Swedish Royal Academy of Sciences

Protein Quality Control in Health and Disease

May 28-29,2026

A few words from the organizers

The viability of all organisms depends on maintaining a healthy proteome. Endogenous and exogenous challenges, including developmental programs, environmental insults, and disease conditions, jeopardize protein homeostasis. The heat shock response, integrated stress response, and unfolded protein response are examples of complex molecular systems that detect and respond to proteotoxic stress. In addition, ribosome quality control has emerged as a key regulator of proteome integrity. The importance of proteostasis is underscored by the many human diseases associated with or caused by malfunctions in translation quality control and stress responses. These include many neurodegenerative disorders and non-neurological conditions, such as diabetes, cardiac, lung, and liver diseases, infections, and cancer. The diverse pathologies underscore the importance of promoting a concerted multidisciplinary effort to understand the players and rules of proteostasis.

The conference brings together leading researchers in various aspects of proteostasis, offering a unique platform for exchanging ideas and presenting cutting-edge findings. Key topics will include protein synthesis, folding, and degradation; the effectors and regulators of the quality control machinery and stress responses; and the regulation of these processes in aging and disease.

Venue

Broadcast

Contact

Program

May 28

9.00 – 9.10 Conference opening *(Maria Masucci, Gunnar von Heijne, Nico Dantuma)*

Session I - Protein folding and molecular chaperones

Chairperson: Gunnar von Heijne, Stockholm University

9.10 – 10.00 David Balchin, The Crick Institute, London, UK

"Molecular logic of chaperone generalists"

10.00 – 10.50 Manu Hegde, LMB, Cambridge, UK

"The machinery and mechanisms of membrane protein biogenesis"

10.50 – 11.10 Coffee break

11.10 – 12.00 Gunnar von Hejne, Stockholm University, Sweden

"Cotranslational compaction and folding of a multidomain protein"

12.00 – 13.30 Lunch

Session II – Transcriptional and Ribosomal stress responses

Chairperson: Vicent Pelechano, Karolinska Institutet

13.30 – 14.20 Claudio Joazeiro, Heidelberg University, Heidelberg, Germany

"Ribosome-associated Quality Control (RQC): mechanisms, evolution, and roles in neurodegeneration."

14.20 – 15.10 Jesper Svejstrup, University of Copenhagen, Copenhagen, Denmark

"*Transcriptional buffering of RNA polymerase II availability*"

15.10 – 15.30 Coffee break

Short Talks

Chairperson: Neus Visa, Stockholm University

15.30 – 15:50 Oscar Fernadez-Capetillo, Karolinska Institutet, Solna, Sweden

"The accumulation of orphan ribosomal proteins as a hallmark of neurodegeneration"

15.50 – 16.10 Anniina Vihervaara, Royal Institute of Technology, Stockholm, Sweden

"Transcriptional responses to proteotoxicity: from the instant heat shock response to the slow progression of neurodegeneration."

16.10 – 16.30 Per Nilsson, Karolinska Institutet, Solna, Sweden

"The role of autophagy in amyloid beta and tau metabolism in Alzheimer's disease"

16.30 – 16.50 Claes Andreasson, Stockholm University, Stockholm, Sweden

"Generalist and dedicated chaperones at the ribosome"

Dinner at the KVA club villa for speakers & organizers

May 29

Session III - Proteostasis and the ubiquitin-proteasome system

Chairperson: Maria Masucci, Karolinska Institutet

9.00 – 9.50 Sylvie Urbé, University of Liverpool, Liverpool, UK

"Targeting and harnessing DUBs to modulate protein and organellar quality control"

9.50 – 10.40 Nico Dantuma, Karolinska Institutet, Stockholm, Sweden

"Hide and seek at mitochondria: accelerating proteasomal degradation of neurodegeneration- associated proteins"

10.40 – 11.00 Coffee break

Session IV - Proteostasis and autophagy

Chairperson: Nico Dantuma, Karolinska Institutet

11.00 – 10.50 Terje Johansen, University of Tromso, Norway

"The selective autophagy receptors NBR1 and p62/SQSTM1: Modes of action, evolution and interplay"

11.50 – 12.40 Fulvio Reggiori University of Aarhus, Denmark

"Selective degradation of protein aggregates by autophagy"

12.40 – 14.10 Lunch

Session V - Proteostasis in disease

Chairperson: Axel Abelein, Karolinska Institutet

14.10 – 15.00 Anne Bertolotti, MRC Laboratory of Molecular Biology, Cambridge, UK

"Therapeutic and structural insights on the integrated stress response"

15.00 – 15.50 Thorsten Hoppe, University of Cologne

"Cellular mechanisms to organismal aging: proteostasis in longevity and disease."

15.50 – 16.10 Coffee break

16.10 – 17.00 Lea Sistonen, Åbo Akademi University, Turku, Finland

"Regulation of Heat Shock Transcription Factors (HSFs) in Cell Stress and Cancer"

17.00 – 17.50 Giovanna Mallucci, University of Cambridge, UK

"Remodeling translation in neurodegeneration"

17.50 – 18.00 Concluding remarks ***(Maria Masucci, Gunnar von Heijne, Nico Dantuma)***

David Balchin, The Crick Institute, London, UK

David Balchin, Ph.D., is a Group Leader and head of the Protein Biogenesis Laboratory at the Francis Crick Institute in London, UK, which he joined in 2020. He completed his Ph.D. at the University of the Witwatersrand, Johannesburg, South Africa, in 2014, working in the group of Heini Dirr, before moving to the Max Planck Institute of Biochemistry in Martinsried, Germany, as an EMBO Long-Term Fellow with F. Ulrich Hartl. There, he studied the mechanisms of molecular chaperones and demonstrated how cellular factors can shape protein-folding pathways. Balchin's research focuses on the early steps of de novo protein folding as nascent polypeptides emerge from the ribosome. His lab studies cellular protein synthesis and folding networks in vitro and in vivo using cell-biological, biochemical, biophysical, and structural approaches, including hydrogen/deuterium exchange mass spectrometry, crosslinking mass spectrometry, cryo-EM, fluorescence microscopy, and proteomics. Current research interests span the influence of the ribosome on co-translational folding in bacteria and humans, the role of molecular chaperones in guiding this process, and mechanisms of co- and post-translational assembly of protein complexes. Balchin has received several prestigious recognitions. In 2022, he received a European Research Council (ERC) Starting Grant to study how proteins fold into unique 3D structures during synthesis on the ribosome, with particular focus on the role of molecular chaperones. Most recently, he was awarded the 2026 FEBS Anniversary Prize of the Gesellschaft für Biochemie und Molekularbiologie (GBM), in recognition of outstanding achievements in Biochemistry and Molecular Biology by researchers under 40.

Abstract

Molecular logic of chaperone generalists

Molecular chaperones promote protein folding by forming temporary complexes with their clients. Many chaperones have a broad remit, binding 100s to 1000s of different clients, yet selecting specific folding intermediates based on their conformation. This is exemplified by ribosome-bound chaperones, which cater to a large fraction of the nascent proteome. How do such general-purpose chaperones recognize and fold clients with highly diverse sequences and native structures? I will discuss the structural and biophysical underpinnings of chaperone promiscuity in the context of cotranslational folding, and detail how ribosome-associated chaperones shape cytosolic protein biogenesis.

Manu Hegde, LMB, Cambridge, UK

Ramanujan S. Hegde, FRS, is a Group Leader and Head of the Cell Biology Division at the MRC Laboratory of Molecular Biology (LMB), Cambridge, UK, a position he has held since 2011, with divisional leadership since 2019. He was educated at the University of Chicago and the University of California, San Francisco, where he received both his Ph.D. (1998) and MD (1999), conducting doctoral research on protein targeting and translocation at the endoplasmic reticulum under Vishwanath R. Lingappa. He subsequently established his independent laboratory at the NIH before joining the LMB. Hegde's research addresses two fundamental questions in cell biology: how newly synthesized proteins reach their correct cellular destinations and assemble into functional complexes, and how cells recognize and eliminate errors during protein maturation. His group discovered a widely conserved pathway required by a subset of proteins to reach their correct membrane-embedded destinations. It showed that even modest failures in protein localization can cause neurodegeneration. Key discoveries include the identification of the ER membrane protein complex (EMC) as a transmembrane-domain insertase, an intramembrane chaperone for multipass membrane proteins, and novel quality-control factors that recognize "orphan" unassembled protein subunits. Hegde was awarded the R.R. Bensley Award in Cell Biology in 2008, elected a member of the European Molecular Biology Organization (EMBO) in 2013, and elected a Fellow of the Royal Society (FRS) in 2016. He is also a Fellow of Trinity College, Cambridge, and contributes to the landmark textbook *Molecular Biology of the Cell*.

Abstract

The machinery and mechanisms of membrane protein biogenesis

The human genome encodes ~5000 integral membrane proteins, almost all of which are inserted co-translationally into the ER membrane. For decades, the paradigm for their biogenesis involved the sequential insertion of transmembrane helices via the Sec61 protein translocation channel. We have discovered that this textbook model of membrane protein biogenesis is incomplete. Instead, cells contain specialized machinery for membrane insertion that cooperates with Sec61. We and others have identified the key components of this membrane insertion machinery, determined their structures in different states, identified their substrates, and shown how these factors dynamically assemble at a membrane-associated translating ribosome. These findings have led us to a new paradigm for membrane protein biogenesis that rationalizes a wide range of observations over the past few decades and provides a new unifying framework for future studies.

Gunnar von Hejne, Stockholm University, SE

Gunnar von Heijne, Ph.D., is Professor of Theoretical Chemistry at Stockholm University and Director of the SciLifeLab National Cryo-EM Facility. Von Heijne is best known for discovering the "positive-inside rule" governing membrane protein orientation and for developing widely used prediction algorithms, including SignalP, TMHMM, and TopPred. His work has provided fundamental insight into signal peptides, protein translocation, and the energetics of membrane protein assembly. He received the 2020 Biophysical Society's Anatrace Membrane Protein Award for his contributions to understanding membrane protein biosynthesis.

Abstract

Cotranslational compaction and folding of a multidomain protein

Claudio Joazeiro, Heidelberg University, Heidelberg, Germany

Claudio Joazeiro, Ph.D., is Professor of Molecular Biology at the Center for Molecular Biology of Heidelberg University (ZMBH) and holds a joint appointment at UF Scripps Research. He studied Biological Sciences and Biochemistry at the University of São Paulo and received his Ph.D. in Biology from the University of California San Diego in 1996. He subsequently carried out postdoctoral work at the Salk Institute, where he made the landmark discovery that c-Cbl acts as an E3 ligase towards receptor tyrosine kinases. This work led to the realization that the RING domain functions as a catalytic domain for ubiquitination, establishing a major principle in ubiquitin biology. Joazeiro's laboratory is best known for discovering Ribosome-associated Quality Control (RQC), a conserved surveillance pathway that detects and eliminates aberrant nascent proteins generated by ribosome stalling during translation. This finding established the principle that proteolytic targeting can begin while proteins are still associated with ribosomes. His group subsequently discovered an ancestral form of RQC in bacteria and showed that ribosome collisions act as conserved translational stress signals across domains of life, revealing that fundamental mechanisms of translational surveillance emerged early in evolution. His studies have also linked defects in RQC factors to neurodegeneration in mice and humans. Together, his body of work has established key principles of translational quality control and proteostasis in health and disease.

His contributions have been recognized through several awards and honors, including an ERC Advanced Grant for the project "Surveillance of Translation: From Molecular Mechanisms to Roles in Disease." He has also played an active role in shaping the ubiquitin and proteostasis fields through the organization of numerous international scientific meetings with EMBO, FASEB, AACR, and Keystone.

Abstract

Ribosome-associated Quality Control (RQC): mechanisms, evolution, and roles in neurodegeneration

Ribosome stalling during translation sequesters ribosomal subunits and generates incomplete nascent chains with proteotoxic potential, posing a fundamental challenge to cells across all domains of life. It elicits multiple responses, most notably the GCN2 branch of the integrated stress response (ISR) and ribosome-associated quality control (RQC) pathways, which mitigate this threat by decreasing translation and by targeting the aberrant nascent chains for degradation, respectively. Over the past decade, this field has expanded rapidly, revealing links to physiology, disease, and therapeutics.

In my presentation, I will provide an overview of RQC proteolytic mechanisms from bacteria to mammals. Key factors include the E3 ligase Listerin (LTN1), which ubiquitinates incomplete nascent chains on ribosomes, and its associated factor NEMF. Our work established that NEMF orthologs from bacteria to mammals modify incomplete nascent chains with C-terminal polyalanine tracts (“Ala-tails”) that function as degrons. In mammals, this mechanism defines an alternative RQC pathway that operates independently of LTN1.

I will also discuss our recent findings from mouse genetics that provide physiological evidence for the existence and functional interplay of these LTN1-dependent and -independent RQC pathways. Unexpectedly, the data indicate that Ala-tailing has context-dependent effects on proteostasis, acting under certain conditions as a driver of proteotoxicity and neurodegeneration. Together, these findings uncover a critical role for Ala-tails as a deeply conserved degron that contributes to proteostasis.

Jesper Svejstrup, University of Copenhagen, Copenhagen, Denmark

Jesper Qualmann Svejstrup, FRS, FMedSci, is a biochemist and molecular biologist serving as Professor and Deputy Head of Research at the Institute of Cellular and Molecular Medicine (ICMM) at the University of Copenhagen. He was born in Aarhus, Denmark, attended Aarhus University, where he earned a degree in biology in 1989, and later completed his Ph.D. in molecular biology at the same institution. He subsequently pursued postdoctoral training at Stanford University School of Medicine in the USA, working in Roger Kornberg's laboratory. He was previously a Senior Group Leader at the Francis Crick Institute (2015–2020) and before that headed the Mechanisms of Gene Transcription Laboratory at Cancer Research UK's London Research Institute. He remains a Visiting Scientist at the Crick. Svejstrup has unpicked the molecular mechanisms by which cells transcribe DNA into messenger RNA and demonstrated how they avoid DNA damage during this process, with relevance to cancer and neurodevelopmental disorders. His lab employs a multidisciplinary approach combining biochemistry, cell biology, genetics, and cutting-edge omics technologies. Svejstrup's many distinctions reflect the breadth and impact of his research. He was elected to EMBO in 2003, to the Royal Society in 2009, and to the Royal Danish Academy of Sciences and Letters in 2016. He was elected Fellow of the Academy of Medical Sciences in 2018. He is the recipient of two ERC Advanced Grants and serves on several scientific boards, including the Danish National Research Council. He also holds honorary professorships at University College London, Imperial College London, and Aarhus University, and received the Carlsberg Foundation Research Prize in 2024.

Abstract

Proteolysis of RNA Polymerase II in response to transcription stress

Apoptosis is a form of programmed cell death, essential for maintaining tissue homeostasis and eliminating damaged or unwanted cells. Recently, a new apoptosis pathway was discovered, triggered by degradation of RNA polymerase II (RNAPII), the enzyme which transcribes all protein-coding genes. Intriguingly, it is already known that when RNAPII stops at DNA damage, cells rapidly detect and often degrade the troubled enzyme to protect genome stability.

Our recent discoveries have revealed a second, unexpected layer of transcriptional surveillance that operates in the absence of DNA damage. In this pathway, RNAPII is degraded when it fails to pass early transcription checkpoints. I will describe results which connect this quality-control degradation pathway to the newly discovered RNAPII-directed apoptosis pathway, directly linking transcription quality assessment with programmed cell death.

Oscar Fernadez-Capetillo, Karolinska Institutet, Solna, Sweden

Óscar Fernández-Capetillo, Ph.D., is Head of the Genomic Instability Group and Director of the Molecular Oncology Program at the Spanish National Cancer Research Center (CNIO), Madrid, and Professor at the Karolinska Institute, Sweden. He completed his Ph.D. at the University of the Basque Country under Dr. Ana Zubiaga, working on mouse models of autoimmunity, before joining the laboratory of André Nussenzweig at the US National Cancer Institute as a postdoctoral fellow, where he began his work on DNA repair and the role of histone H2AX. He established his independent laboratory at CNIO in 2005. Fernández-Capetillo's research has pioneered our understanding of replicative stress — a form of DNA damage that arises during cell division — and its links to cancer and aging. Among his group's key discoveries was the development of inhibitors of the ATR kinase and demonstration of their potential for cancer therapy. More recently, his group has expanded into mechanisms of drug resistance and neurodegeneration and developed image-based chemical screens at Karolinska. Fernández-Capetillo received the Carmen y Severo Ochoa Research Award in Molecular Biology in 2015, with the panel unanimously recognizing his outstanding discoveries in the field of replicative stress. In 2014, he was selected by the journal *Cell* as one of the 40 most relevant researchers under 40 worldwide. He also received the 2009 Eppendorf Award for Young European Investigators.

Abstract

The accumulation of orphan ribosomal proteins as a hallmark of neurodegeneration

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease of poor prognosis, for which age is the strongest risk factor. Despite significant progress in the discovery of ALS-associated mutations, no model explains how such a diversity of mutations converges on a common pathology. In addition, most ALS cases are sporadic and lack known genetic drivers. We recently reported that arginine-rich peptides arising from the *C9ORF72* mutation trigger a widespread accumulation of orphan ribosomal proteins (oRP). Here, we show that oRP accumulation is a shared feature across other ALS mutations, such as hnRNPA1^{D290V} or TDP-43^{A315T}.

Furthermore, the transcriptional signature of patients with sporadic ALS resembles that of Diamond-Blackfan anemia (DBA), a known ribosomopathy. Notably, similar alterations occur during normal aging. A transcriptional signature defined from our mutation models provides diagnostic and prognostic value in ALS patients. We propose that, by promoting the accumulation of oRPs, ALS-related mutations trigger accelerated aging of motor neurons, thereby promoting their premature loss.

Anniina Vihervaara, Royal Institute of Technology, Stockholm, Sweden

Anniina Vihervaara, Ph.D., is an Assistant Professor of Gene Technology and a SciLifeLab Fellow at the KTH Royal Institute of Technology, Stockholm, Sweden. She completed her doctoral research at Åbo Akademi University in Turku, Finland, in the laboratory of Professor Lea Sistonen, focusing on how Heat Shock Factors (HSFs) regulate transcription in response to cellular stress and during development. For her postdoctoral work, she joined the laboratory of Professor John T. Lis at Cornell University - a world leader in nascent RNA sequencing - where she applied genome-wide precision run-on sequencing (PRO-seq) to dissect transcriptional mechanisms at nucleotide resolution. Vihervaara's research focuses on the dynamic regulation of RNA Polymerase II (Pol II) at promoters, enhancers, and enhancer clusters, and how transcriptional programs are rapidly rewired in response to stress, disease, and differentiation. Her key contributions include demonstrating that transcriptional stress responses are pre-wired by promoter and enhancer architecture and discovering mechanisms of stress-induced transcriptional memory, including accelerated Pol II pause-release for faster induction, and retention of transcripts from downregulated genes at chromatin. She has developed innovative methodologies, including PRO-IP-seq, which tracks Pol II modifications at nucleotide resolution. Vihervaara received the Elias Tillandz Prize in 2013 and Harry Elving’s legat in 2014 for her PhD work, and Alfred Tissiéres Young Investigator Award in 2025 for her independent research. She is a fellow of the Cell Stress Society International, has received prestigious funding for independence from the Sigrid Jusélius Foundation and the Academy of Finland, and was appointed a SciLifeLab Fellow at KTH, one of Sweden's most competitive early-career research fellowships.

Abstract

Transcriptional Responses to Proteotoxicity: From the Instant Heat Shock Response to the Slow Progression of Neurodegeneration

Cells counteract protein-damaging stress by producing molecular chaperones. While acute heat stress triggers instant activation of chaperone genes, neurodegenerative diseases accumulate protein damage and transcriptional changes over decades. Here, we track molecular mechanisms of acute stress responses by measuring gene activation, RNA Polymerase II progression, mRNA expression, and protein synthesis. We find synchronous activation of HSF1-driven genes that launch waves of transcription, thereby timing mRNA and protein production in the order of chaperone complex function. Comparing RNA expression programs in response to heat shock, HSP90 inhibition, and polyQ aggregation reveals fundamentally different transcriptional changes, coordinated by distinct sets of *trans*-activators. We find no support for increased chaperone expression in polyQ mice, a model for Huntington's disease (HD). Instead, polyQ aggregation increases the expression of RNAs associated with transcriptional repression, chromatin remodeling, and autophagy. Importantly, mice under chronic stress exhibit a systemic defect in launching acute responses, hampering not only chaperone production but also the general ability to reprogram RNA synthesis. Taken together, transcriptional stress responses are tailored to the protein damage and tissue environment. Moreover, RNA expression across tissues and during aging emphasizes stage-dependent timing of HD treatments, and targeting pathways of energy metabolism, detoxifying enzymes, and autophagy in the late-stage HD.

Per Nilsson, Karolinska Institutet, Solna, Sweden

Per Nilsson, Ph.D., is Associate Professor (Docent) and Vice Head of the Division of Neurogeriatrics, Department of Neurobiology, Care Sciences and Society, at Karolinska Institutet, Solna, Sweden, where he leads the research group on autophagy and Alzheimer's disease. He completed his Ph.D. at Uppsala University, followed by postdoctoral training at the RIKEN Brain Science Institute in Japan, where he developed expertise in animal models of Alzheimer's disease and their use in elucidating disease mechanisms. Nilsson's research focuses on the molecular and cellular mechanisms underlying Alzheimer's disease (AD), with a particular emphasis on autophagy as a key clearance pathway in the brain. His laboratory investigates autophagy as a drug target to improve protein homeostasis in the AD brain, focusing on how this pathway regulates both amyloid-beta and tau metabolism and how its dysfunction links the two cardinal pathological events in the disease. His group uses state-of-the-art knock-in mouse models, proteomics, and advanced imaging to investigate disease mechanisms and has identified SPPL2b as a novel therapeutic target in AD. His group also explores how mitophagy dysfunction drives neuroinflammation via the cGAS-STING pathway. Nilsson has received research support from several prestigious funding bodies, including the Alzheimer's Association, Cure Alzheimer's Fund, and multiple Swedish foundations, including Alzheimerfonden and Olle Engkvists Stiftelse. He is involved in several larger European and American research consortia.

Abstract

The role of autophagy in amyloid beta and tau metabolism in Alzheimer's disease

Claes Andreasson, Stockholm University, Stockholm, Sweden

Claes Andréasson, Ph.D., is a Professor and Deputy Head at the Department of Molecular Biosciences, The Wenner-Gren Institute, Stockholm University, Sweden. He completed his undergraduate studies in biology at Stockholm University, conducting his thesis at the Ludwig Institute for Cancer Research on the Karolinska campus, before pursuing his Ph.D. in cell signaling, which he defended in 2004. During his doctoral work, he discovered a novel protease, sparking an interest in proteolytic enzymes that led him to pursue postdoctoral training with Bernd Bukau at ZMBH-DKFZ in Heidelberg, Germany, where he pivoted to studying molecular chaperones. He returned to Sweden, supported by the Swedish Research Council, and established his independent laboratory at the Wenner-Gren Institute. Andréasson's research focuses on the molecular mechanisms by which cells maintain proteostasis. His laboratory uses yeast as a model system to dissect the functional roles of chaperones in the proteostasis network, including how they guide protein folding, disaggregation, and quality-control degradation, and how the heat shock transcription factor Hsf1 senses proteotoxic stress and orchestrates the heat shock response. Key discoveries include elucidating how Hsp70 titration by misfolded proteins activates nuclear Hsf1, the mechanistic basis of nucleotide exchange factors in releasing misfolded substrates from the Hsp70 system, and the discovery of a novel ribosome-associated chaperone for translation elongation factor eEF1A.

Abstract

Generalist and dedicated chaperones at the ribosome

Cotranslational protein folding and targeting of newly synthesized proteins depend on generalist chaperones and biogenesis factors that engage the highly diverse nascent chains emerging from translating ribosomes. While the intrinsic complexity of these polypeptides readily explains the presence of generalist factors at the crowded ribosomal polypeptide exit tunnel, it remains less clear to what extent dedicated chaperones associated with specific nascent chains also occupy this site. We have found that the universal cotranslational machinery at the ribosome adapts to accommodate the challenging biogenesis of the translation elongation factor eEF1A. Up to 3% of all ribosomes synthesize eEF1A, posing a formidable challenge to the folding of this multidomain GTPase. The dedicated chaperone for elongation factor 1 (Chp1) is cotranslationally recruited to the ribosome via the generalist nascent polypeptide–associated complex (NAC) to bind the nascent eEF1A G-domain, maintaining it in an unfolded state to prevent premature nucleotide binding and ensure proper folding control. Subsequent synthesis of domain II and nucleotide loading cooperatively trigger G-domain folding, Chp1 release, and handover to the downstream chaperone Zpr1. Failure of this coordinated pathway leads to eEF1A misfolding, rapid proteolysis, proteostasis collapse, and impaired cellular fitness. Thus, eEF1A is an intrinsically difficult-to-fold G protein that, due to its exceptionally high rate of synthesis, requires dedicated cotranslational folding factors at the ribosome to safeguard the proteostasis network.

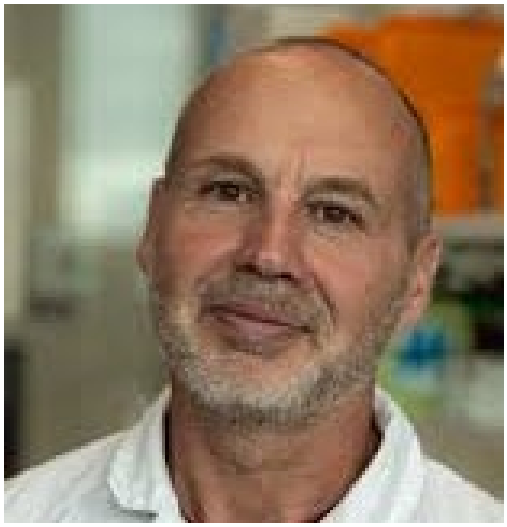
Sylvie Urbé, University of Liverpool, Liverpool, UK

Sylvie Urbé, Ph.D., is Professor of Molecular and Cellular Physiology at the University of Liverpool, UK. She was educated in Luxembourg and Germany, receiving her Diploma in Biology from the University of Heidelberg/EMBL, where she began studying Rab GTPases. She then completed her Ph.D. in cell biology at the Imperial Cancer Research Fund/University College London, where she worked on secretory granule biogenesis in neuroendocrine cells. Her postdoctoral research at the University of Liverpool focused on the endosomal scaffold protein HRS and its role in growth factor receptor trafficking. Urbé's research has made fundamental contributions to our understanding of the ubiquitin system and membrane trafficking. Working closely with Professor Michael Clague, she characterized endosomal deubiquitinases (DUBs), providing the first example of a ubiquitin chain-linkage specific enzyme (AMSH) and establishing an important new paradigm whereby the balance between E3 ligase and DUB activity on endosomes determines receptor fate. Urbé and Clague have contributed to the development of highly selective tool compound inhibitors against multiple DUBs (USP7, USP9X, USP28, USP30) that have yielded new insights into their biology and therapeutic potential. Current research focuses on mitophagy and the role of DUBs and E3 ligases in Parkinson's disease and other neurodegenerative conditions. Urbé has held consecutive Wellcome Trust Career Development and Cancer Research UK Senior Fellowship Awards. She has received sustained funding from the MRC, BBSRC, Cancer Research UK, the Wellcome Trust, Parkinson's UK and the Michael J. Fox Foundation for Parkinson's Research. She is an academic founder and scientific advisory board member of Entact Bio, a Biotech targeting DUBs therapeutically, reflecting the translational reach of her foundational discoveries in ubiquitin biology. In 2025, she joined the Board of Directors of the Company of Biologists (CoB), a non-profit publishing organization dedicated to supporting and inspiring the biological community.

Abstract

Targeting and harnessing DUBs to modulate protein and organellar quality control

Nico Dantuma, Karolinska Institutet, Stockholm, SE



Nico Dantuma, Ph.D., is Professor of Molecular Cell Biology at Karolinska Institutet since 2011. He earned his Ph.D. from Utrecht University (1993-1997) in Biochemical Physiology. He has a long-standing interest in the role of the ubiquitin system, which is critically involved in maintenance of protein homeostasis by tightly regulating intracellular protein degradation. It is therefore not surprising that this journey brought him into the realm of immunology, cancer and neurodegenerative disorders. His team has developed cellular and transgenic mouse models for functional analysis of ubiquitin-dependent protein degradation using fluorescent based reporter substrates. These models have been widely used in the field for studying the functionality of this proteolytic pathway in physiological and pathological conditions. With these reporter systems, the Dantuma lab has studied the functionality of ubiquitin-dependent degradation in various neurodegenerative diseases as well as the potential of the ubiquitin system as drug target in cancer therapy. His laboratory has made contributions to understanding how cells manage misfolded and damaged proteins, with particular emphasis on Alzheimer's disease and other neurodegenerative conditions.

Abstract

Hide and seek at mitochondria: Accelerating proteasomal degradation of neurodegeneration-associated proteins

A common hallmark of many neurological disorders, like Alzheimer's, Parkinson's and Huntington's disease, is the presence of aggregation-prone proteins. The timely degradation of misfolded proteins is mediated by the ubiquitin-proteasome system (UPS). To identify potential therapeutic candidates for stimulating clearance of misfolded proteins, we performed a genome-wide CRISPR/Cas9 screen for suppressors of UPS activity using an aggregation-prone reporter protein. This resulted in the identification of translational elongation-initiation factor 5A (eIF5A), a protein previously implicated in mitochondrial homeostasis. Genetic or pharmacological inhibition of eIF5A reduced the levels of the misfolded reporter as well as the neurodegeneration-associated proteins huntingtin and α-synuclein by promoting ubiquitin-dependent proteasomal degradation. A shared feature of these aggregation-prone proteins is their tendency to (mis)localize to mitochondria. Notably, eIF5A deficiency resulted in release of these proteins with mitochondria, which coincided with enhanced proteasomal clearance. These findings suggest that mitochondria behave as a protective holdout compartment shielding aggregation-prone proteins from ubiquitylation and subsequent degradation. We propose that preventing mitochondrial localization of neurodegeneration-associated proteins may provide a means to accelerate their clearance and offer new avenues for therapeutic intervention.

Terje Johansen, University of Tromso, Norway

Terje Johansen, Ph.D., is Professor at the Department of Medical Biology and Scientific Leader of the Proteomics and Metabolomics Core Facility (PRiME) at UiT, The Arctic University of Norway, Tromsø. He completed his academic training at UiT, obtaining a Cand. scient. Degree in 1985 on vector construction and DNA transformation in *Physarum polycephalum*, followed by his Ph.D. in 1988, both under the supervision of Professor Finn Haugli in the Cell Biology group. He conducted postdoctoral research (1988–1991) in the Virology group before serving as an Associate Professor in the Biotechnology Group (1990–1991). VR Johansen is a world leader in selective autophagy research, having made seminal contributions to understanding how cells selectively degrade damaged organelles and protein aggregates. His laboratory discovered and characterized p62/SQSTM1 and NBR1 as the first selective autophagy receptors, establishing the paradigm that these cargo receptors recognize ubiquitinated substrates and deliver them to autophagosomes via interactions with ATG8 family proteins through LC3-interacting region (LIR) motifs. Current research focuses on selective autophagy receptors, ATG8 family proteins, and their protein-protein interactions in cancer, neurodegeneration, aging, inflammation, and host defense. Johansen serves on the editorial boards of major autophagy journals. He has organized international workshops and conferences on autophagy and contributed definitive reviews that have shaped the field's understanding of cargo receptor biology.

Abstract

The selective autophagy receptors NBR1 and p62/SQSTM1: Modes of action, evolution and interplay

Autophagy is an evolutionarily conserved lysosomal degradation pathway for surplus or damaged cytosolic components to maintain cellular homeostasis. Autophagy declines with age and its function or dysfunction impacts major diseases including cancer, neurodegenerative diseases, myopathies, cardiovascular- and liver diseases, ageing, infections and inflammation. Autophagy can be both selective and non-selective. Selective autophagy mediates specific degradation of excessive or toxic structures, including protein aggregates, organelles, and intracellular pathogens. Our group identified the first selective autophagy receptor, p62/SQSTM1, binding to ubiquitinated cargos. In collaboration with the groups of Ivan Dikic and Masaaki Komatsu we also identified NBR1 as the second mammalian autophagy receptor. We showed that their degradation depends on a direct interaction with ATG8 family proteins present at the inner surface of forming autophagosomes, and that binding is mediated by a short linear amino acid sequence motif we named LIR (LC3-interacting region). p62 polymerizes via its N-terminal PB1 domain and forms filaments, which, together with ubiquitinated cargos recognized by the C-terminal UBA domain, form biological condensates called p62 bodies. Phylogenomic and domain-structure analyses reveal that NBR1 is the archetypal autophagy receptor, likely present in the last eukaryotic common ancestor (LECA). p62/SQSTM1 appears first in the early Metazoan lineage following a gene duplication of the ancestral NBR1 gene. Mechanistic studies are starting to shed light on the collaboration between mammalian NBR1 and p62 in the autophagic degradation of protein aggregates (aggrephagy). Our work on these two autophagy receptors will be presented, as well as new data on how NBR1 shuttles between the cytoplasm and nucleus and contributes to the formation of nuclear p62 bodies. Unpublished data on how membrane- and ubiquitin binding is regulated by interactions between an amphipathic helix and the UBA domain of NBR1 and how this affects the collaboration with p62 in aggrephagy will also be presented.

Fulvio Reggiori University of Aarhus, Denmark

Fulvio Reggiori, Ph.D., is Professor of Biochemistry at the Department of Biomedicine, Aarhus University, Denmark, where he joined in 2022. He studied Biochemistry at the University of Fribourg, Switzerland. He obtained his Ph.D. in 1997 in the laboratory of Professor Andreas Conzelmann, where he worked on the remodeling of GPI-anchored proteins and sphingolipid biosynthesis in yeast. He subsequently pursued postdoctoral training at the MRC Laboratory of Molecular Biology in Cambridge with Dr. Hugh Pelham, and later at the University of Michigan with Professor Daniel Klionsky, where he began his work on the molecular mechanisms of autophagy. In 2005, he was appointed tenured Assistant Professor at the University Medical Center Utrecht, before rising to full Professor at the University Medical Center Groningen. Reggiori's research focuses on macroautophagy — the conserved cellular pathway that sequesters damaged proteins, dysfunctional organelles, and intracellular pathogens within double-membrane autophagosomes for lysosomal degradation. His laboratory investigates the mechanisms and regulation of autophagy, host-pathogen interactions, and the role of autophagy dysfunction in neurodegeneration and other diseases. Reggiori has received numerous competitive research awards throughout his career. He was awarded a VIDI grant in 2006 and a VICI grant in 2013, both prestigious awards from the Dutch Organization for Scientific Research (NWO).In 2022, he received a Novo Laureate Research Grant from the Novo Nordisk Foundation to establish his laboratory at Aarhus University. He also serves on several journal editorial boards and as a founding agency. He is the chair of the EMBO Conference on Autophagy.

Abstract

Selective degradation of protein aggregates by autophagy

Perturbations in protein quality control lead to the accumulation of misfolded proteins and protein aggregates, which can compromise health and lifespan. One key mechanism eliminating protein aggregates is aggrephagy, a selective type of autophagy. Here, we reveal that fragmentation is required before autophagic clearance of various types of amorphous aggregates. This fragmentation requires both the 19S proteasomal regulatory particle and the DNAJB6-HSP70-HSP110 chaperone module. These two players are also essential for aggregate compaction, which leads to clustering of selective autophagy receptors and initiates the autophagic removal of the aggregates. We also found that the same players delay the formation of disease-associated huntingtin inclusions. This study assigns a novel function to the 19S regulatory particle and the DNAJB6-HSP70-HSP110 module and uncovers that aggrephagy is a piecemeal process, with relevance to proteinopathies.

Anne Bertolotti, MRC Laboratory of Molecular Biology, Cambridge, UK

Anne Bertolotti, Ph.D., joined the Medical Research Council Laboratory of Molecular Biology (LMB) in Cambridge in 2006, where she continues to be a group leader and joint Head of the Neurobiology Division. She completed her doctoral training at the University of Strasbourg, France, under Pierre Chambon and Laszlo Tora, working on transcription, and subsequently conducted postdoctoral research with David Ron at the Skirball Institute of Biomolecular Medicine, NYU Medical Center, where she discovered components of the integrated stress response. Bertolotti's research has made seminal contributions to understanding protein quality-control mechanisms and cellular defenses against misfolded proteins that accumulate in neurodegenerative diseases, including Alzheimer's, Parkinson's, Huntington's, and motor neuron diseases. Her laboratory has translated these discoveries into therapeutic strategies, identifying molecules that boost cellular defense mechanisms — two of which demonstrated efficacy in phase 2 and phase 2a clinical trials for ALS. Her many honors include election as an EMBO Young Investigator (2005), an ERC Consolidator Grant (2013), EMBO Membership (2013), the Hooke Medal (2014), Fellowship of the National Academy of Medical Sciences UK (2017), Wellcome Trust Investigator and Discovery Awards (2017, 2024), the GlaxoSmithKline Award from the Biochemical Society (2018), and the IUBMB Jubilee Award Lecture (2025).

Abstract

Therapeutic and structural insights into the integrated stress response

Life depends on the ability to survive challenges. Our work focuses on vital signaling pathways that evolved to ensure cell survival in the face of challenges or stresses. I will present my scientific journey, from the discovery of components of the integrated stress response (ISR) to pioneering strategies that harness these pathways to enhance cellular resilience. This modality is broadly applicable to improving fitness across diverse diseases, including age-related neurodegenerative diseases. Some of the small molecules we reported have progressed to human clinical trials: Guanabenz was found to be efficacious in a Phase 2 trial in ALS, and Phase 2 trials are ongoing with Sephin1, following successful Phase 1 and Phase 2a trials.

Expanding our toolbox, we recently made the unexpected discovery that widely used ATP-competitive inhibitors of one eIF2 kinase can paradoxically activate a related one, thereby activating a pathway they were designed to inhibit. These findings have broad relevance.

Our work is driven by an understanding of fundamental cellular processes, which in turn bring therapeutic opportunities. Going full circle, the small molecules we discovered also raise fundamental questions. The work on Guanabenz, Sephin1, and Raphin1 has stimulated our interest in the termination of the ISR controlled by dedicated phosphatases. We have deployed a combination of approaches to characterize these poorly understood enzymes and elucidate the mechanism by which ISR phosphatases recruit their large substrate. This revealed the mechanisms terminating ISR signaling, a question that had been unresolved for 50 years.

Thorsten Hoppe, University of Cologne, Cologne, Germany

Thorsten Hoppe, Ph.D., is a Full Professor at the Institute for Genetics and the CECAD Cluster of Excellence for Aging Research at the University of Cologne, Germany, since 2008, where he also serves as Deputy Coordinator of CECAD. He completed his Ph.D. in 2000 under Professor Stefan Jentsch at the University of Heidelberg and the Max Planck Institute of Biochemistry, where he identified a new class of E4 polyubiquitylation enzymes. After postdoctoral research in Munich, he established his research group in 2003 at the Center for Molecular Neurobiology in Hamburg. Hoppe's research focuses on the ubiquitin/proteasome system (UPS) and proteostasis networks from molecular mechanisms to organismal physiology. Using *C. elegans* as a model, he pioneered the study of protein degradation in the context of aging. His group has made groundbreaking discoveries, including the identification of a muscle-specific quality-control pathway fundamental to human myopathies and of chromatin-associated protein degradation mechanisms important for DNA replication and the DNA damage response. His team has also elucidated how ubiquitin-dependent degradation of the insulin receptor coordinates proteostasis and longevity. His honors include the EMBO Young Investigator Award (2007), the Walther-Flemming Medal of the German Society for Cell Biology, and the Felix-Jerusalem Award of the German Society for Muscular Diseases (both in 2008), as well as an ERC Advanced Grant.

Abstract

Organellar Proteostasis Mechanisms

Mitochondrial proteostasis ensures that mitochondria can adjust their function to meet changing demands. Multiple quality-control pathways, including mitochondria-associated degradation (MAD), mitochondrial protein translocation-associated degradation (mitoTAD), mitochondria-derived vesicles (MDVs), mitochondria-derived compartments (MDCs), and mitophagy, support this dynamic regulation. The mitochondrial proteome is highly adaptable; for example, the total mitochondrial protein mass in yeast more than doubles under respiratory versus fermentative growth conditions. However, specific nutrient signals and the mechanisms that control this metabolic reshaping of the mitochondrial proteome remain unknown.

Communication between the mitochondria and the cytosol is critical for cellular adaptation to metabolic changes. The outer mitochondrial membrane (OMM), located at the interface between the cytosol and mitochondria, plays a key role in this crosstalk. OMM proteins coordinate protein import, metabolite transport, mitochondrial fusion and fission, and interactions with other organelles. Altered OMM proteostasis could thus coordinate changes in the cellular environment with mitochondrial activity. Nevertheless, whether and how nutrient signals affect OMM proteostasis during cellular adaptation remain largely unexplored.

Degradation of many OMM proteins is regulated by the ubiquitin-proteasome system (UPS); we therefore explored the role of ubiquitin-dependent regulation of OMM proteostasis in metabolic adaptation. To identify metabolic control of OMM protein stability, we conducted a genetic screen in Caenorhabditis elegans using a newly developed GFP-based reporter system that monitors UPS-mediated degradation of OMM-localized substrates. This approach unexpectedly revealed amino acid metabolism, particularly the branched-chain amino acid (BCAA) leucine, as an essential modulator of OMM protein degradation that tunes respiratory activity, in a manner dependent on the conserved amino acid sensor GCN2. The HRD1 E3 ubiquitin ligase cofactor SEL1L is downregulated by leucine specifically at mitochondria, which leads to stabilization of OMM substrates and enhancement of mitochondrial respiration. A disease-associated mutation in BCAT2, a key enzyme in leucine catabolism, stabilizes OMM proteins and impairs fertility under stress in C. elegans. Moreover, human lung cancer cells with elevated intracellular BCAA levels exhibit reduced OMM ubiquitylation and increased resistance to mitochondrial import inhibition. Together, our results identify a conserved mechanism by which leucine regulates OMM proteostasis and mitochondrial function, linking amino acid availability to mitochondrial remodeling and organismal health.

Lea Sistonen, Åbo Akademi University, Turku, Finland

Lea Sistonen, Ph.D., is Professor of Cell and Molecular Biology at Åbo Akademi University, Turku, Finland, and Group Leader at the Turku Bioscience Center — positions she has held since 2000 and 1994, respectively. She completed her Ph.D. in 1990 under Professor Kari Alitalo at the University of Helsinki, followed by postdoctoral training with Professor Richard I. Morimoto at Northwestern University (1990–1993). This formative experience shaped her lifelong focus on stress biology. Sistonen's research has made landmark contributions to understanding how Heat Shock Factors (HSFs) regulate genome-wide transcriptional programs in response to stress, during normal development, and in malignant transformation. She demonstrated that HSF family proteins can mediate different transcription programs depending on the type of stress they encounter — a finding with significant implications for cancer biology. Her laboratory has pioneered the use of ChIP-seq and PRO-seq to map HSF occupancy, chromatin architecture remodeling, and de novo transcription at genes and enhancers. It has established distinct roles for HSF family members as stage-specific regulators of breast tumorigenesis. Her honors include a five-year Academy Professorship from the Academy of Finland (2004) — one of Finland's highest research distinctions — and the 2023 Chancellor's Grand Prize from Åbo Akademi University for her groundbreaking research on cellular stress responses. In 2018, I was elected as an EMBO member, and I served as the President of the Cell Stress Society International during 2022-2023.

Abstract

Regulation of Heat Shock Transcription Factors (HSFs) in Cell Stress and Cancer

Heat shock factors (HSFs) are the main transcriptional regulators of the evolutionarily conserved heat shock response and other acute cellular stress responses. Among the HSF family members, HSF1 is the major stress-responsive factor, and its contribution to malignant transformation has been widely studied. In contrast, although HSF2 has been associated with physiological and pathological processes, the underlying regulatory mechanisms have remained unknown. We have analyzed HSF1 and HSF2 in a comprehensive selection of human tissues and found that they display distinct expression and subcellular localization patterns in benign tissues. HSF1 localizes to the nucleus in all epithelial cell types, whereas HSF2 shows a robust cytoplasmic expression of HSF2 across all studied smooth muscle and endothelial cells, including the smooth muscle cells surrounding the vasculature and the high endothelial venules in lymph nodes. Surprisingly, HSF2 localized at cell-cell adhesion sites in a broad selection of tissue types, such as the cardiac muscle, liver, and epididymis. In cancer, specifically at the primary stages of breast cancer, *i.e.,* ductal carcinoma in situ (DCIS), HSF2 is localized to the nucleus of rapidly proliferating cells in the breast duct. To characterize the function of HSF2 in malignant transformation, we treated human breast cancer cells with transforming growth factor-beta (TGF-beta) to mimic activation of invasiveness involved in epithelial-mesenchymal plasticity. TGF-beta stimuli dramatically downregulated HSF2 levels and activated target genes crucial for the acquisition of pro-metastatic behavior. Intriguingly, forced expression of HSF2 disrupted the TGF-beta-mediated gene program by dysregulating the expression of cell cycle regulators, extracellular matrix, and adhesion-related genes. Accordingly, cells expressing ectopic HSF2 displayed induced cell proliferation and reduced migration both *in vitro* and *in vivo*. Our findings expand the physiological and pathological landscape of HSFs, demonstrating that HSF2 acts as a stage-specific switch between proliferation and invasion in breast cancer.

Giovanna Mallucci, University of Cambridge, UK

Giovanna Mallucci, MD, PhD, FMedSci, is a founding Principal Investigator of Altos Labs, Cambridge Institute of Science, UK, and Honorary Professor of Molecular Neuroscience at the University of Cambridge. Previously, she was the Center Director of the UK Dementia Research Institute and the van Geest Professor of Clinical Neurosciences at the University of Cambridge, following positions as Head of Neurobiology at the MRC Toxicology Unit in Leicester and Program Leader at the MRC Prion Unit in London. She obtained undergraduate degrees in Physiological Sciences and Medicine from the University of Oxford and from University College London, and her PhD from London University, during which she generated the first adult-onset mouse model of prion protein knockout — work that paved the way for her discoveries about the reversibility of early neurodegeneration and underlying mechanisms. Her lab pioneered the understanding of the role of the Unfolded Protein Response (UPR) in neurodegenerative diseases and of its therapeutic manipulation for neuroprotection, including the discovery of repurposable drugs now in clinical trials. Her interest in neuroprotection led to her discovery of the role of 'hibernation' proteins in synapse regeneration that can be targeted therapeutically to prevent dementia. She was elected Fellow of the Academy of Medical Sciences in 2017; received the Potamkin Prize for Research in Pick's, Alzheimer's and Related Disorders in 2021, and the Masland Award Medal at the World Congress of Neurology in 2021, and was awarded Doctor Honoris Causa from the Sorbonne University in Paris in 2024. Until recently, she was also a practicing neurologist specializing in dementia

Abstract

Remodeling translation in neurodegeneration

Organizers

Maria G. Masucci, M.D., Ph.D., is Professor of Virology at the Department of Cell and Molecular Biology, Karolinska Institutet. Her research focuses on the intersection of virology, cell biology, and the ubiquitin-proteasome system, with particular emphasis on how viruses manipulate host cellular machinery to evade immune responses. Her laboratory has made important discoveries on viral ubiquitin deconjugases, demonstrating that herpesviruses encode enzymes that inhibit selective autophagy. Her work has elucidated how viral deubiquitinases regulate topoisomerase II activity, ribosomal quality control, and innate immune signaling during infection.

Gunnar von Heijne, Ph.D., is Professor of Theoretical Chemistry at Stockholm University and Director of the SciLifeLab National Cryo-EM Facility. Von Heijne is best known for discovering the "positive-inside rule" governing membrane protein orientation and for developing widely used prediction algorithms, including SignalP, TMHMM, and TopPred. His work has provided fundamental insight into signal peptides, protein translocation, and the energetics of membrane protein assembly. He received the 2020 Biophysical Society's Anatrace Membrane Protein Award for his contributions to understanding membrane protein biosynthesis.

Nico P. Dantuma, Ph.D., is Professor of Molecular Cell Biology at the Department of Cell and Molecular Biology, Karolinska Institutet. His research focuses on the ubiquitin-proteasome system (UPS) and its role in neurodegenerative diseases and cancer. His laboratory has made seminal contributions to understanding how aggregation-prone proteins—including polyglutamine proteins, α-synuclein, and mutant ubiquitin (UBB+1) - compromise proteasome function and accumulate in affected neurons in diseases such as Alzheimer's, Parkinson's, and Machado-Joseph disease. He developed the first transgenic mouse model for real-time in vivo monitoring of the UPS.

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