 "Antonio Feltrinelli Prize". The Commission unanimously awarded the Prize - destined for Molecular and Cellular Pathology, Oncology, Immunology, Microbiology and Medical Genetics - to Professor Dejana for her brilliant career and her many discoveries in the field of angiogenesis and, in particular, for her studies on the pathogenesis and experimental treatment of Cerebral cavernous Malformation, considered to be of great relevance and importance.

All these results confirm IFOM as a leading international Institute for research on cancer.



Interdisciplinarity, transnationality
and competitiveness

The author:



Tomas Lindahl

Emeritus Director of Cancer Research UK, Clare Hall Laboratories

Tomas Lindahl completed medical studies at the Karolinska Institute in Stockholm and has consistently been active in research. He worked as a post-doctoral fellow on nucleic acid biochemistry with J. Fresco at Princeton and G. Edelman at Rockefeller University, joining the faculty of the Karolinska Institute in 1969.

He became Professor of Medical Chemistry at the University of Gothenburg in 1978. In 1981 he was appointed Head of the Mutagenesis Laboratory at the ICRF Mill Hill Laboratories in London. From 1984 to 2006 he was Director of the Clare Hall

Laboratories at ICRF and Cancer Research UK, also serving as Deputy Director of Research. Amongst many distinctions, Tomas Lindahl is a member of EMBO, a fellow of the Royal Swedish Academy of Sciences, and the Royal Society, London. He was the Royal Society Croonian Lecturer in 1996 and received a Royal Medal in 2007, INSERM Prix Etranger in 2009, and the Copley Medal in 2010 of the Royal Society.

He has received honorary doctorates from the Universities of Gothenburg, Oslo, Sheffield, and Sussex. He is now Emeritus Director of Cancer Research

UK, Clare Hall Laboratories, and involved in various scientific activities.

Visiting Professor of the Chinese Academy of Science 2009 - 2012
2010 – Scientific Advisor, Beijing Inst. of Genomics
2010 - Scientific Advisory Board, IFOM Milan
2010 - Scientific Advisory Board, Cancer and Ageing Centre, University of Nice, France
2010- Hon. Professor in Medical Oncology, University of Sheffield.



Drug repositioning A rapid and economic alternative to 'traditional' drug development

The case of cavernomas and an old chemotherapeutic that the industry was phasing out of production

by Francesco Brancati

Milan – The first was thalidomide, a drug used against morning sickness in pregnancy, that was responsible for more than 20,000 birth defects worldwide in the late 50's. A controversial banned drug, for which even recently there was talk of reparations for victims. But its 'rehabilitation' had already begun in 1992 with the news from a study published in *Lancet* that it is useful as treatment for *Lupus Erythematosus*. This story was soon followed by many others. News agencies began reporting on new published clinical studies: 'Delays the development of AIDS' ('93); 'might be useful against blindness' ('94); 'Thalidomide returns as therapy for myeloma' ('99).

The case of thalidomide is perhaps the first striking example of 'drug repositioning', or the use of known medications to treat diseases other than those for which they were designed. This re-proposal for different indications drew much attention in the international press because of the scandal surrounding its teratogenic effects.

The press was very attentive to these facts, especially since even before being scientific news,

reviving a drug created to cure one disease and using it against another is itself 'news'. Simple like that. Adding that the drug was banned because it is teratogenic, only increases interest in the story.

A chemotherapeutic for treating cavernomas - Elisabetta Dejana and the role of the media

How do you proceed if the old drug was abandoned and no one wants to produce it now, even though it could save lives? In Italy, about 300,000 people are affected, and 25-30% is children and adolescents under 20 years old. This is the case of one derivative of a cancer drug that was abandoned by the manufacturer, off-patent and off the market for years, and then 're-tested' on laboratory mice by IFOM researchers led by Elisabetta Dejana. It has now given new hope to people with CCM (Cerebral Cavernous Malformations, also called cavernomas), by demonstrating that it can reduce brain lesions caused by the disease. In this case 'repositioning the drug' met an additional obstacle: the pharmaceutical company that had produced it and then withdrawn it said 'No'. Putting it back into production "was not profitable enough."

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Elisabetta Dejana conducted a battle on several fronts that, helped by the ‘clamour’ raised by the Italian National Associated Press Agency (ANSA) and the Media including the Association of Journalists reporting on Health and Research (UNAMSI), has managed to start convincing an Italian pharmaceutical company to give new life to this old drug, moving it even closer to clinical trials. “It was a excellent example – wrote Elisabetta Dejana – of how high quality Media reporting can make an important positive contribution to the success of biomedical research.”

‘Traditional’ development of a drug can cost 4.6 billion dollars

But ‘Drug Repositioning’ is still a winning strategy that has been very successful in recent years mainly because it has enormous advantages over the creation of new drugs. Today development of a drug requires at least 10-15 years of studies and experiments, not to mention controls by regulatory authorities, with costs in the order “of \$4.6 billion,” according to Tim Wright, Global Head of Development in the Swiss multinational Novartis. These enormous sums are reflected in the final drug cost and inevitably cause problems for universal health systems (such as the Italian system) that guarantee health care to all citizens. The amount of time required is also impracticable, considering that the FDA approves no more than thirty medicines per year.

In this bleak landscape, investigating the molecular mechanisms involved in the onset of a disease (today quite possible) and discovering that a drug has already been developed and approved, albeit with different indications, may be the solution to all these problems: it reduces both time and costs... drastically.

EndMT contributes to the onset and progression of cerebral cavernous malformations.

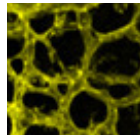
Cerebral cavernous malformation (CCM) is a vascular dysplasia, mainly localized within the brain and affecting up to 0.5% of the human population. CCM lesions are formed by enlarged and irregular blood vessels that often result in cerebral haemorrhages. CCM is caused by loss-of-function mutations in one of three genes, namely CCM1 (also known as KRIT1), CCM2 (OSM) and CCM3 (PDCD10), and occurs in both sporadic and familial forms. Recent studies have investigated the cause of vascular dysplasia and fragility in CCM, but the in vivo functions of this ternary complex remain unclear. Postnatal deletion of any of the three Ccm genes in mouse endothelium results in a severe phenotype, characterized by multiple brain vascular malformations that are markedly similar to human CCM lesions. Endothelial-to-mesenchymal transition (EndMT) has been described in different pathologies, and it is defined as the acquisition of mesenchymal- and stem-cell-like characteristics by the endothelium. Here we show that endothelial-specific disruption of the Ccm1 gene in mice induces EndMT, which contributes to the development of vascular malformations. EndMT in CCM1-ablated endothelial cells is mediated by the upregulation of endogenous BMP6 that, in turn, activates the transforming growth factor- β (TGF- β) and bone morphogenetic protein (BMP) signalling pathway. Inhibitors of the TGF- β and BMP pathway prevent EndMT both in vitro and in vivo and reduce the number and size of vascular lesions in CCM1-deficient mice. Thus, increased TGF- β and BMP signalling, and the consequent EndMT of CCM1-null endothelial cells, are crucial events in the onset and progression of CCM disease. These studies offer novel therapeutic opportunities for this severe, and so far incurable, pathology. [PMID 23748444]



A Japanese study and an IFOM research project

A recent Japanese study published this February in *ScientificWorldJournal* (*Drug repositioning for gynecologic tumors: a new therapeutic strategy for cancer*), summarizes the repositioning of several drugs, such as anti-diabetic metformin, effective for endometrial cancer, or anti-inflammatory COX-2 inhibitors that have shown effects in cervical cancer. The study's authors point out that "the use of 'repositioned' drugs in combination and current cancer drugs, can increase efficacy and reduce adverse reactions. Thus, the repositioning of a drug – they concluded - can become a fundamental method for treating gynecologic cancers."

This is an area in which Italian researchers are producing excellent results. For example, the IFOM research group led by Marco Foiani (Scientific Director of the Institute) discovered that valproic acid, an anticonvulsant widely used in the therapy of epilepsy, and the immunosuppressant rapamycin, are able to counteract some molecular mechanisms that lead to tumor transformation of cells. They published their results in *Nature* (*HDACs link the DNA damage response, processing of double-strand breaks and autophagy*, 2011)



New strategies to inhibit tumor angiogenesis
Elisabetta Dejana



Drug repositioning - A rapid and economic alternative to 'traditional' drug development
by Francesco Brancati

Drug repositioning - A rapid and economic alternative to 'traditional' drug development

The authors:



Francesco Brancati

Science Journalist and Director of UNAMSI, the Association of Italian Journalists reporting on Health and Research

Francesco Brancati, a professional journalist since 1974, has dedicated over 40 years to 'news agency journalism', the primary source of information for the Media, in the Milan office of ANSA.

A versatile journalist, he has been involved in every sector, from crime to sports, from judicial to entertainment (reporting for 30 years on opera productions at La Scala Theater).

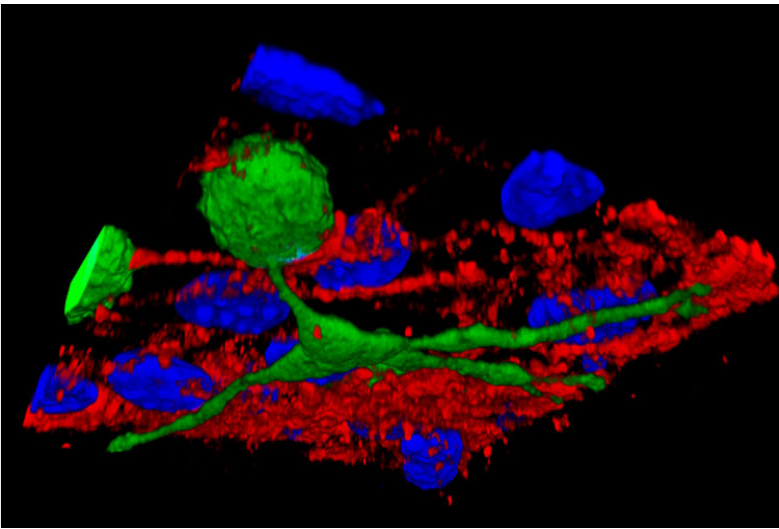
Since the eighties he has been in the front lines for Health and

Biomedical Research, dispatched by ANSA to cover countless conferences in Italy and in major cities worldwide. Among other things, he participated in the 1989 scientific expedition to Mt. Everest 'EV-K2-CNR', directed by Ardito Desio.

Professor in the Master in 'Health Communication' program in the Faculty of Pharmacy, at the University of Milan, he has won some of the highest awards for science journalism, including the Glaxo Prize, the Fiuggi Prize,

Voltolino Prize, the SOI Prize. Member of the College of Arbitrators of the UGIS (Union of Italian Scientific Journalists) and since February 2010 President of UNAMSI (National Union of Scientific Medical Information).

In 2014 he was chosen as an expert in communication for the technical and scientific committee of the Nutrition Foundation of Italy (NFI).



Cell therapy for muscular dystrophy: a step towards efficacy.

Commentary on Elisabetta Dejana's paper published on *EMBO Molecular Medicine*

by Giulio Cossu

Background:

Duchenne Muscular Dystrophy (DMD) is severe and common, affecting one born male every 4,000. It is due to mutations in the dystrophin gene, the largest of our genome (larger than the whole genome of a bacterium), which was heroically cloned almost thirty years ago (Hoffman et al Cell 51,919,1987). It was then thought that, with the gene identified, the cure would have followed. It did not.

The gene encodes for a large cytoskeletal protein that links the contractile apparatus to the membrane of the muscle fibre and adsorbs the mechanical stress of contraction. In its absence the membrane is damaged and the fibre dies. Initially, new fibres are formed by resident stem cells, termed "satellite cells" that share the same genetic defect and thus the same fate. If satellite cells are stem cells, they are amateur and not professionals like the hematopoietic stem cells, since muscles are made to last and do not turnover daily like blood. The sad evidence for this is observed in the biopsies of patients at late stages of the disease, where most muscles are gone,

as are satellite cells, and have been replaced by scar and fat. At this stage no therapy will work. Patients progressively lose their motility and are confined to a wheelchair, followed by assisted ventilation and heart failure. Improved medical care has increased length and quality of life but a cure is still missing.

Cell therapy for muscular dystrophy.

In the last ten years the therapeutic landscape for DMD changed from a desert to a very busy field with many approaches entering clinical trials and some proceeding to Phase III (Mercuri & Muntoni Curr Op Neur 25,701,2013). Importantly, even if successful these therapies will be available only for subsets of patients (depending on the specific mutation) and many patients would not be eligible for any. This justifies the cell therapy approach that our group started many years. Skeletal muscle is stable and, if fixed, would require no further therapy. However it is the most abundant tissue of our body and therapy requires billions of cells. Moreover dystrophic muscle is affected by inflammation and fibrosis

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that make life hard for transplanted cells. Finally, since muscle fibres are multinucleated one healthy or “corrected” nucleus must work for all the others.

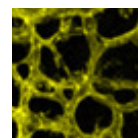
The previous work.

We tested cell transplantation in three mouse and one canine models of muscular dystrophy, using a cell type, termed “mesoangioblast” that we had identified in the blood vessel wall and characterized as a subset of pericytes, the cells that wrap the endothelium. The advantage of these cells, over resident satellite cells, that were subject of previous trials in the 90’, is their ability of crossing the vessel wall, when injected intra-arterially, which allow their even distribution in all the downstream muscles. However it appeared clear that in doing so, mesoangioblasts are less efficient than “professional” leukocytes, specifically endowed with all the molecular apparatus to get in and out the blood stream and reach the tissues where their action is needed. Nevertheless the results of the pre-clinical work were encouraging and led us to a “first in man” Phase I/IIa clinical trial with donor mesoangioblasts from an HLA-matched brother in five DMD patients. The trial (Cossu *et al.* in preparation) was safe but also showed limited efficacy. This was likely due to number of reasons, e.g. advanced age of patients and consequently a low level of engraftment, insufficient for a long-lasting significant clinical benefit. In a classic “from bench to bedside and back” approach, we are now dissecting each step of transplantation, aiming at increasing them all to finally reach efficacy.

Targeting endothelial junctional adhesion molecule-A/ EPAC/ Rap-1 axis as a novel strategy to increase stem cell engraftment in dystrophic muscles.

Muscular dystrophies are severe genetic diseases for which no efficacious therapies exist. Experimental clinical treatments include intra-arterial administration of vessel-associated stem cells, called mesoangioblasts (MABs). However, one of the limitations of this approach is the relatively low number of cells that engraft the diseased tissue, due, at least in part, to the sub-optimal efficiency of extravasation, whose mechanisms for MAB are unknown. Leukocytes emigrate into the inflamed tissues by crossing endothelial cell-to-cell junctions and junctional proteins direct and control leukocyte diapedesis. Here, we identify the endothelial junctional protein JAM-A as a key regulator of MAB extravasation. We show that JAM-A gene inactivation and JAM-A blocking antibodies strongly enhance MAB engraftment in dystrophic muscle. In the absence of JAM-A, the exchange factors EPAC-1 and 2 are down-regulated, which prevents the activation of the small GTPase Rap-1. As a consequence, junction tightening is reduced, allowing MAB diapedesis. Notably, pharmacological inhibition of Rap-1 increases MAB engraftment in dystrophic muscle, which results into a significant improvement of muscle function offering a novel strategy for stem cell-based therapies. [PMID 24378569]

New strategies to inhibit tumor angiogenesis
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by Giulio Cossu



The work we did.

Among the steps to be improved, adhering to and crossing the endothelium are crucial because they determine what fraction of the injected cells actually gets to the muscle. JAM-A (Junctional Adhesion Molecule A) is an endothelial protein that tightens the endothelium regulating cells transmigration. The group of Elisabetta Dejana at IFOM, long term collaborator, found that deleting this protein from the endothelium (or blocking it with a specific antibody) almost triples the amount of mesoangioblasts that cross the vessel wall both *in vitro* and *in vivo* (Giannotta et al EMM 6,239,2014). Notably, pharmacological inhibition of JAMA downstream effectors exerts the same effect thus suggesting possible drug-cells combined approach.

What next?

The natural follow up of the work on JAM-A would be clinical development of the inhibitor and/or the antibody, which however requires collaboration of a company. Alternatively, nanoparticles, charged with specific RNA inhibitors of JAM-A could be tested in mice: these particles have already been approved for clinical use and their clinical translation would thus be faster, easier and cheaper.



Cell therapy for muscular dystrophy:
a step towards efficacy.

The authors:



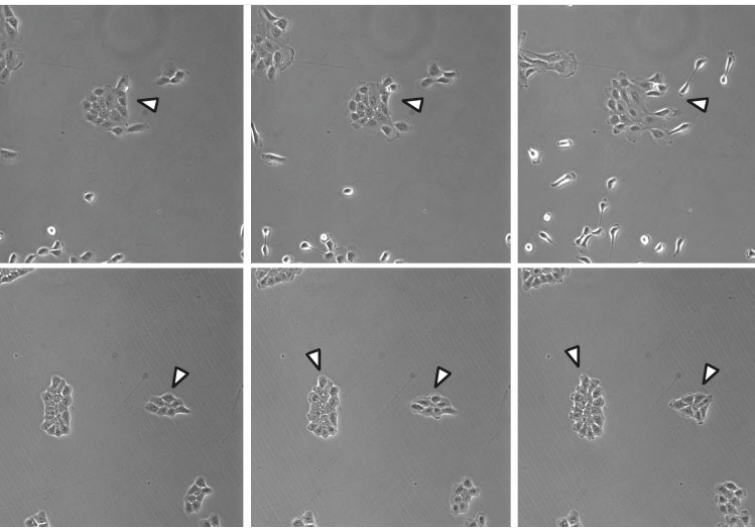
Giulio Cossu

Constance Thornley Professor of Regenerative Medicine, University of Manchester.

Giulio Cossu received his MD degree from the University of Rome. He was a Fogarty fellow at the University of Pennsylvania and then became Professor of Histology and Embryology in Rome. In 2000 he became Director of the “Stem Cell Research Institute” and then of the Division of Regenerative Medicine at San Raffaele in Milan.

In 2012 he moved to University College London and in 2013 to the University of Manchester as Professor of Regenerative Medicine. He is EMBO Member, Member of the European Academy of Science, Fellow of the Academy of Medical Sciences and of the Accademia dei Lincei. He was Chairperson for Panel LS7 for the European Research Council and served as

member of the CAT at EMA. Giulio Cossu is internationally recognized for his pioneering work on muscle development and on the cell therapy for muscular dystrophies. He has published more than 200 peer-reviewed papers and secured grants for his research for more than 10 M€. He is Senior Editor of EMBO Molecular Medicine and in the Board of many journals.



Breaking up is hard to do: role of an endocytic adaptor protein in epithelial cell cohesion and breast tumor metastasis

Commentary on Giorgio Scita's paper published in *Developmental Cell*

by Andrew Craig

Epithelial cells are normally polarized and form extensive cell-cell contacts that allow for a barrier to be formed between apical and basolateral surfaces. Cadherin-based adherens junctions (AJs) are critical for epithelial cohesion, and alterations in cadherin expression or surface expression are hallmarks of epithelial-mesenchymal transition (EMT) and the acquisition of a motile phenotype. In metastatic epithelial cancers, the EMT program allows some tumor cells to breach local basement membrane barriers and reach blood or lymphatic vessels to disseminate to other tissues. *A recent study by the Scita laboratory has implicated the F-BAR protein CIP4 (Cdc42-Interacting Protein-4) in mediating several key steps in breast cancer progression, including EMT, epithelial scattering, and breast cancer cell invasion (1). The authors also correlated high levels of CIP4 in human breast tumors with the highly metastatic HER2+ molecular subtype and risk of disease relapse.*

In normal breast epithelial cells, epidermal growth factor (EGF) induces cell scattering and invasion of extracellular matrix (ECM). However,

silencing of CIP4 led to increased epithelial cell cohesion, and impaired cell scattering and invasion. This correlated with defects in actomyosin contractility in CIP4 knock-down (KD) cells, which was measured using an elegant tension sensor for E-Cadherin based on Forster resonance energy transfer. EGF-treated CIP4 KD cells displayed reduced tension across AJs compared to control cells, and reduced rates of E-cadherin internalization. In normal breast epithelial cells, EGF signaling induced CIP4 localization to AJs and binding and activation of Src protein-tyrosine kinase. Since Src promotes E-cadherin internalization and cell scattering, defects in junctional Src activation may explain the requirement for CIP4 in AJ dissolution. Together, these findings likely explain the increased epithelial cohesion and reduced cell scattering phenotypes observed in CIP4 KD cells.

To undergo EMT, epithelial cells exposed to TGF- β 1 initiate a signaling pathway that targets junctional E-cadherin for rapid internalization, and cadherin switching marked by silencing of

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Cdh1 gene encoding E-cadherin, and upregulation of *Cdh2* encoding N-cadherin. Consistent with some recent studies in other cell types, they show that TGF- β 1 promotes CIP4 upregulation in breast epithelial cells, and CIP4 KD impairs the rate and extent of completing EMT in these cells. Mechanistically, there was no overt role for CIP4 in TGF- β 1-induced activation of Smads, but Src activation was short-lived in CIP4 KD cells. This may contribute to non-canonical TGF- β 1 signaling pathways that enhance expression of EMT drivers such as Snail1 and N-cadherin, which were both delayed or impaired in CIP4 KD cells.

To extend their study to human breast cancer, CIP4 expression was profiled in human breast tumor tissue microarrays. High levels of CIP4 was significantly associated with aggressive molecular subtypes (HER2+) and disease relapse. Interestingly, our group performed a similar study in an independent cohort of breast cancer patients, and found significantly increased risk of metastasis in patients with high CIP4 levels in their primary tumors (2). Since CIP4 was significantly associated with HER2+ tumors, Rolland and co-workers also tested the role of CIP4 in a model of ductal carcinoma in situ (DCIS)-to-invasive ductal carcinoma (IDC) conversion of MCF10A cells expressing an inducible ErbB2/HER2 allele. CIP4 silencing in this model impaired HER2-driven cell scattering and invasion, and limited DCIS-to-IDC conversion in mouse xenograft assays, based on loss of the myoepithelial marker α smooth muscle actin (1). Our study also tested the effects of CIP4 silencing *in vivo*, but focused instead on triple negative breast cancer (TNBC) models. We found that CIP4 silencing impairs TNBC metastasis to the lungs in mice (2).

The CDC42-interacting protein 4 controls epithelial cell cohesion and tumor dissemination.

The role of endocytic proteins and the molecular mechanisms underlying epithelial cell cohesion and tumor dissemination are not well understood. Here, we report that the endocytic F-BAR-containing CDC42-interacting protein 4 (CIP4) is required for ERBB2- and TGF- β 1-induced cell scattering, breast cancer (BC) cell motility and invasion into 3D matrices, and conversion from ductal breast carcinoma in situ to invasive carcinoma in mouse xenograft models. CIP4 promotes the formation of an E-cadherin-CIP4-SRC complex that controls SRC activation, E-cadherin endocytosis, and localized phosphorylation of the myosin light chain kinase, thereby impinging on the actomyosin contractility required to generate tangential forces to break cell-cell junctions. CIP4 is upregulated in ERBB2-positive human BC, correlates with increased distant metastasis, and is an independent predictor of poor disease outcome in subsets of BC patients. Thus, it critically controls cell-cell cohesion and is required for the acquisition of an invasive phenotype in breast tumors.

[PMID 25203208]

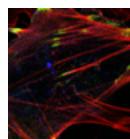


Breaking up is hard to do:
role of an endocytic adaptor protein in epithelial cell
cohesion and breast tumor metastasis
by Andrew Craig

Despite a relatively simple domain organization, it is interesting to note that CIP4 and related adaptor proteins play key roles in a growing list of diverse processes in normal cells and cancer cells. The study by Rolland and co-workers provides many fascinating insights into the localization and function of CIP4 in key steps in epithelial cell conversion to highly invasive and ultimately metastatic cancer cells. In future, it will be critical to fully elucidate the molecular mechanisms that could be best exploited to prevent metastasis and improve survival of cancer patients.

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Mechanisms of Tumor Cell Migration
Giorgio Scita



Breaking up is hard to do:
role of an endocytic adaptor protein in epithelial cell
cohesion and breast tumor metastasis
by Andrew Craig

Breaking up is hard to do:
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The author:



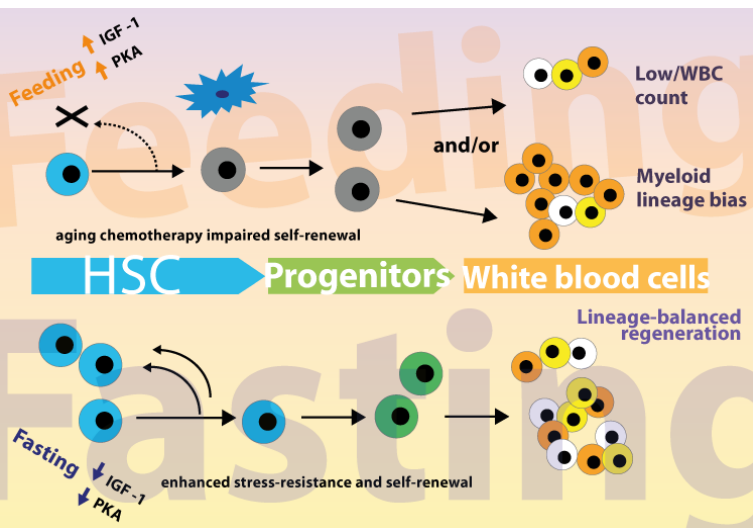
Andrew Craig

*Principal Investigator, Cancer Biology & Genetics division, Queen's Cancer Research Institute
Queen's University, Kingston, Ontario, Canada*

Andrew Craig earned his BSc in Biochemistry at Queen's University (1993) prior to completing his PhD in the field of post-transcriptional regulation of gene expression in Dr Nahum Sonenberg's lab at McGill University (PhD 1998). PDF training in cancer biology and transgenic mouse models was performed with Dr Peter Greer at Queen's Cancer Research Labs (1998-2002) prior to starting his own lab in the Department of Biochemistry at Queen's (since 2002).

Dr Craig has received numerous research awards including Canadian Institutes of Health Research New Investigator award (2004-9) and the 2011 Young Investigator award from the Canadian Cancer Society. The Craig lab studies tyrosine kinase signaling pathways that regulate cell motility, tissue invasion and inflammation. Current projects focus on mast cells, inflammation, chronic diseases, and tumour progression.

The lab also studies F-BAR proteins and microRNAs that are altered in metastatic cancer models using both cell culture and mouse models.



Regeneration of Hematopoietic Stem Cells and immunosuppression recovery: the power of prolonged fasting

Commentary on Valter Longo's paper published on *Cell Stem Cell*

by Nicoletta Guaragnella

All living organisms are continuously exposed to various stresses, but only vertebrates possess a sophisticated defense mechanism, called immune system. While along life, the immune system is an active component against environmental pathogenic stress, over the years, it undergoes a progressive functional decline, which can play a major role in increasing susceptibility to onset of malignancies, including cancer. Immunosuppression is one of the most relevant side effects of conventional cancer-based therapy. In particular, chemotherapy causes a significant myelosuppression with a specific damage in bone marrow activity and high incidence of mortality. This represents a dose limit in chemotherapy treatment because damage to adult stem/progenitor cells impairs tissue repair and regeneration. With this regard, a great interest exists on the development of Hematopoietic Stem Cells (HSCs) and their use in clinical application. HSCs are normally maintained in a quiescent state, but in response to external stresses, such as chemotherapy, they should proliferate extensively to sustain hematopoietic cell self-renewal.

At the moment, understanding the basis to counteract immune system defects represents a central issue in both aging and diseases processes

In the last decade Valter Longo, Professor of Gerontology, Director of the Longevity Institute at University of Southern California LA and recently appointe as senior group leader at IFOM, is focusing his research on the potential benefits of fasting practices on longevity, adaptive cellular response and cancer prevention and treatment. His studies on mice and humans have revealed that prolonged fasting (PF), lasting 2 or more days, enhances cellular resistance to toxins, in part by reducing circulating Insulin-like growth factor (IGF-1) [1-3]. Increase in IGF-1, normally required for proper growth in children, has been implicated in the risk of different kind of cancer in men and women older than 40, but can also render normal cells sensitive to stresses including chemotherapy.

The article by Dr. Longo's group and colleagues has now shown that PF reduces circulating IGF-1 in various cell populations

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and promotes HSC-based regeneration [4]. This effect is mediated by reduced Protein Kinase A (PKA), which acts downstream of IGF-1. PKA is known to directly phosphorylate and negatively regulate factors implicated in stem cell differentiation, but its role in hematopoietic regeneration is poorly understood [5]. This work connects the reduced level of IGF-1 caused by cycles of PF to PKA signaling and establish their crucial role in regulating hematopoietic stem cell protection, self-renewal and regeneration. A definitive confirmation of these results comes from the data obtained with knock-out mice, deficient in either IGF-1 or PKA, in which the effects of PF on increased stress resistance and hematopoietic recovery are recapitulated. Accordingly, exogenous IGF-1 can blunt the effect of PF on stimulation of HSC self-renewal. Remarkably, the hematopoietic regeneration may have also occurred in cancer patients monitored in a phase I clinical trial in which the association of PF and chemotherapy was shown to prevent defects in the hematological profile. In accordance with these preliminary human data, multiple cycles of fasting abated the immunosuppression and mortality caused by chemotherapy in mice. PF could also reverse the effects of aging in causing unbalances in the profile of different blood cell types, leading to the apparent rejuvenation of the immune system profile.

That impairment of PKA signaling could protect against stress and increases lifespan was shown many years ago by the Longo lab (6), indicating an evolutionary conserved mechanism from yeast to mammals [2,3]. Also in this paper, Valter does not forget to highlight how it is important to learn from model organisms to intervene against human disease and aging by showing that yeast cells

Prolonged fasting reduces IGF-1/PKA to promote hematopoietic-stem-cell-based regeneration and reverse immunosuppression.

Immune system defects are at the center of aging and a range of diseases. Here, we show that prolonged fasting reduces circulating IGF-1 levels and PKA activity in various cell populations, leading to signal transduction changes in long-term hematopoietic stem cells (LT-HSCs) and niche cells that promote stress resistance, self-renewal, and lineage-balanced regeneration. Multiple cycles of fasting abated the immunosuppression and mortality caused by chemotherapy and reversed age-dependent myeloid-bias in mice, in agreement with preliminary data on the protection of lymphocytes from chemotoxicity in fasting patients. The proregenerative effects of fasting on stem cells were recapitulated by deficiencies in either IGF-1 or PKA and blunted by exogenous IGF-1. These findings link the reduced levels of IGF-1 caused by fasting to PKA signaling and establish their crucial role in regulating hematopoietic stem cell protection, self-renewal, and regeneration. [PMID 24905167]



Regeneration of Hematopoietic Stem Cells and immunosuppression recovery: the power of prolonged fasting
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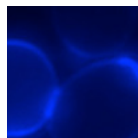
over-expressing an inhibitory subunit of PKA show higher resistance to oxidative stress. Valter started his career working with the yeast *Saccharomyces cerevisiae* and identified for the first time key regulators of longevity and stress resistance [2,6]. Yeast has been also the filrouge between myself and Valter. I had the great opportunity to meet him in Los Angeles, to spend a period in his laboratories, to enjoy his intellectual generosity and to tighten a solid friendship.

The commented work reinforces the potential effects of a natural intervention, such as PF, on aging processes and diseases treatments. Indeed, the physiological changes caused by PF are much more pronounced than those caused by calorie restriction or fasting lasting 24 hours or less. In fact, PF triggers a full metabolic switch from a carbohydrate-based to a fat-and ketone body-based catabolism. This change in the energy metabolism could be a relevant determinant for the observed HSC self-renewal. These findings provide also the basis for a potential therapy to be applied in both chemotherapy

treatments, aging and all diseases in which the hematopoietic and immune system are impaired.

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Longevity and Cancer
Valter Longo

Regeneration of Hematopoietic Stem Cells and immunosuppression recovery: the power of prolonged fasting
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Regeneration of Hematopoietic Stem Cells and immunosuppression recovery: the power of prolonged fasting

The author:



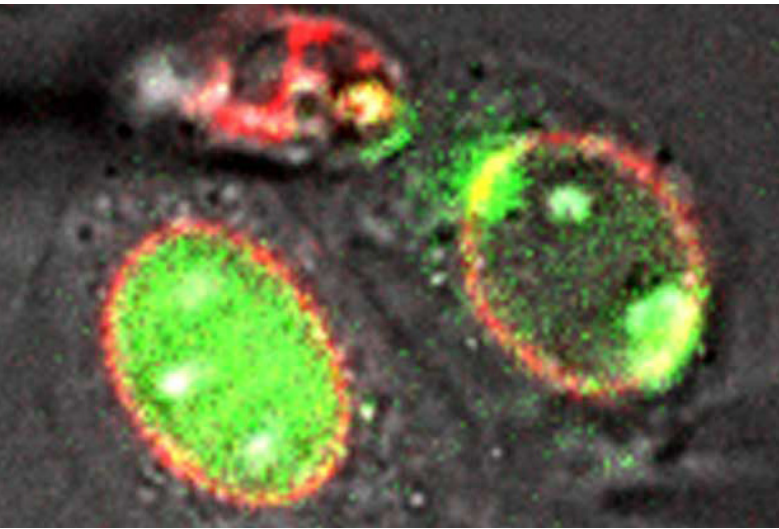
Nicoletta Guaragnella

Research associate at National Research Council-Institute of Biomembranes and Bioenergetics (CNR-IBBE) in Bari

Nicoletta Guaragnella has a permanent position as a research associate at National Research Council-Institute of Biomembranes and Bioenergetics (CNR-IBBE) in Bari (Italy) since 2010. Her major scientific interests are: pro-survival and pro-death signaling in cell stress response; mitochondria to nucleus communication, known as mitochondrial retrograde signaling and heterologous expression of human oncosuppressors, such as BRCA2 (Breast Cancer Susceptibility gene), in the model

organism yeast *Saccharomyces cerevisiae*. She is now expanding her scientific experience working on the molecular mechanisms of cell stress response in wild yeast used for biotechnological applications. During her PhD in Biochemistry and Molecular Biology, she was trained as a junior fellowship in the laboratory of Ronald Butow in Dallas at University of Texas, Southwestern Medical School. In 2013 she has been visiting scientist in Valter Longo' laboratory and worked

on the relations between sir2 and apoptosis in yeast aging cells. At CNR-IBBE she is also involved in mentoring programs for undergraduate students and is responsible for the activities of scientific communication and dissemination. She coordinates the organization of public events for scientific dissemination and actively collaborates with CNR Press Office in Rome, Almanacco della Scienza, Scienza in Rete, Rivista dell'Ordine Nazionale dei Biologi.



“An entirely new perspective in which chromosomes are considered as mechanical objects”

Commentary on Marco Foiani's paper published in *Cell*

by Nancy Kleckner

Normal functioning of living cells begins and ends with the genetic material, DNA. DNA not only provides the information for gene expression but is, itself, the fundamental basis for the ability of cells to propagate themselves, by duplication and segregation. Human cells contain 6×10^9 basepairs (6000 Mb) of DNA, housed in 46 chromosomes (22 pairs of homologous maternal and paternal chromosomes plus two sex chromosomes, XX in female or XY in male). Every time a cell divides, all of this DNA must be accurately duplicated, after which the resulting sister chromosomes must be faithfully segregated into two daughter cells. Both of these basic processes present intrinsic challenges. DNA comprises two plectonemically intertwined strands. As DNA is duplicated, this intertwining presents a topological challenge: the two strands must be unwound in front of the progressing replication fork, implying that inter-strand intertwinings must somehow be removed or displaced. Further, in order for sisters to segregate cleanly, the DNA must be compacted into short, fat discrete units, within which the two

sister units (chromatids) are well-individualized. The extent of the compaction required is dramatic: the contour length of the DNA in an average chromosome is ~ 3.5 cm and, even with ~ 7 -fold compaction achieved by wrapping of DNA around nucleosomes, ~ 5 mm. In contrast, the distance between segregated groups of chromosomes is only $\sim 20 \mu\text{m}$ (2×10^{-2} mm).

Like all basic aspects of chromosome biology, these events are orchestrated by a complex series of molecular/biochemical processes that must be coordinated with one another and also monitored for successful progression by regulatory surveillance mechanisms. Dr. Foiani's work focuses on one of these regulatory surveillance molecules, the essential PI3 kinase ATR (Ataxia telangiectasia and Rad3-related). In human, mutations in ATR underlie Seckel syndrome, a severe disease characterized by mental retardation, dwarfism and defects in the DNA damage response.

Foiani's recent work has emerged from a long-

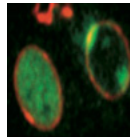
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standing interest in the nexus between replicating DNA and the nuclear envelope (NE). Chromatin domains are often connected to the NE and this connection is prominent for late-replicating regions. Foiani and colleagues have previously shown that when a DNA replication fork approaches a NE-associated chromatin region, DNA strands in front of the fork acquire aberrant topological states which, if not removed, trigger genome rearrangements. The authors also showed that the cell deals with such blocks by triggering release of the involved chromatin regions from the NE, thereby permitting regular continuation of replication and preventing genome damage. Moreover, this release is mediated by ATR.

In considering the basis for this effect, Foiani came to the idea that the ATR-mediated signal transduction involved in releasing forks from the NE might involve direct mechanical signaling within the DNA/chromatin/NE ensemble.

ATR mediates a checkpoint at the nuclear envelope in response to mechanical stress.

ATR controls chromosome integrity and chromatin dynamics. We have previously shown that yeast Mec1/ATR promotes chromatin detachment from the nuclear envelope to counteract aberrant topological transitions during DNA replication. Here, we provide evidence that ATR activity at the nuclear envelope responds to mechanical stress. Human ATR associates with the nuclear envelope during S phase and prophase, and both osmotic stress and mechanical stretching relocalize ATR to nuclear membranes throughout the cell cycle. The ATR-mediated mechanical response occurs within the range of physiological forces, is reversible, and is independent of DNA damage signaling. ATR-defective cells exhibit aberrant chromatin condensation and nuclear envelope breakdown. We propose that mechanical forces derived from chromosome dynamics and torsional stress on nuclear membranes activate ATR to modulate nuclear envelope plasticity and chromatin association to the nuclear envelope, thus enabling cells to cope with the mechanical strain imposed by these molecular processes. [PMID 25083873]



Genome Integrity
Marco Foiani

This notion required integration of several considerations. (i) Since changes in the topological state of the DNA duplex comprise deformations of the molecule out of its most energetically favorable state, they comprise mechanical stress. (ii) The central fundamental feature of a mechanical system is that a change at one position is automatically transmitted to other positions nearby. In a chromosomal context, the DNA is part of a complex elastic protein/DNA meshwork; and the NE is a deformable elastic structure. Thus, both components are ideal for absorbing and/or transducing mechanical stimuli, between/among the nucleus, the chromosomes and the surrounding cytoskeleton. (iii)



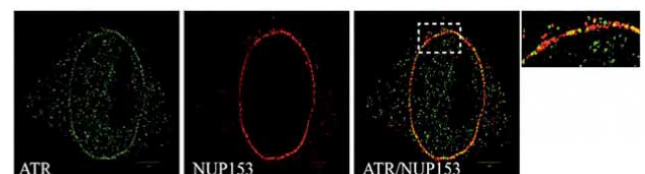
“An entirely new perspective in which chromosomes are considered as mechanical objects”
by Nancy Kleckner

If mechanical forces are present in a biological system, the further implication is that specific molecules, known traditionally to have standard biochemical activities, will also play roles in sensing and transducing mechanical signals. ATR comprises a large array of helical repeat units plus a terminal kinase domain, and such helical repeats domains are known to have a spring-like behavior. Thus, ATR would be an attractive candidate to transduce chromosome/NE stress into desired molecular outcomes.

Acting on this intuition, the Foiani group has now demonstrated (*Cell* 158: 633–646) that a fraction of ATR always localizes to the NE and that this targeting is dramatically increased if the NE is subjected to stretching, either by osmotic stress or by whole cell mechanical manipulation. Moreover, this effect is direct, rather than being an indirect consequence of checkpoint activation by stretching-induced chromosome damage.

Stimulated by this finding, Foiani and colleagues proceeded to explore the general implications of their results. Chromatin/NE associations occur and are modulated not only during DNA replication but also during the dramatic chromosome compaction that precedes segregation (above). At an initial stage of this process, chromosomes are tightly associated with the NE. Then, as compaction progresses, chromosomes must be released from the NE, which concomitantly breaks down in preparation for chromosome segregation. Foiani and colleagues reasoned that ATR might also play a role in chromatin/NE release at this stage. Their reasoning is proving correct: they find that, without active ATR, onset and completion of chromatin compaction at prophase are significantly delayed and NE breakdown is incomplete. And once again, these effects do not arise indirectly from a DNA damage response.

Traditional investigations of chromosomal processes have focused on identification of the molecules involved, their biochemical activities, and their physical and functional interactions. The recent study of Foiani and colleagues spearheads an entirely new perspective in which chromosomes are considered as mechanical objects. This new perspective opens a new approach to understanding chromosomal processes and, thus, why and how these processes go awry in cancer and other disease conditions. Foiani's study is also significant because it further supports the idea that ATR is not only involved in mediating checkpoint responses to chromosome damage but also plays roles in regulating and modulating basic chromosomal events in an entirely unperturbed cell cycle. Such roles help to explain why, as shown by Seckel syndrome, the functioning of ATR is important even for an individual that is not afflicted by cancer or disease.



Super-resolution image of a prophase cell stained with anti-ATR (green) and -NUP153 (red) antibodies, illustrating localization of ATR to the NUP153-marked nuclear periphery. (Figure 1B of Kumar et al., 2014).



“An entirely new perspective in which chromosomes are considered as mechanical objects”
by Nancy Kleckner

“An entirely new perspective in which chromosomes are considered as mechanical objects”

The author:



Nancy Kleckner

Herchel Smith Professor of Molecular Biology at Harvard University

Professor Kleckner earned her undergraduate degree from Harvard, where she worked with Matthew Meselson on recombination in bacteriophage λ . She got her PhD from the Massachusetts Institute of Technology (MIT) working with Ethan Signer on DNA replication, also λ . In postdoctoral work with David Botstein at MIT, she showed that bacteria possessed segments of DNA encoding antibiotic resistance genes that ‘jump around’ from site to site on the chromosome, a process known as DNA transposition.

A member of the Harvard faculty since 1977, Dr. Kleckner’s research began with genetic and biochemical experiments on DNA transposition. She elucidated the cut-and-paste nature of the transposition process, the unique chemistry of the reaction and the roles protein/DNA complexes (transpososomes). She concomitantly elucidated regulatory processes that, collectively, allow the transposon (IS10/Tn10) to stably inhabit its host. This work included identification of the first small anti-sense RNA that inhibits protein translation (of IS10 transposase) and the discovery that cellular conditions alter transposition outcome by

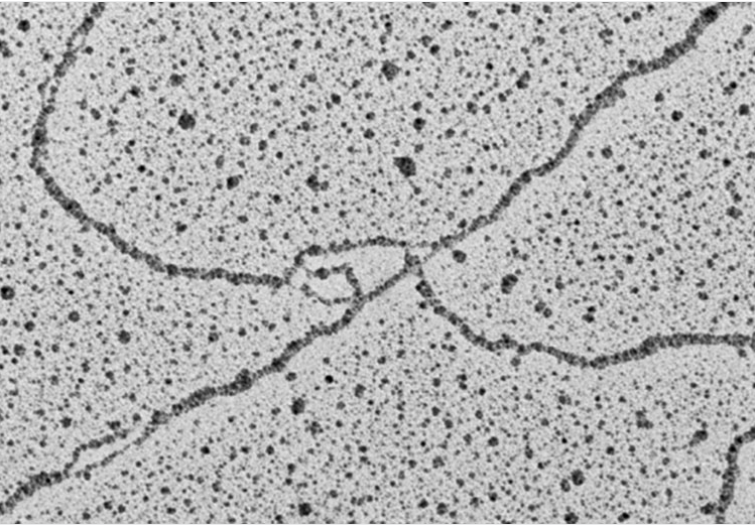
modulating mechanical stress in a transpososome DNA loop.

Her research then transited to new subjects. She initiated modern approaches to analyzing chromosomal events of meiosis, the modified cellular program that yields haploid gametes (sperm and egg) for sexual reproduction. This work uncovered the molecular nature of meiotic recombination and showed that homologous chromosomes can identify one another and pair even without recombination. Her group carried out the first chromatin immunoprecipitation mapping of a chromosome-associated proteins and her then-post-doctoral-fellow Job Dekker invented chromosome conformation capture (3C) methodology, which has revolutionized analysis of chromosome architecture and its role in chromosome function.

Her studies in meiosis led Kleckner to propose a new conceptual view in which chromosomes are considered as mechanical objects. By this idea, chromosome functionalities are governed by accumulation, relief and redistribution of mechanical stress, with key chromosomal molecules acting as sensors and transducers of such stress. This idea emerged from a stress-based

model for how chromosomal features become evenly spaced along chromosomes, and her group recently found that Topoisomerase II, a mediator of mechanical stress, is involved in such a process. Her laboratory has also pioneered 4D (3D over time) analysis of whole chromosome dynamics. 4D studies in both mammalian cells and in the bacterium *E.coli* have defined global dynamic behavior that involves cyclic accumulation and relief of stress. Mammalian analysis concomitantly defines, for the first time, how chromosomes develop the short, compact organization required for segregation of duplicated copies to daughter cells.

Dr. Kleckner was awarded the GSA Medal of the Genetics Society of America in 1990 and elected to the American Academy of Arts and Sciences in 1991, to the U.S. National Academy of Sciences in 1993, and as a Foreign Associate member of the European Molecular Biology Organization in 2004. She has founded international meetings in the fields of DNA transposition, bacterial chromosomes and meiosis. At Harvard University, she is the founder of the PhD Track in Engineering and Physical Biology (EPB).



Seeing is believing: catching template- switching in the act

Commentary on Dana Branzei's paper published on Nature Structural & Molecular Biology

by Michael Lichten

Every time a cell replicates its genome, it runs the risk of breaking it. Replication involves copying millions to billions of nucleotides, and this must be done faithfully if two identical versions of the genome are to be passed on to the next generation. Evolution has selected for DNA replication enzymes that accomplish this task with efficiency and fidelity, but on occasion even this marvelous machine breaks down. DNA damage, both spontaneous and induced, creates lesions that cannot be copied, resulting in breaks in the vicinity of the replication fork. If these breaks cannot be repaired rapidly and faithfully, they can lead to mutations and rearrangements that alter genome content and place critical genes in inappropriate regulatory contexts. These are a leading source of genetic disease and a leading cause of cancer.

As a consequence, mechanisms have evolved that preserve genome integrity by tolerating replication-blocking DNA lesions. Two are generally used: the bypass of lesions by error-

prone polymerases that introduce mutations at the site of damage; and error-free mechanisms that use homologous recombination to copy correct information from an undamaged template, creating a patch that bypasses the lesion and restores genome integrity and function at the site of damage. This latter mechanism, called template switching, is a major form of lesion bypass in normal cells, as evidenced by findings that most DNA damage is repaired without mutation or genome alteration.

Mechanisms of template switching have been the subject of intense focus, in particular at the IFOM. Much progress has been made in understanding the proteins and enzymatic activities involved, using genetic and cytological approaches, through *in vitro* biochemical studies, and using gel electrophoresis-based approaches that allow inference about template switching intermediate structures. However, until now, the somewhat indirect nature of these approaches has produced incomplete understanding. In particular, progress has been

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limited by an inability to distinguish between two alternative models for template switching. In one, a stalled replication fork regresses to form a four-armed DNA structure in which DNA synthesis, followed by fork restoration, creates a patch to cover a lesion. In the second, the fork does not stall, but leaves behind single-strand DNA gaps, which are used by homologous recombination activities to prime new DNA synthesis, generating a lesion-covering patch. Both models can accommodate existing genetic and biochemical data, and both are expected to produce the intermediate structures detected on gels. Because template switching occurs at relatively low frequencies, and at many places in the genome, distinguishing between these and other models has been stymied by the fact that we have not been able to actually see the DNA molecules that are engaged in template switching—until now.

The work that filled this gap was performed at the IFOM by the group of Dana Branzei and her collaborators. They solved the problems of low frequency and multiple locations by creating a budding yeast strain that contains a high-copy minichromosome, present in dozens of copies in a single cell, that can be directly seen on agarose gels. They then used methyl methanesulfonate to induce template switching at high levels, and combined methods to stabilize template-switching intermediates and methods to separate these intermediates from the bulk of genomic DNA on 2-dimensional agarose gels. Branzei and colleagues were then able to extract these intermediates from gels and directly visualize

Visualization of recombination-mediated damage bypass by template switching

*Template switching (TS) mediates damage bypass via a recombination-related mechanism involving PCNA polyubiquitination and polymerase δ -dependent DNA synthesis. Using two-dimensional gel electrophoresis and EM, here we characterize TS intermediates arising in *Saccharomyces cerevisiae* at a defined chromosome locus, identifying five major families of intermediates. Single-stranded DNA gaps of 150–200 nt, and not DNA ends, initiate TS by strand invasion. This causes reannealing of the parental strands and exposure of the nondamaged newly synthesized chromatid, which serves as a replication template for the other blocked nascent strand. Structures resembling double Holliday junctions, postulated to be central double-strand break–repair intermediates but so far visualized only in meiosis, mediate late stages of TS before being processed to hemicatenanes. Our results reveal the DNA transitions accounting for recombination-mediated DNA-damage tolerance in mitotic cells and replication under conditions of genotoxic stress. [PMID 25195051]*

Article's image: Enlarged view of a double Holliday Junction-like intermediate junction

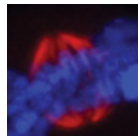


Seeing is believing:
catching template-switching in the act
by Michael Lichten

their structures in the electron microscope.

This remarkable study represents the first time in that eukaryotic repair intermediates have been visualized on a specified DNA molecule, and it has provided unprecedented insight into template switching mechanisms. In particular, the spectrum of intermediate structures Branzei and colleagues detect is inconsistent with fork regression being the dominant template switching mechanism. Rather, they point to mechanisms where DNA at a single-strand gap, left behind by the replication fork, interacts with homologous DNA on the undamaged sister chromatid and initiates new synthesis, ultimately liberating an intact strand that repairs the damaged chromosome. One prediction of this model is that repair products frequently should be linked by two intertwined single strands in a structure called a hemicatenane. Previous work at the IFOM has shown that these structures can frequently be produced when template switching is induced.

In summary, Branzei and colleagues have provided insight into template switching at an unparalleled level of molecular detail. Their study points the way for future approaches, not just in the study of template switching, but also of other homology-based recombination processes that play additional important roles in preserving genome integrity.



DNA Repair
Dana Branzei



Seeing is believing:
catching template-switching in the act
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Seeing is believing:
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The author:



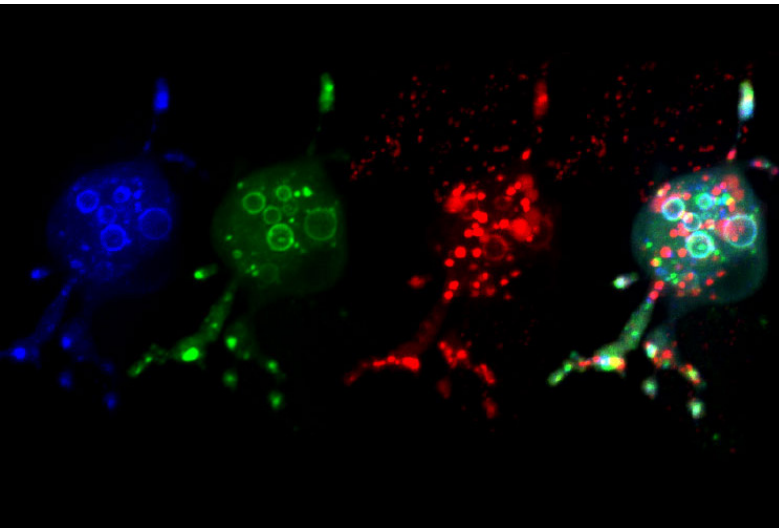
Michael Lichten

*Senior Investigator at the Laboratory of Biochemistry and Molecular Biology
Center for Cancer Research, National Cancer Institute*

Dr. Michael Lichten is a Senior Investigator at the Laboratory of Biochemistry and Molecular Biology, Center for Cancer Research, National Cancer Institute. He received a Ph.D. in 1982 from M.I.T. (with Maurice S. Fox) and postdoctoral training at Brandeis University (with Dr. James E. Haber).

He joined the NCI as a Senior Staff Fellow in 1987, became a Senior Investigator in 1995, and became a member of the Senior Biomedical Research Service in 2000. He is co-Director of the NIH-Johns Hopkins Graduate Partnership Program in Cellular, Molecular, Developmental Biology, and serves on editorial boards

of PLOS Biology, PLOS Genetics, PLOS ONE, the Annual Review of Genetics, and Faculty of 1000. His group's research focuses on the mechanism and control of homologous recombination, with a particular interest in events that occur during meiosis in budding yeast.



On the fast track to invasion: intracellular trafficking drives tumor metastasis

Commentary on Giorgio Scita's paper published on *Journal of Cell Biology*

by Stefan Linder

Metastasis, the escape of cancer cells from a primary tumor, and their subsequent dissemination in the body, is invariably coupled with poor patient prognosis. Prevention of metastasis is thus one of the most critical issues in public health management, requiring an in-depth understanding of the regulatory mechanisms. To metastasize, cancer cells have to de-attach from the primary tumor, to both enter and exit the bloodstream, and re-invade into other tissues. During these processes, the cells have to cross a variety of tissue barriers and also to migrate through the dense meshwork of the extracellular matrix (ECM), a fibrillar network that surrounds and connects cells in tissues. To navigate through these terrains, cancer cells have to be able to both adhere to ECM fibres, but also to cleave them to avoid getting stuck. This balancing act is achieved by proteins exposed on the cell surface, in particular by matrix receptors such as integrins and by matrix-lytic enzymes such as metalloproteinases (MMPs). Key proteins of either family are $\beta 3$ integrins and the matrix

metalloproteinase MT1-MMP, both of which are known to drive cancer cell invasion. Accordingly, they are enriched at invadopodia, finger-like protrusions of cancer cells, that are also sites of matrix adhesion and -degradation.

Both $\beta 3$ integrin and MT1-MMP are anchored to the cell surface by transmembrane domains, which also enables their recycling by internalization, intracellular transport in vesicles and re-exposure at the cell surface. This cycle ensures the dynamic presence of both “grip- and clip-” functions on the surface of cancer cells during their migration through a changing environment. Intracellular trafficking is thus expected to have a critical impact on cancer cell migration. The paper by Giorgio Scita's lab now identifies a particularly efficient trafficking pathway, which is characterized by two members of the RabGTPase family, Rab5A and Rab4, and ensures swift recycling of $\beta 3$ integrin and MT1-MMP during cell invasion.

Analysing the data from 980 breast cancer

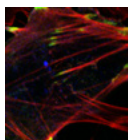
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cases, Frittoli *et al.* found a striking correlation between expression levels of RAB5A and patient prognosis. In particular, cells from lymph node metastasis showed elevated levels compared to those from primary tumors, indicating a critical role for RAB5A in metastasis, which could also be confirmed in a mouse model. On a cellular level, the Scita group could show that RAB5A is both necessary and sufficient to drive MT1-MMP-dependent cell invasion, which is based on the formation of invadopodia and invadopodia-associated matrix degradation. A closer examination of potential recycling pathways led to the identification of RAB4 and its effector RABENOSYN-5. The latter, being able to bind both RAB4 and RAB5A, apparently acts as the connecting link between both arms of the pathway. Accordingly, the Scita group demonstrated that RAB4 is required for RAB5A-dependent recycling of MT1-MMP and $\beta 3$ integrin, as well as the formation of invadopodia.

Frittoli *et al.* thus developed a model in which a

A RAB5/RAB4 recycling circuitry induces a proteolytic invasive program and promotes tumor dissemination.

The mechanisms by which tumor cells metastasize and the role of endocytic proteins in this process are not well understood. We report that overexpression of the GTPase RAB5A, a master regulator of endocytosis, is predictive of aggressive behavior and metastatic ability in human breast cancers. RAB5A is necessary and sufficient to promote local invasion and distant dissemination of various mammary and nonmammary tumor cell lines, and this prometastatic behavior is associated with increased intratumoral cell motility. Specifically, RAB5A is necessary for the formation of invadosomes, membrane protrusions specialized in extracellular matrix (ECM) degradation. RAB5A promotes RAB4- and RABENOSYN-5-dependent endo/exocytic cycles (EECs) of critical cargos (membrane-type 1 matrix metalloprotease [MT1-MMP] and $\beta 3$ integrin) required for invadosome formation in response to motogenic stimuli. This trafficking circuitry is necessary for spatially localized hepatocyte growth factor (HGF)/MET signaling that drives invasive, proteolysis-dependent chemotaxis in vitro and for conversion of ductal carcinoma in situ to invasive ductal carcinoma in vivo. Thus, RAB5A/RAB4 EECs promote tumor dissemination by controlling a proteolytic, mesenchymal invasive program. [PMID 25049275]



Mechanisms of Tumor Cell Migration
Giorgio Scita

RAB5A- and RAB4-dependent circuitry drives fast recycling of MT1-MMP and $\beta 3$ integrin, thus promoting the formation of matrix-lytic invadopodia. Coming full circle, this model was confirmed by the identification of high levels of RAB4 in invasive breast cancers, and also by reducing the invasiveness of cancer cells, through expression of an inactive mutant of RAB4 in a mouse model of metastasis.

Elegantly combining a wealth of *in vivo* and *in*



On the fast track to invasion:
intracellular trafficking drives tumor metastasis
by Stefan Linder

vitro data, this paper identifies two specific RAB GTPases, RAB5A and RAB4, in the intracellular trafficking of key cargo proteins of invadopodia formation and function. The Scita group thus makes a very strong case for paying more attention to RAB proteins in the prediction of clinical outcome, and also for considering these drivers of fast recycling and metastasis formation as potential therapeutic targets.

As most things in nature, however, also RAB5A has a flip side. In primary macrophages, it acts not as a positive, but as a negative regulator of MT1-MMP surface exposure (Wiesner et al., J. Cell Sci., 2013). Discussing and contrasting these findings from our labs has been a pleasure and led to a co-authored commentary article (Linder and Scita, Small GTPases, in press). The Frittoli et al paper is thus a perfect example of not only presenting rock-solid and highly relevant data, but also of sparking discussions, which is the hallmark of great science.

Article's image: 3D morphology analysis by spinning disc microscopy of HeLa cells embedded in 3D matrigel expressing CFP-RAB5-, GFP-RAB4-, and Cherry-MT1-MMP



On the fast track to invasion:
intracellular trafficking drives tumor metastasis
by Stefan Linder

On the fast track to invasion:
intracellular trafficking drives tumor metastasis

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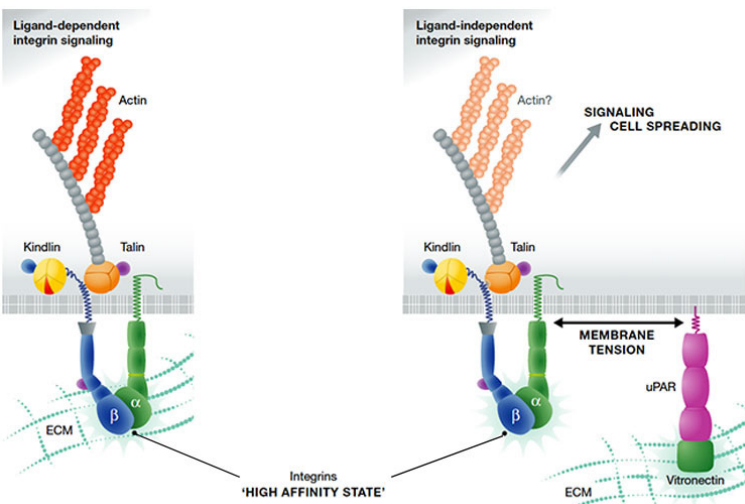
After receiving a PhD in cell biology, Stefan Linder worked at the Ludwig Maximilians-University in Munich as a postdoc and later as a group leader, before moving to the University Medical Center Eppendorf, Hamburg, as a professor for cellular microbiology.

His lab works on the cytoskeletal regulation of primary human cells, especially of macrophages and endothelial cells, with a focus on actin- and tubulin-related

regulation of cell adhesion, intracellular trafficking, invasion and phagocytosis. His primary passion, however, are podosomes.

He is a founding member and co-president of the Invadosome Consortium (www.invadosomes.org), an international group of labs interested in the mechanisms of cell invasion, and served as a coordinator of the invadosome-oriented

“Tissue Transmigration Training Network” (T3Net), which was funded by the European Union’s FP7 program from 2009 to 2013. He is an editorial board member of *Faculty of 1000/Biology/Cytoskeleton* and *Faculty of 1000/Research*, and an editor for *European Journal of Cell Biology* since 2009. He has seen several million podosomes in his career and expects to see a couple more.



Stepping up the tension in uPAR mediated cell signaling by integrins

Commentary on Nicolai Sidenius's paper published on *EMBO Journal*

by Michael Ploug

Tissue invasion and metastasis constitutes the last of the six hallmarks of cancer that was originally coined by Hanahan and Weinberg in their seminal reviews in *Cell* in 2000 and 2011. As both these processes are critically involved in the late stage systemic disease dissemination, they are considered major causative risk factors for the high mortality rates that are observed in many patients diagnosed with certain types of solid cancers. An intense research effort has accordingly been devoted to identifying components that are directly involved in and preferably rate limiting for disease progression via control of the invasive and metastatic potential. In this quest, the extracellular matrix in the tumor-stroma microenvironment represented one of the major focus areas as these insoluble structures limits invasion due to their barrier function, but at the same time they also promote migration by providing the essential structures needed for adhesion and cellular traction. Along these lines of arguments, the molecular mechanisms underlying either proteolytic remodeling of the extracellular matrix or impacting cell-matrix adhesion and

migration have received a lot of attention in the ongoing search for potential druggable protein targets, where a given pharmaceutical intervention is predicted to attenuate disease dissemination.

One of the proteolytic systems that is generally found upregulated at the tumor-stromal microenvironment of many solid cancers is the urokinase-type plasminogen activator (uPA) cascade, which catalyzes the conversion of the abundant proenzyme plasminogen to the active protease plasmin. Both stromal and cancer cells at the invasive fronts of the cancer lesions frequently express a high affinity receptor for uPA. The protein responsible for the high affinity uPA binding is the glycolipid-anchored uPA receptor (uPAR or CD87), which drives focalized plasminogen activation to the membrane surface of these cells. Numerous studies from different laboratories on resected tumor lesions or plasma from patients with solid cancer unanimously agree that high levels of uPAR expression either at the lesion site or shed into the circulation are powerful prognostic biomarkers entailing a

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poor overall patient survival. To further mature this translational potential of uPAR in a clinical setting several groups are presently developing new strategies for the non-invasive imaging of uPAR expression in patients by positron emission tomography and the first safety study in humans have just been completed (NCT02139371; ClinicalTrials.gov).

In the last two decades it has nonetheless also become increasingly clear that uPAR regulates other cellular processes not related to proteolysis. Early work pioneered by Nicolai Sidenius elegantly demonstrates that the interaction between the glycolipid-anchored uPAR at the cell surface and vitronectin immobilized onto an artificial rigid surface potently stimulates cell adhesion and migration (Madsen *et al.* 2007). The structure-functional rationale behind this observation has now been clarified in great detail. A combination of different biophysical measurements clearly demonstrates that the three-domain structure of unoccupied uPAR predominantly populates an open conformation, but ligation with uPA drives it into a closed and compact conformation (Mertens *et al.* 2012). Importantly, the closed conformation of uPAR represents the vitronectin binding proficient form setting the stage for an allosteric regulation of uPAR-mediated adhesion to vitronectin by uPA. In a biological perspective uPAR may thus induce a rendezvous between proteolytic remodeling and cell adhesion and migration. One essential part of the molecular puzzle underlying uPAR-induced cell adhesion remained, nonetheless, still to be solved.

The interaction between uPAR and vitronectin triggers ligand-independent adhesion signalling by integrins.

The urokinase-type plasminogen activator receptor (uPAR) is a non-integrin vitronectin (VN) cell adhesion receptor linked to the plasma membrane by a glycolipid anchor. Through structure-function analyses of uPAR, VN and integrins, we document that uPAR-mediated cell adhesion to VN triggers a novel type of integrin signalling that is independent of integrin-matrix engagement. The signalling is fully active on VN mutants deficient in integrin binding site and is also efficiently transduced by integrins deficient in ligand binding. Although integrin ligation is dispensable, signalling is crucially dependent upon an active conformation of the integrin and its association with intracellular adaptors such as talin. This non-canonical integrin signalling is not restricted to uPAR as it poses no structural constraints to the receptor mediating cell attachment. In contrast to canonical integrin signalling, where integrins form direct mechanical links between the ECM and the cytoskeleton, the molecular mechanism enabling the crosstalk between non-integrin adhesion receptors and integrins is dependent upon membrane tension. This suggests that for this type of signalling, the membrane represents a critical component of the molecular clutch.

[PMID 25168639]



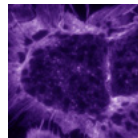
Stepping up the tension in uPAR
mediated cell signaling by integrins
by Michael Ploug

Being a glycolipid anchored membrane protein uPAR obviously lacks a *bone fide* signal transducing domain enabling the communication between extracellular ligand binding events and intracellular effector signal cascades. A central publication in Science by Wei *et al.* 1996 reporting that uPAR regulates integrin function by direct lateral interactions created the so far unopposed paradigm that uPAR-mediated signal transduction was caused by direct lateral molecular interactions between uPAR and various integrins.

Whereas it is beyond any reasonable doubt that integrin signaling indeed is essential for the uPAR-mediated effects on cell adhesion and migration, I have personally always had some concerns about the part of the model stating a direct and defined molecular interaction between uPAR and the

reconcile with the formation of a well-defined protein-protein interface.

Following this reasoning I find the alternative model for uPAR-mediated signal transduction in cell adhesion and migration that is proposed by Dr Sidenius and coworkers in The EMBO Journal (Ferraris *et al.* 2014) quite appealing. An important feature of their model is that it does not require direct protein-protein interactions between uPAR and the integrin heterodimers in question. Changes in membrane tension elicited by the uPAR interaction with vitronectin immobilized on rigid surfaces is according to this model allegedly sufficient to transmit signals from activated



Cell Matrix Signaling
Nicolai Sidenius

integrins in question.

Reviewing the literature on this alleged protein interaction it is accordingly very difficult to find hard core biophysical evidence proving the existence of such a direct molecular interaction as most data merely rely on circumstantial evidence indicating spatial proximity (e.g. FRET) or co-partitioning (co-IP) rather than a true molecular protein-protein interaction. In addition, the fact that uPAR did not appear selective but was described as a promiscuous regulator of integrin function was also in my opinion a bit difficult to



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integrins in a process that is independent of a direct integrin ligation to the matrix *per se*. To develop this controversial model for ligand-independent integrin signaling, Dr Sidenius conscientiously dissected the impacts of each of the participating component by uncoupling their function individually using cleverly designed intervention strategies. In the present commentary, I will only highlight one of these experiments, which I find particularly well-conceived.

The impact from the uPAR-vitronectin interaction in cellular signaling was ingeniously scrutinized using a vitronectin binding deficient uPAR^{T54A} mutant, which preferably populates the open receptor conformation. The mere addition of uPA or its small receptor binding growth factor-like domain to this construct momentarily switches uPAR^{T54A} into a vitronectin binding proficient state by driving it into its closed conformation. Using this molecular switch in combination with vitronectin mutants with mutated integrin binding site (RDG versus RAD) Dr Sidenius could elegantly isolate the individual contributions from integrins and uPAR engagements with the immobilized vitronectin.

By tethering different membrane proteins to rigid surfaces Dr Sidenius furthermore demonstrates that this alternative ligand-independent integrin signaling via increased membrane tension may represent a more general concept rather than

being limited to uPAR-vitronectin dependent signaling.

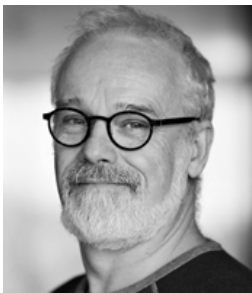
Bearing in mind that these initial hypothesis generating studies for obvious reasons were conducted entirely *in vitro* in cell cultures, it will be interesting to follow whether the same concept can be recapitulated in a more complex physiological setting.

From a cancer invasive and metastasis perspective it will furthermore be interesting to explore if the increased tissue rigidity introduced at some cancer lesions by the desmoplastic reaction is associated with a shift in the prevailing integrin mediated signaling pathways.



*Stepping up the tension in uPAR
mediated cell signaling by integrins*

The author:



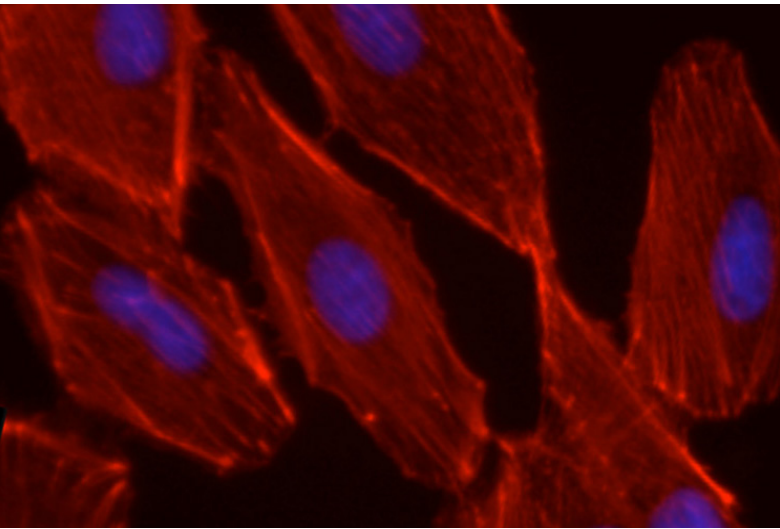
Michael Ploug

*Group Leader at Finsen Laboratory,
Rigshospitalet and Biotech Research & Innovation Centre*

Michael Ploug received his PhD in 1986 and dr.scient. in 2003 from University of Copenhagen for his work on structure-function relationships in the urokinase-type plasminogen activator receptor (uPAR) performed at the Finsen Laboratory headed by professor Keld Danø. The early part of his research was conducted in collaboration with IFOM Deputy Director professor Francesco Blasi (1988-1992) and their joint paper demonstrating

that uPAR is attached to the cell surface by a glycolipid anchor has been cited more than 500 times. Among other achievements Dr Ploug and collaborators solved the first X-ray structures of human and mouse uPAR, proved uPAR to be absent from cells isolated from paroxysmal nocturnal hemoglobinuria patients, discovered the allosteric regulation of vitronectin binding by uPA, and defined the underlying molecular basis. Based

on structural considerations he has recently advanced the design of a highly efficient peptide-based PET tracer for the non-invasive detection of uPAR expression in vivo in cancer patients and the first phase-1 safety study in humans has just been completed unveiling the full translational potential of this targeting peptide in a clinical setting. Dr Ploug has published approximately 100 peer-review articles yielding an H-factor of 41.



PREP1: a TALE of transcription factors, EMT and metastasis

Commentary on Francesco Blasi's paper published on *PNAS*

by Pasquale Verde

Epithelial Mesenchymal Transition (EMT) is a reversible process that triggers the loss of epithelial cell features, such as apico-basal polarity and intercellular adhesions, along with the gain of mesenchymal characteristics, including cytoskeletal rearrangements, individual migratory ability and invasiveness. In addition to its roles in embryo development and organ formation, EMT is involved in pathological conditions, such as wound healing, tissue fibrosis and cancer.

EMT is controlled by hierarchically organized transcription factors (EMT-TFs) belonging to multiple classes of nuclear proteins, such as Zn finger (SNAIL1, SNAIL2/SLUG, ZEB 1 and ZEB2/SIP1) and bHLH (TWIST1 and TWIST2) families.

In response to ectopically re-expressed EMT-TFs, EMT is involved in the key steps of metastatic colonization. TGF-beta, secreted by both autocrine and paracrine mechanisms often mediated by cancer-stromal cell interactions at the invasive front of tumors, is one of the major inducers of tumor-associated EMT.

My group is currently studying the EMT controlled by the AP-1 complex and specifically the FOS-family component FRA-1, recently implicated in metastasis mechanisms. My interest for the AP-1 oncoproteins began long time ago, when I was a post-doctoral fellow in Francesco Blasi's laboratory, while studying the transcription factors controlling the human urokinase gene (*PLAU*) in response to oncogenic signals. In the meanwhile, starting from the identification of the nuclear factors cooperating with AP-1 in the control of the *PLAU* enhancer, Francesco Blasi has undertaken a highly successful all-round study of PREP1, a TALE family transcription factor.

The TALE (Three Aminoacids Length Extension) homeodomain subfamily includes 4 Pbx, 3 Meis and 2 Prep/Pknox genes. Blasi and collaborators have investigated all major biological roles of PREP1 in mouse models and *in vitro* cell systems. In addition to studying various aspects of *PREP1* in mouse development, Francesco Blasi has recently characterized *PREP1* as a haploinsufficient tumor suppressor involved in both hematopoietic and

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solid tumorigenesis. In addition to elucidating the PREP1 role in maintenance of genome stability, Francesco Blasi, in collaboration with Miguel Torres (CNIC, Madrid), has elucidated the mechanisms of target site selection by the dimeric TALE homeoprotein complexes, by genome-wide analyses of the PREP1/PBX1/MEIS1 DNA-binding profiles. Importantly, Blasi and coworkers have recently shown how PREP1 oncosuppressor activity results from the PREP1 competition with the MEIS1 for PBX1 binding, affecting the MEIS1 stability and tumorigenic activity.

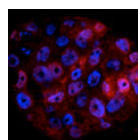
By identifying the PREP1 transcript as a target of miR-19a, belonging to the miR-17-92 *oncomir* cluster, my group had previously stumbled upon PREP1. To understand the significance of the miR-19-mediated regulation of PREP1, we analyzed the effects of PREP1 in NSCLC cell lines. When my PhD student Maurizio Risolino, observed striking morphological changes in PREP1-overexpressing cells, I had a great occasion to start a new collaboration with Francesco Blasi, many years after the *PLAU* enhancer story. Francesco enthusiastically agreed with our incursion into his preferred gene product, and hosted my PhD student Nadia Mandia for a short but fruitful stay in his laboratory at IFOM.

By investigating various EMT markers along

Transcription factor PREP1 induces EMT and metastasis by controlling the TGF- β -SMAD3 pathway in non-small cell lung adenocarcinoma.

Pre-B-cell leukemia homeobox (Pbx)-regulating protein-1 (Prep1) is a ubiquitous homeoprotein involved in early development, genomic stability, insulin sensitivity, and hematopoiesis. Previously we have shown that Prep1 is a haploinsufficient tumor suppressor that inhibits neoplastic transformation by competing with myeloid ecotropic integration site 1 for binding to the common heterodimeric partner Pbx1. Epithelial-mesenchymal transition (EMT) is controlled by complex networks of proinvasive transcription factors responsive to paracrine factors such as TGF- β . Here we show that, in addition to inhibiting primary tumor growth, PREP1 is a novel EMT inducer and prometastatic transcription factor. In human non-small cell lung cancer (NSCLC) cells, PREP1 overexpression is sufficient to trigger EMT, whereas PREP1 down-regulation inhibits the induction of EMT in response to TGF- β . PREP1 modulates the cellular sensitivity to TGF- β by inducing the small mothers against decapentaplegic homolog 3 (SMAD3) nuclear translocation through mechanisms dependent, at least in part, on PREP1-mediated transactivation of a regulatory element in the SMAD3 first intron. Along with the stabilization and accumulation of PBX1, PREP1 induces the expression of multiple activator protein 1 components including the proinvasive Fos-related antigen 1 (FRA-1) oncoprotein. Both FRA-1 and PBX1 are required for the mesenchymal changes triggered by PREP1 in lung tumor cells. Finally, we show that the PREP1-induced mesenchymal transformation correlates with significantly increased lung colonization by cells overexpressing PREP1. Accordingly, we have detected PREP1 accumulation in a large number of human brain metastases of various solid tumors, including NSCLC. These findings point to a novel role of the PREP1 homeoprotein in the control of the TGF- β pathway, EMT, and metastasis in NSCLC.

[PMID 25157139]



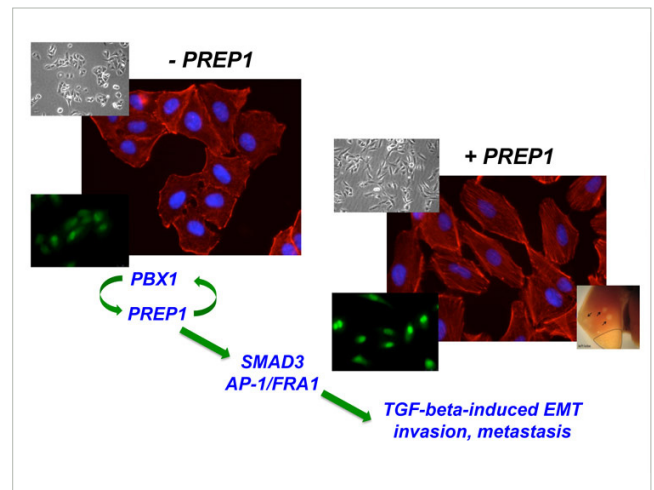
*Transcriptional Regulation
in Development and Cancer*
Francesco Blasi

PREP1: a TALE of transcription factors,
EMT and metastasis
by Pasquale Verder

with cell motility and invasion, Risolino, *et al.* showed that the observed modifications reflected the mesenchymal transition triggered by PREP1. Mechanistic analysis revealed that PREP1 positively controls the TGF-beta-SMAD pathway, with an effect at least partially mediated by PREP1-mediated transactivation of *SMAD3*. PREP1, in addition causes the accumulation of its heteromeric partner PBX1 and of the FRA-1 oncoprotein, both required for the PREP1-induced mesenchymal transition.

Lung colonization assays revealed that PREP1-overexpressing cells, but not the poorly invasive control (A549) cells, gave rise to lung nodules. Accordingly, in collaboration with Michel Mittelbronn (Frankfurt Medical School), PREP1 accumulation was detected in a large number of human brain metastases of solid tumors, including NSCLC. These findings seem to contradict the previously reported tumor suppressor role of *PREP1*. Such discrepancy, however, is only apparent, since, differing from lung nodules, the PREP1-overexpressing xenografts exhibited decreased growth. Thus, PREP1 seems to play a dual function that might reflect the dual role (antiproliferative vs pro-metastatic) of the TGF-beta pathway in tumorigenesis. While a previous report from Michael Cleary's group, based on the analysis of *Pbx1* knockout mice, had suggested the possible role of *Pbx1* in the responses to TGF-beta, Risolino *et al.* provided the first evidence on the involvement of human PREP1 in EMT and metastasis, by TGF-beta-SMAD-dependent mechanisms.

Therefore, thanks to the open mind and generosity of Francesco Blasi, our fruitful collaboration resulted in the identification of a novel player in the complex network of transcription factors implicated in EMT.



Phase-contrast and phalloidin staining show the mesenchymal changes exhibited by PREP1 overexpressing vs parental A549 cells. Green fluorescence shows the nuclear accumulation of SMAD3. Arrows in the bottom-right image indicate the nodules formed by A549PREP1 cells in nude mice.

PREP1: a TALE of transcription factors,
EMT and metastasis

The author:



Pasquale Verde

Research Director at the CNR Institute of Genetics and Biophysics, Naples

Pasquale Verde graduated in Medicine (1981, University of Naples Federico II) with an experimental Thesis on transcriptional control in prokaryotes (Regulation of the His operon in *E. Coli*). Pasquale Verde has been a post-doctoral fellow in the laboratory of Francesco Blasi, where he worked on the transcriptional regulation of the human urokinase gene, at the CNR

International Institute of Genetics and Biophysics (Naples), where he was appointed as Researcher in 1984. During 1986-1987 he moved as Visiting Fellow at the Columbia University Comprehensive Cancer Center (NYC, NY), directed by Dr. ME Gottesmann. Since 1992, as group leader at CNR IIGB, he has been studying multiple aspects of the AP-1 complex in neoplastic transformation, with

recent focus on the transcription factor FRA-1. Presently, he is CNR Research Director and his research interests are focussed on the regulatory interactions between transcription factors (FRA-1, TALE homeoproteins, p53) and miRNAs in epithelial-mesenchymal-transition and neoplastic transformation.

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Corporate profile

IFOM, the FIRC Institute of Molecular Oncology, is an Italian highly technology, non-profit research centre supported by FIRC, the Italian Foundation for Cancer Research. Research conducted at IFOM aims to understand the molecular processes responsible for the onset and development of cancer.

To meet the demands of modern-day science, IFOM created a research environment where scientists from the major national scientific institutions in the Milan area could collaborate and pool their organisational, economical and cultural resources. The creation of a research institute “network” was the first of its kind in Italy and has made IFOM an internationally competitive research centre in molecular oncology and functional genomics.

IFOM has been recognised as a Centre of Excellence for Research by the Lombardy Regional Council, which also contributed to IFOM's development.

Having established a solid base in basic research, IFOM is now concentrating its efforts on translational research for the rapid transfer of scientific findings from the laboratory to diagnostic and therapeutic clinical practice. IFOM has adopted a strong international approach, fostering partnerships with world-class research institutes in Singapore and India. Thanks to these agreements, IFOM is becoming an important player in the global landscape of cancer research institutions.

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