2015

A YEAR IN REVIEW

IFOM
FIRC INSTITUTE OF MOLECULAR ONCOLOGY

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About IFOM Review

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

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

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

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

Marco Foiani

Francesco Blasi

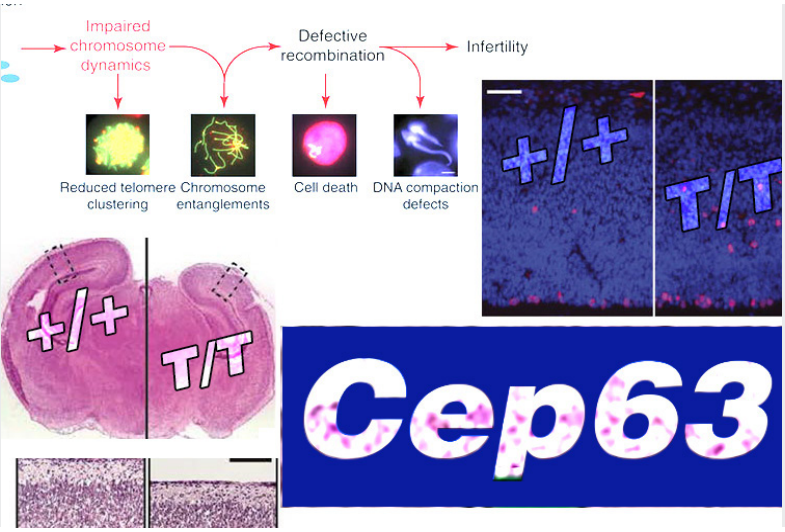
The authors:

Marco Foiani
Scientific Director

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

Francesco Blasi
IFOM Deputy Director

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



p53-dependent apoptosis: novel insight into the basis underlying microcephaly

A commentary on Vincenzo Costanzo's paper published in *Nature Communications*

by Penny Jeggo

Autosomal recessive primary microcephaly (MCPH) and Seckel Syndrome (SS) are overlapping disorders characterised by a reduced head circumference. MCPH has no or mild growth delay; growth delay in SS can be severe. Many causal genes for microcephaly encode centrosomal proteins although DNA damage response (DDR) genes have also been described. CEP63 is the causal defect in one MCPH/SS family with marked microcephaly and mild growth delay1. CEP63 co-localises with pericentrin (PCNT), a well-studied centrosome protein, and regulates the centrosomal localisation of CEP152, a conserved centrosome duplication factor 2. CEP152/63 form a ring like structure around the parental centriole, and CEP63 loss in patients causes centrosome loss.

To investigate how CEP63 loss causes microcephaly, Costanzo, Stracker and colleagues examined neuronal development in mice with inactivated Cep63 3. Cep63 T/T, like CEP63 deficient patients, displayed growth delay and small head size. The mice showed abnormal Cep152 localisation in the embryonic neocortex and cells with monopolar spindles or abnormal spindle poles. Strikingly, in the embryonic neural stem cell region, the ventricular/subventricular zone (VZ/SVZ), the mitotic cell number was modestly increased with mitotic cells being frequently mislocalised. Enhanced apoptosis was observed throughout the neocortex. p53 is a DDR protein that regulates apoptosis. Strikingly, apoptosis was suppressed in p53-/-Cep63T/T mice and normal head size completely restored, although aberrant mitotic cell localisation remained. Thus, a striking finding is p53-dependent apoptotic activation arising from centrosome/mitotic abnormalities.

The embryonic VZ/SVZ cells proliferate rapidly from E11.5 to E16.5, initially via symmetric division to generate two daughter stem cells; subsequently, a switch to asymmetric division occurs producing a daughter destined to become a neuron. Premature switching to asymmetric division will diminish stem cell accrual and has been proposed as a mechanism underlying reduced brain size4. Centrosome dysfunction has been proposed to promote premature switching. However, centrosome loss remains in p53-/-

Cep63T/T mice suggesting that this cannot directly confer microcephaly. Cilia emanate from centrioles, the centrosome basal body and centrosome dysfunction impairs cilia signalling, providing a further possible causal mechanism. However, this defect will also remain in p53-/-Cep63T/T mice.

Elevated apoptosis correlates with microcephaly in other situations, such as radiation exposure or mouse models defective in the major DNA double strand break (DSB) repair pathway. LigIV-/- mice (DSB repair deficient) are embryonic lethal due to extensive neuronal apoptosis, which is rescued by p53 loss 5. Such apoptosis is DSB driven and ATM (a DDR kinase)-dependent; aberrant replication can activates ATR-dependent apoptosis. Yet DNA damage was not detected in Cep63T/T mice. Previous studies have observed p53 activation following centrosome loss. Importantly, two recent studies have provided mechanistic insight into a p53-dependent centrosome surveillance pathway, which is activated by centrosome loss or extended mitotic duration without detectable DNA damage 6, 7. p53 activation prevented cell cycle progression in the system examined.

So why does apoptotic induction preferentially confer microcephaly. Recent studies examining the haematopoietic system suggest that proliferating progenitors are sensitive to apoptosis whilst quiescent stem cells are resistant[8]. Adult neural SVZ stem/progenitor cells appear to behave similarly[9]. Rapid proliferation in the embryonic VZ/SVZ generates a large number of apoptotic-sensitive proliferating progenitor cells. Indeed, apoptosis in the VZ/SVZ of mice hypomorphic for LigIV is greater than in most other tissues[10]. Thus, the embryonic brain may be exquisitely sensitive to apoptosis because it has an abundance of sensitive cells. Since replication ceases by E16.5, further progenitor replenishment may be precluded.

Cells from multiple SS patients display supernumerary centrosomes, which also likely prolongs mitosis 11. Thus, activation of apoptosis by centrosome abnormalities may be a common mechanism driving microcephaly in patients. However, abnormal mitoses persist in p53-/-Cep63T/T mice, potentially causing neuronal dysfunction despite normal head size. Patients lacking ATM do not show microcephaly but rather progressive ataxia, and it is tempting to speculate that the persistence of damaged neurons could be a contributing factor.

In summary, this significant study demonstrates that activation of p53-dependent apoptosis due to Cep63 loss confers microcephaly. This could represent a common mechanism for microcephaly since neuronal development produces many apoptotic-sensitive progenitor cells. Understanding the basis underlying microcephaly is currently important to evaluate the impact of the Zika virus.

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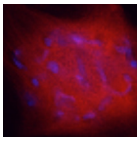
CEP63 deficiency promotes p53-dependent microcephaly and reveals a role for the centrosome in meiotic recombination

CEP63 is a centrosomal protein that facilitates centriole duplication and is regulated by the DNA damage response. Mutations in CEP63 cause Seckel syndrome, a human disease characterized by microcephaly and dwarfism. Here we demonstrate that Cep63-deficient mice recapitulate Seckel syndrome pathology. The attrition of neural progenitor cells involves p53-dependent cell death, and brain size is rescued by the deletion of p53. Cell death is not the result of an aberrant DNA damage response but is triggered by centrosome-based mitotic errors. In addition, Cep63 loss severely impairs meiotic recombination, leading to profound male infertility. Cep63-deficient spermatocytes display numerical and structural centrosome aberrations, chromosome entanglements and defective telomere clustering, suggesting that a reduction in centrosome-mediated chromosome movements underlies recombination failure. Our results provide novel insight into the molecular pathology of microcephaly and establish a role for the centrosome in meiotic recombination.
[PMID 26158450]



DNA metabolism
Vincenzo Costanzo

p53-dependent apoptosis: novel insight into the basis underlying microcephaly

The author:

Penny Jeggo

University of Sussex, Brighton, UK

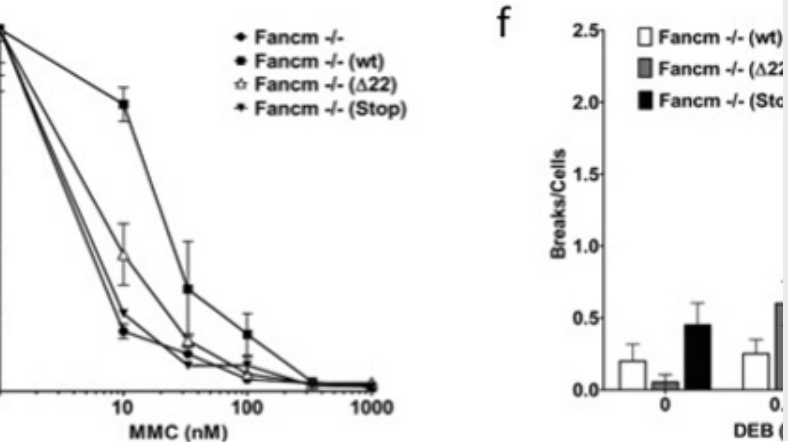
Penny Jeggo undertook her PhD in Dr. Robin Holliday's laboratory at the National Institute of Medical Research (NIMR), London and post doctoral fellowships with John Cairns at the Imperial Cancer Research Fund and Miroslav Radman at the Universite Libre de Bruxelles. These early studies exploited model organisms to study the DNA damage response.

In 1980, Penny returned to NIMR to identify genes conferring radiosensitivity in mammalian cells. In 1989, Penny moved to the Cell Mutation Unit at Sussex University and in 2001 became a founding member of the Genome Damage and Stability Centre with the School of Life Sciences, University of Sussex.

Penny isolated radiosensitive rodent cell lines that proved to be defective in DNA double strand break repair. These studies led to the identification of genes required for DNA non-homologous end-joining (NHEJ) and mechanistic insight into the process. Subsequently, she identified patients defective in NHEJ, revealing the link to microcephaly.

Penny has contributed to committees and workparties considering radiation effects, particularly those of relevance to radiation protection. She has been chair of UK's Association for Radiation Research and is currently secretary-treasurer of the International Association for Radiation Research.

Penny received the Bacq and Alexander Award from the ERRS in 2011, the Silvanus Thompson Award from the BIR in 2013 and Genome Damage and Stability Network Award in 2013. She was elected a fellow of the Academy of Medical Sciences in 2012.



FANCM - a new cancer susceptibility gene?

Commentary on Paolo Peterlongo's paper published in *Human Molecular Genetics*.

by William D Foulkes

science

Breast cancer susceptibility genes

Over twenty years ago, the important breast cancer susceptibility genes, BRCA1 and BRCA2 were discovered. Since this time, the search for "BRCA3" has been vigorously pursued by many laboratories around the world. Several candidate susceptibility genes have been identified, but none match the unique properties held by mutations in BRCA1 and BRCA2 – that is, being both highly penetrant and quite frequent in most populations. Nevertheless, an international collaborative group, including Dr. Paolo Peterlongo and myself, showed in 2014 that PALB2 is a bona fide cancer susceptibility gene associated with a clinically significant risk for breast (and possibly other) cancers.

The challenge now is to validate the many other candidate breast cancer susceptibility genes that have emerged from large-scale studies in Europe and North America. One such study has been led by Dr. Paolo Peterlongo, from IFOM, the FIRC Institute of Molecular Oncology, in Milan and has uncovered an association between the presence of likely pathogenic mutations in the gene encoding FANCM, a member of the Fanconi Anemia (FA) protein family, and risk for breast cancer.Cell therapy for muscular dystrophy.

How was *FANCM* discovered?

FANCM, initially known as FAAP250, was identified in 2005 as a human ortholog of the ancient bacterial DNA repair protein, Hef1, via mass spectrometry analysis of FA protein complexes. While its role as a true FA protein is questionable (see below) it does have key DNA repair functions, briefly outlined below. Since nearly all existing breast cancer susceptibility genes appear to have roles in DNA repair, *FANCM* is a priori a candidate breast cancer susceptibility gene.

What does it do?

There are 19 FA associated proteins. Among many functions, it is believed that *FANCM* acts as a DNA translocase, and interacts with a number of partners to recognise stalled replication forks and activate the FA pathway. Other FA core components are then recruited to the DNA

lesion. However, it is not clear that *FANCM* is a bona fide FA gene, since several homozygous mutation carriers have been found not to have any molecular or clinical signs of FA, and the only known carrier of biallelic mutations in *FANCM* was later found to have mutations in FANCA, another FA gene, as well.

How was FANCM linked to breast cancer?

A study of multiple-case breast cancer families identified a single affected woman who was heterozygous for a variant in *FANCM* known as c.5791C>T (rs144567652). Further analysis of several thousand cases suggested that this variant was associated with breast cancer risk, but the sample size, while large in the first study, was not definitive, because the variant was only seen in about 3 in 1000 women with breast cancer. A subsequent study, lead by Dr. Peterlongo, which analysed 8635 familial breast cancer cases and 6625 controls from several different countries for this single mutations c.5791C>T, found an association between this mutation and breast cancer risk [odds ratio = 3.9 (95% confidence interval = 1.3–12.1; P = 0.017)]. Functionally, it was shown that this mutation causes an out-of-frame deletion of exon 22, resulting from the creation of a de novo binding site for the pre-mRNA processing protein hnRNP A1; moreover, genetic complementation analyses showed that the c.5791C>T mutation can influence the DNA repair activity of *FANCM*. Along with another study, suggesting that a Finland-specific *FANCM* mutation is associated with triple negative breast cancer, these observations are quite compelling. Additional support for these data comes from a large study of 4034 cases of a total of 12 tumor types, published in Nature Communications in 2015, which revealed that using a total frequency test *FANCM* was significantly enriched for germline truncating mutations in breast cancer – in fact, *FANCM* was the third most-frequently mutated gene, after BRCA1 and BRCA2, but this excess did not cross the 5% false discovery rate threshold.

FANCM c.5791C>T nonsense mutation (rs144567652) induces exon skipping, affects DNA repair activity and is a familial breast cancer risk factor.
Numerous genetic factors that influence breast cancer risk are known. However, approximately two-thirds of the overall familial risk remain unexplained. To determine whether some of the missing heritability is due to rare variants conferring high to moderate risk, we tested for an association between the c.5791C>T nonsense mutation (p.Arg1931; rs144567652) in exon 22 of FANCM gene and breast cancer. An analysis of genotyping data from 8635 familial breast cancer cases and 6625 controls from different countries yielded an association between the c.5791C>T mutation and breast cancer risk [odds ratio (OR) = 3.93 (95% confidence interval (CI) = 1.28-12.11; P = 0.017)]. Moreover, we performed two meta-analyses of studies from countries with carriers in both cases and controls and of all available data. These analyses showed breast cancer associations with OR = 3.67 (95% CI = 1.04-12.87; P = 0.043) and OR = 3.33 (95% CI = 1.09-13.62; P = 0.032), respectively. Based on information theory-based prediction, we established that the mutation caused an out-of-frame deletion of exon 22, due to the creation of a binding site for the pre-mRNA processing protein hnRNP A1. Furthermore, genetic complementation analyses showed that the mutation influenced the DNA repair activity of the FANCM protein. In summary, we provide evidence for the first time showing that the common p.Arg1931* loss-of-function variant in FANCM is a risk factor for familial breast cancer.*
[PMID 26130695]

Are *FANCM* mutations found in other cancers/ conditions?

In the abovementioned Nature Communications study, germline *FANCM* mutations were unexpectedly frequent in persons with head and neck squamous cell carcinoma (HNSCC) and clear cell carcinoma of the kidney (RCC). Many of the germline *FANCM* mutations were associated with LOH, suggesting that they might be biologically important. Notably, using a Wilcoxon rank-sum test, *FANCM* mutations were associated with a greater number of somatic mutations in HNSCC and RCC, than in tumors without *FANCM* mutations.

Where do we go next?

Validation of *FANCM* as a breast cancer susceptibility gene will require much larger studies than already been conducted; to disprove that BRIP1 was a breast cancer susceptibility gene required genotyping for one variant in a combined total of 91,000 cases and controls, and full sequencing of the gene in a further 24,000 women. These types of sample sizes are needed for rare variants with modest effects. Thus, along with functional studies, further sequencing is in order, but Dr. Peterlongo has certainly identified a strong candidate breast cancer susceptibility gene – no mean feat.

FANCM – a new cancer susceptibility gene?

The author:

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William Foulkes MBBS PhD FRCP FRCPC is a clinician-scientist who investigates the causes and consequences of inherited cancers.

He trained in medicine at Barts Hospital in London and completed his training, in cancer genetics, at McGill, where he is presently a James McGill Professor in the Departments of Human Genetics, Medicine and Oncology.

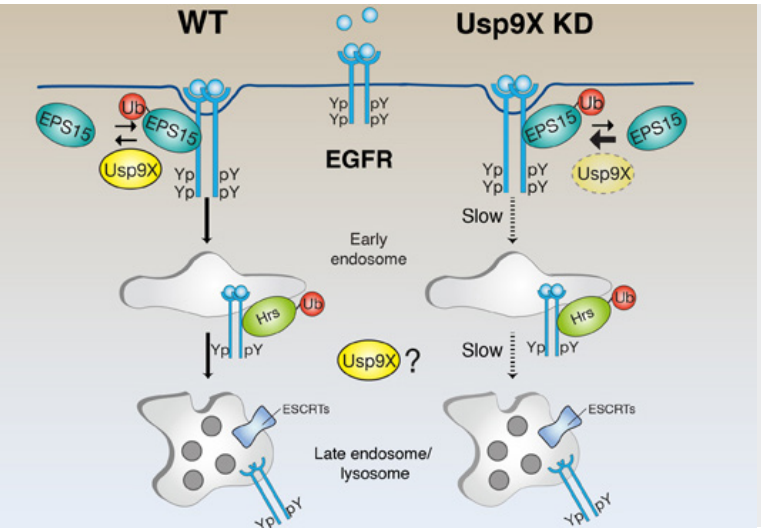
In addition to his contributions to our knowledge of inherited susceptibility to cancer, he has played a major role in translating research findings to the clinic, most extensively on susceptibility to breast, colorectal and ovarian cancer.

In 2005, he established the BRCA symposium, a biennial international symposium on hereditary breast and ovarian cancer, which has become the leading conference in the world on this subject.

Recently, he began to investigate rare pediatric cancer susceptibility syndromes, such as that caused by germ-line mutations in the gene called DICER1. He has published over 400 papers, many in leading journals including Nature Genetics, the New England Journal of Medicine, JAMA and the Journal of the National Cancer Institute; his work has been cited over 15,000 times.

He is an Associate Editor of the Journal of Pathology. In 2010, Dr. Foulkes was made a Scholar of the Susan G. Komen Foundation (US), and in 2013 he was awarded the prestigious O. Harold Warwick Prize for Cancer Control of the Canadian Cancer Society.

He was elected to the Canadian Academy of Health Sciences in 2014.



Deubiquitination enzymes in the limelight

Commentary on Simona Polo's paper published on *Current Biology*

by Yossi Yarden

science

Although mutations affecting critical genes are the major drivers of cancer, tumor cells, especially those starting their journey to full malignancy, depend on growth factors for renewed cycles of proliferation, attraction of blood vessels, as well as for their resistance to chemo- and radiotherapy. Some tumors free themselves from the reliance on growth factors by expressing constitutively active, mutant forms of either the respective receptors or the downstream biochemical pathways. A typical example is provided by the epidermal growth factor (EGF) family. All members of this group avidly bind with a cell surface receptor, called EGFR, the cytoplasmic portion of which harbors an enzymatic activity, namely a tyrosine-specific protein kinase. By simultaneously phosphorylating multiple substrates, EGFR initiates several biochemical and metabolic pathways playing essential roles in tumor progression and colonization of distant organs. Normally, the cellular "ON" state is rapidly downregulated by means of EGF-induced ubiquitination of EGFR and subsequent ubiquitin-dependent sorting of activated receptors to internalization and degradation in lysosomes. However, oncogenic mutant forms of EGFR, such as mutants frequently detected in lung cancer, evade endocytosis or they rapidly recycle back to the plasma membrane.

An elegant report published in Current Biology in 2015 by the research team of Dr. Simona Polo sheds new light on the important process that targets EGFR, and possibly additional growth factor receptors, to intracellular degradation. Because covalent tagging of EGFRs with ubiquitin instigates the whole process, CBL, the enzyme in charge of receptor ubiquitination, for example is stealing the limelight from other molecules engaged by EGFRs while en route. Especially interesting are the deubiquitinating enzymes (denoted DUBs), which reverse ubiquitination, and scaffold proteins like HRS, EPS15, EPSIN and STAM, which bind ubiquitin, lipids or membrane coat proteins associated with the endocytic process. What complicates the matter is the observation, originally made in yeast cells, that scaffold ubiquitination, similar to cargo ubiquitination, is necessary for receptor

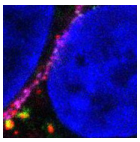
endocytosis, and both entail mono-ubiquitination. To dig deeper into the roles played by cargo and scaffold ubiquitination, Polo and her colleagues employed a library of small RNAs, each blocking expression of one of the approximately 100 DUBs encoded by the human genome. As readout of functional interference, they assayed degradation of EGFRs while using highly sensitive quantitative tests their laboratory previously established. This genome-wide systematic approach permitted identification of a remarkably large group of 18 candidate molecules, including some DUBs previously identified by other teams, all affecting the rate of EGF-induced degradation of EGFR.

Although the Polo lab focused on one DUB, USP9X, the other 12 new enzymes they identified will likely open many windows into the main receptor desensitization process and its manipulation in malignancies. For example, by using RNA interference screens, my own group identified in 2012 another DUB, OTUD7/Cezanne-1, as an enzyme that directly deubiquitinates EGFR by forming a physical complex with the receptor and preventing its sorting for intracellular degradation. In line with the ability of OTUD7/Cezanne-1 to augment EGFR signaling, the corresponding gene is amplified in approximately one third of human breast tumors, and high transcript levels predict an aggressive disease course. Unlike OTUD7/Cezanne-1, which modifies cargoes, Simona and her colleagues clearly showed that USP9X affects one or more scaffolds of the endocytic process, primarily EPS15. As befits a non-catalytic scaffold, EPS15 comprises several structural motifs, including two ubiquitin interacting motifs, UIMs. In 2002 Simona reported in Nature that the UIMs of several scaffolds (e.g., EPS15, EPS15R, Epsins and HRS) is responsible for two activities: ubiquitin recognition and monoubiquitination of the scaffold. After clearly establishing that USP9X modifies EPS15 rather than directly EGFR, the team showed that this DUB is nevertheless necessary for rapid internalization and degradation of EGFR, while other receptors tested, for example the transferrin receptor, are not be regulated by the DUB they identified.

USP9X Controls EGFR Fate by Deubiquitinating the Endocytic Adaptor Eps15.
Following activation by its cognate ligand(s), the epidermal growth factor receptor (EGFR) is rapidly routed to the lysosome for degradation in a ubiquitination-dependent fashion. This pathway represents the major mechanism of long-term attenuation of EGFR signaling, and its deregulation is a significant feature in different types of cancers. Here we demonstrate, through a systematic RNAi-based approach, that several deubiquitinating (DUB) enzymes extend or decrease EGFR half-life upon EGF stimulation. We focus on USP9X, whose depletion severely affects EGFR turnover, interfering with its internalization and trafficking. We identify the endocytic protein Eps15 as one of the critical substrates of USP9X, and we map the Eps15 ubiquitination sites. We found that Eps15 monoubiquitination occurs already at minimal dose of EGF stimulation and is essential for EGFR internalization. Overall, our findings identify USP9X as a novel regulator of EGFR endocytosis and suggest a model whereby cycles of ubiquitination and deubiquitination events on endocytic accessory proteins may regulate the internalization and trafficking of the EGFR toward the lysosomes.
[PMID 26748853]

The availability of new information and reagents able to modify the interaction between USP9X and EPS15, including a mutant form of EPS15 that undergoes no ubiquitination, will surely inspire renewed attempts to resolve the roles played by the coordinated monoubiquitination of both cargo and scaffold molecules. The prevailing dogma assumes that the scaffolds attach to cargo's ubiquitins, but scaffold monoubiquitination instigates an intramolecular folding responsible for dissociation of the scaffold-cargo complex. Repeated cycles of cargo engagement might underlay sorting of receptors at the plasma membrane and also later, at the early and late endosomes, toward lysosomes. In line with this model, Polo and her team demonstrated that USP9X is involved in EGFR sorting occurring at the plasma membrane, as well as at subsequent, intracellular trafficking stations. Still, their results attribute an interesting role for EPS15 in sustaining the interaction with cargoes, as well as call for re-examination of the current dogma.

Highlighting all of the future streams of research opened by the elegant study performed by Simona and colleagues would be quite challenging. One example is provided by the identification, made by another laboratory, of an ubiquitin ligase potentially mediating EPS15 monoubiquitination. The ligase, called Parkin, is one of a few genes mutated in patients with familial Parkinson's disease, a degenerative disorder of the central nervous system, mainly affecting the motor system. Treatment of cells with EGF stimulates Parkin binding to both EPS15 and the EGFR and promotes ubiquitination of EPS15. Conceivably, the interplay between Parkin and USP9X normally regulates EGFR signaling and protects motor neurons from apoptosis, but this steady state is defective in familial and other forms of Parkinson's disease, leading to some symptoms of Parkinson's disease. Thus, the 2015 publication from IFOM might provide novel keys to understanding not one but two major diseases, cancer and Parkinson's disease.



Ubiquitin and Signal Transduction
Simona Polo

Deubiquitination enzymes in the limelight

The author:

Yossi Yarden
Department of Biological Regulation

Born in Israel, Yosef Yarden received his B.Sc. in Biological and Geological Sciences from the Hebrew University of Jerusalem (1980), and a Ph.D. in Molecular Biology from the Weizmann Institute of Science (1985). His postdoctoral training was undertaken at Genentech, Inc. (c/o Axel Ullrich) in San Francisco, and at the Massachusetts Institute of Technology (c/o Robert A. Weinberg). In November 1988, he returned to the Weizmann Institute of Science as an Assistant Professor and was appointed Associate Professor in 1992, and Full Professor in 1996. His past administrative responsibilities at the Weizmann Institute include Dean of the Faculty of Biology (1997-1999), Vice-President for Academic Affairs (1999-2001), Director of the M.D. Moross Institute for Cancer Research (1999-2001), and Dean of the Feinberg Graduate School (2001-2007).

On the national level, Prof. Yarden served as Chair of the Research Committee of the Israel Cancer Association, and the Israel National Committee on Biotechnology, an advisory body of the Government of the State of Israel.

In January 2011 he was elected President of the Federations of Israel Societies of Experimental Biology (FISEB/ILANIT).

Among Yarden's honors and awards are the John F. Kennedy Award (1984), The Chaim Weizmann and the Irvington House Institute Fellowships (1985 and 1986), the Alon Fellowship of the Israel Council for High Education (1988), the H. Dudley Wright Research Award (1990), a Research Career Development Award from ICRF (1990), the Shlomo Hestrin Prize of the Israel Society for Biochemistry and Molecular Biology (1991), the Somech Sachs Prize in Chemistry (1992), the Sergio Lombroso Prize in Cancer Research (1994), the Andre Lewoff Prize (1995), the Michael Bruno Memorial Award of Yad Hanadiv (Rothschild Family Prizes; 2000), the TEVA Founders Prize (2004), the MERIT Award of the U.S. National Cancer Institute (2005), the EMET Prize in Biochemistry (2007), the 2008 Hamilton Fairly Award of the European Societies for Medical Oncology (ESMO), the Gold Medal of the Israeli Societies for Clinical Oncology and Radiation Oncology (ISCORT; 2010), the Ernst W. Bertner Memorial Award of the M.D. Anderson Cancer Center (2011), the Susan G. Komen for the Cure® Brinker Award for Scientific Distinction in Basic Research (2012) and Leoplod Griffuel Award of Fondation ARC pour la Recherche sur le Cancer (2015). In 2007, Yarden was elected member of the Israel Academy of Sciences and Humanities. He is a member of the European Molecular Biology Organization (EMBO) and the Asia-Pacific International Molecular Biology Network (A-IMBN).

At the Weizmann Institute, Prof. Yarden is the Harold and Zelda Goldenberg Professor of Molecular Cell Biology. Currently, Yarden's research is supported by the US National Cancer Institute, a grant from the European Research Council (ERC-AdG), the German Research Foundation (DIP) and a professorship from the Israel Cancer Research Fund (ICRF).

Publications

Blood circulating tumor DNA for non-invasive genotyping of colon cancer patients.

Siravegna G, Bardelli A.

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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.

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