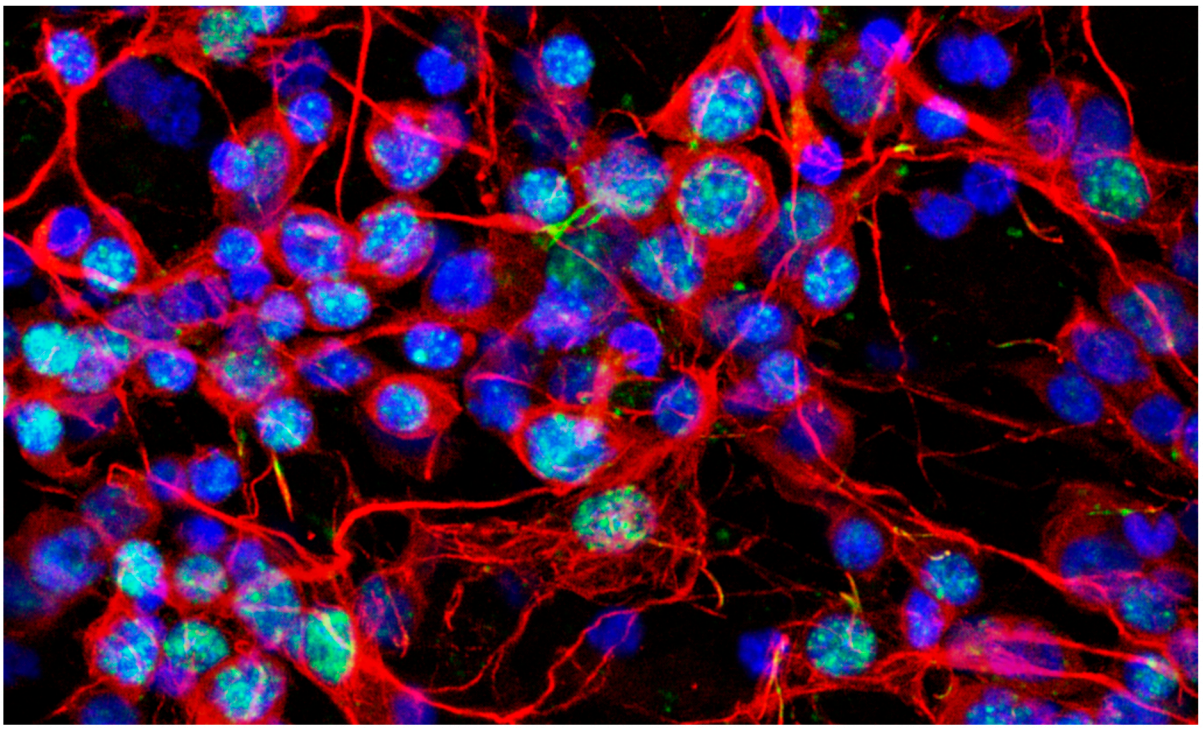
XXXVII JORNADA DE BIOLOGIA DEL DESENVOLUPAMENT

37th DEVELOPMENTAL BIOLOGY MEETING

5 Febrer 2026



Organitzat per la secció de Biologia del Desenvolupament de la SCB

Organitzadores:
Cristina González-Estévez i Teresa Adell
(Universitat de Barcelona i IBUB)

IEC, Sala Prat de la Riba - C/ del Carme 47 Barcelona

XXXVII Jornada de Biologia del Desenvolupament

Dijous 5 de febrer de 2026

PROGRAMA

9:00 Registration

9:25 Welcome by the Organizers

9:30-10:15 **K. Lenhard Rudolph** (Leibniz Institute on Aging-Fritz Lipmann Institute, Jena, Germany)
Development influences on organism aging

10:15-10:30 Marta Morey (UB-IBUB)
Sex-dependent plasticity of adult neural tissue in response to damage

10:30-10:45 Daniel Moreno-Blas (UB-IBUB)
Cellular senescence is required for planarian regeneration

10:45-11:10 Flash Talks

11:10-11:45 Coffee Break and Poster Session

11:45-12:30 **M. Carolina Florian** (IDIBELL, Barcelona)
Aging and rejuvenation of hematopoietic stem cells

12:30-12:45 Sofia J. Araújo (UB-IBUB)
Centrosome loss in embryonic development disrupts axonal pathfinding and muscle integrity

12:45-13:00 Andrea Martí-Sarrias (UB and Barcelonaβeta Brain Research Center)
Induced by SARS-CoV-2 Infection Promotes Neural Regeneration in Human Brain Organoids

13:00-13:15 Lara Barrio (IRB Barcelona)
Developmental consequences to an organismal trisomy

13:15-14:30 Lunch and Poster Session

14:30-15:15 **Vikas Trivedi** (EMBL Barcelona)
Understanding constraints on multicellular systems

15:15-15:30 Ignacio Maeso (UB- IRBio)
Deep conservation of cis-regulatory elements and chromatin organization in echinoderms uncover ancestral regulatory features of animal genomes

15:30-15:45 Victoria Shabardina (IBE CSIC-UPF)
Origin of cell differentiation in animals

15:45-16:00 Iván Sopena-Majós (UB-IBUB)
ROS-mediated PTEN inactivation regulates regeneration in *Drosophila* gut and wing imaginal disc

16:00-16:30 Coffee Break

16:30-16:45 Anna Guixeras (UB-IBUB)
Smed-cdk-17 regulates eye size during planarian regeneration and homeostasis

16:45-17:00 Akshay Jaya Ganesh (UB)
STAU2 coordinates metabolism and RNA regulation in early human neurogenesis

17:00-17:15 Kaustuv Ghosh (IRB Barcelona)
Fatty acid β-oxidation couples metabolism to epigenetics to orchestrate epithelial growth

17:15-17:30 Poster Award and Concluding Remarks

Organizers
Teresa Adell (UB-IBUB)
Cristina González-Estévez (UB-IBUB)

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INVITED SPEAKERS

DEVELOPMENT INFLUENCES ON ORGANISM AGING

K. Lenhard Rudolph

Leibniz Institute on Aging - Fritz Lipmann Institute (FLI), Jena, Germany

Early-life growth and metabolic status establish trajectories that shape aging in adulthood. We focus on defined stem cell populations to determine whether developmental metabolic activity imprints a durable epigenetic memory or accelerates selective processes that bias the aging course of these cells.Our findings provide direct experimental evidence that growth signaling and metabolic load during development and early adulthood influence hallmark aging phenotypes in hematopoietic stem cells (HSCs), notably the expansion of myeloid-biased subpopulations. Moreover, emerging data suggest that developmental modulation of epigenome-regulating genes affects organismal growth and final stem-cell pool sizes. We aim to delineate whether early-life influences extend to healthspan and lifespan and whether the epigenetic memory of developmental growth can be reprogrammed in adulthood. Such insights may ultimately reveal new entry points for interventions that promote healthy aging by revisiting the molecular legacy of early life.

AGING AND REJUVENATION OF HEMATOPOIETIC STEM CELLS

M. Carolina Florian

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Aging is associated with a global decline in stem cell function. To date, several strategies have been proposed to rejuvenate aged stem cells: most of these result in the functional improvement of the tissue where the stem cells reside, but the impact on the lifespan of the whole organism has been less clearly established. Our most recent work dealing with interventions that improve the regenerative capacity of aged hematopoietic stem cells in mice underscores that somatic stem cell rejuvenation represents a strategy to improve tissue homeostasis upon aging. Moreover, we present important evidence that rejuvenating hematopoietic stem cells might have the potential to affect health span and lifespan of the whole organism.

UNDERSTANDING CONSTRAINTS ON MULTICELLULAR SYSTEMS

Vikas Trivedi

European Molecular Biology Laboratory, EMBL Barcelona, Spain; Developmental Biology, EMBL Heidelberg, Heidelberg, Germany.

How do tissue shapes and patterns emerge reproducibly in multicellular systems? Despite over a century of research, it remains unclear how gene regulatory networks, mechanical forces, and cellular metabolic states integrate to self-organize complex structures. An additional challenge is to understand how environmental factors influence development within cell populations.We address this question by studying body axis formation in animals using both in vitro and in vivo approaches that allow us to disentangle the combined effects of these factors. Using embryonic stem cell (ESC) aggregates that mimic early development, we show how mechanochemical coupling regulates tissue rheology and how metabolism influences cell fate by modulating downstream signaling. In a separate study, we combine live imaging with mechanical measurements to explore how zebrafish embryos maintain robustness to temperature changes, focusing on the epithelial layer during gastrulation. Together, our investigations aim to uncover how developing tissues achieve structural and functional reproducibility under a variety of constraints.

ORAL PRESENTATIONS

SEX-DEPENDENT PLASTICITY OF ADULT NEURAL TISSUE IN RESPONSE TO DAMAGE

Marina Recatalá[1]; Manel Bosch[2]; Pedro Gaspar[3]; Alessandro Mineo[3]; Santiago Ríos[1]; Irene Miguel-Aliaga[3]; Marta Morey[1]

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The plasticity of intact adult neural tissue in the vicinity of neural damage helps restore circuit function. Much remains to be learned about the mechanisms regulating this process and the reported sex differences in recovery outcomes. Here, we present the fly gut and its innervation as a simplified model to address these questions. We show that ingestion of damaging agents triggers a reversible increase in adult enteric neural tissue in females, consistent with growth rather than neurogenesis. This growth can be influenced by gut-derived reactive oxygen species (ROS), as suggested by suppression with an antioxidant. Interestingly, males do not display neural plasticity, and masculinization of neurons in females suppresses damage-dependent neural growth. Conversely, feminizing male neurons does not confer plasticity, suggesting that sex-specific cues from surrounding tissues may be required for this response. Blocking plasticity reduces the DSS-induced increase in defecation and further shortens survival, indicating that female-specific neural plasticity supports both gut function and viability. Together, these findings establish a physiological model to dissect cellular, molecular, and sex-dependent regulators of adult neural plasticity relevant to circuit repair.

SENESCENCE IS REQUIRED FOR PLANARIAN REGENERATION

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Cellular senescence is classically viewed as a stable stress response associated with aging and cancer, yet accumulating evidence suggests that transient senescence-like programs can contribute to tissue repair. Here, we investigate whether senescence plays an instructive role during whole-body regeneration in the planarian *Schmidtea mediterranea*.

Using SPiDER-Gal as a marker of senescence, we detected a transient wave of SPiDER-Gal–positive cells during regeneration: signals appear after amputation and progressively decline as regeneration proceeds. To define the molecular state of these cells, we isolated X1 (stem cells), X2 (progenitors), and Xins (differentiated) populations and performed bulk RNA-seq of SPiDER-Gal positive and negative cells at 48 hours post-amputation. Across populations, SPiDER-Gal positivity was associated with a coordinated senescence-like transcriptional program. Core cell-cycle and replication genes were broadly downregulated, consistent with cell-cycle exit. In parallel, we observed strong upregulation of lysosomal/SA-β-gal–related genes and enrichment of secretory and remodeling factors, suggesting a senescence-associated secretory phenotype (planarian SASP) that may shape the regenerative niche.

Functionally, targeting senescent cells with senolytic drugs impaired regeneration, leading to reduced blastema formation, altered mitotic dynamics, disrupted early wound-induced gene expression, and patterning defects (including ectopic eyes and outgrowths).

Together, these data support a model in which a transient senescence program is required for proper remodeling and patterning during planarian regeneration.

CENTROSOME LOSS IN EMBRYONIC DEVELOPMENT DISRUPTS AXONAL PATHFINDING AND MUSCLE INTEGRITY

Beatriz González[1,2] and Sofia J. Araújo[1,2]

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Centrosomes, the primary microtubule-organizing centres (MTOCs), are crucial for early neuronal development, particularly in establishing polarity and promoting axon formation. Traditionally considered non-essential in terminally differentiated cells, recent evidence suggests that centrosomes play vital roles in specialized cellular contexts. In mammalian neurons, centrosome-mediated microtubule remodelling is essential for axon elongation, with centrosome dysfunction leading to axonal misrouting and growth defects. Although active centrosomes have been detected in the tracheal terminal cells of Drosophila melanogaster, their activity in neurons in vivo has not been observed. Their gradual loss during embryogenesis has been reported as non-essential for organogenesis, as adult flies can eclose without centrosomes.

To investigate centrosome activity in neurons, we revisited *Drosophila Sas-4* mutants, which exhibit centrosome loss (CL), and observed that 50% of homozygous mutant individuals fail to hatch as larvae. We analysed their development, focusing on the expressivity and penetrance of nervous system phenotypes, and examined centrosome localization in neurons. Our findings confirm the presence of centrosomes in motor and sensory neurons in *Drosophila* and their localization near the nascent axon. CL conditions resulted in axonal misrouting and muscle developmental abnormalities. Targeted downregulation of Sas-4 in the pioneer motor neurons aCC and RP2 induced axon guidance errors, indicating an autonomous role for centrosomes in axonal navigation. Colocalization of acetylated- and gamma-tubulin with centrosomes in motor neurons further confirmed the presence of functional centrosomes in these cells. Analysis of motor axons revealed that CL leads to axonal tortuosity, a characteristic associated with neurodegeneration. This is the first direct association of CL with axonal morphological phenotypes, highlighting the role of centrosomes in neuronal development and their broader influence on nervous system structure and function.

INDUCED BY SARS-COV-2 INFECTION PROMOTES NEURAL REGENERATION IN HUMAN BRAIN ORGANOIDS

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While SARS-CoV-2 primarily targets the respiratory system, its neurological effects have become a significant clinical concern. Postmortem analyses reveal astrogliosis, neuronal death, and blood–brain barrier dysfunction, yet the interplay between neural injury and endogenous repair remains unclear. Here, we employed human embryonic stem cell–derived brain organoids to examine viral tropism, bystander effects, and regenerative responses following infection. Single-cell transcriptomics and histological assays showed that SARS-CoV-2 productively infects neurons, neural progenitors, astroglia, and choroid plexus cells, triggering widespread apoptosis and senescence in both infected and neighboring cells. Despite low infection rates, organoids activated robust regenerative programs, including axon guidance, Wnt pathway signaling in mature neurons, and radial glia proliferation. Importantly, macrophage migration inhibitory factor (MIF) emerged as a key mediator, being strongly upregulated in both infected and uninfected cells, particularly in the choroid plexus. Recombinant MIF promoted dendritic outgrowth and cortical progenitor activation in uninfected organoids. Computational analyses indicated that MIF stimulates neural regenerative via EGFR signaling and upregulates its own expression in non-infected cells. These findings identify MIF as a molecular link between SARS-CoV-2-induced neural damage and regenerative activation in cortical cells.

DEVELOPMENTAL CONSEQUENCES TO AN ORGANISMAL TRISOMY

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An unbalanced number of chromosomes, or aneuploidy, accounts for most spontaneous abortions, as missegregation of a single chromosome during development is often lethal. In humans, only trisomies of the small chromosomes 13, 18, and 21 are compatible with life; however, affected individuals suffer from severe developmental and growth retardation defects. The compact genome of Drosophila and powerful genetic tools such as compound chromosomes (two homologous chromosomes with a single centromere) make this animal an ideal model organism to understand the consequences of trisomies at the organismal level and to unravel the mechanisms by which aneuploidy affects animal development. One of the main questions in the field is whether the deleterious effects are due to a general imbalance of all genes present in the trisomic chromosome, thereby causing proteome imbalance that can lead to proteotoxic stress, or whether they are due to specific dosage-sensitive genes within each triplicated region. In particular, we have used trisomies of the X and 2L chromosomes, which are not embryonic lethal, and found that both trisomies cause a strong developmental delay and growth retardation at both the systemic and organ levels during larval development. We performed transcriptomic and proteomic analyses of three distinct organs from trisomic larvae to show that changes in chromosome copy number are reflected in the overall output of mRNA and proteins. Contrary to our expectations, we did not identify any evidence of activation of protein quality-control mechanisms. Interestingly, careful characterization of the development of imaginal primordia revealed patterns of cell death and developmental defects that were specific to each trisomy, suggesting the existence of chromosome-specific dosage-sensitive loci that impact the development of different cell fates and tissues.

DEEP CONSERVATION OF CIS-REGULATORY ELEMENTS AND CHROMATIN ORGANIZATION IN ECHINODERMS UNCOVER ANCESTRAL REGULATORY FEATURES OF ANIMAL GENOMES

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Despite the growing abundance of sequenced animal genomes, we only have detailed knowledge of regulatory organization for a handful of lineages, particularly flies and vertebrates. These two taxa show contrasting trends in the molecular mechanisms of 3D chromatin organization and long-term evolutionary dynamics of cis-regulatory element (CREs) conservation. Here, we study the evolution and organization of the regulatory genome of echinoderms, a lineage whose phylogenetic position and relatively slow molecular evolution has proven particularly useful for evolutionary studies. We generated new reference genome assemblies for two species belonging to two different echinoderm classes: the purple sea urchin *Strongylocentrotus purpuratus* and the bat sea star *Patiria miniata* using PacBio and HiC data and characterize their 3D chromatin architecture. We show that these echinoderms have TAD-like domains that, like in flies, do not seem to be associated with CTCF motif orientation. We systematically profiled CREs during sea star and sea urchin development using ATAC-seq, comparing their regulatory logic and dynamics over multiple developmental stages. Finally, our analysis of sea urchin and sea star CRE evolution across multiple evolutionary distances and timescales showed several thousand elements conserved for hundreds of millions of years, revealing a vertebrate-like pattern of CRE evolution that probably constitutes an ancestral property of the regulatory evolution of animals.

ORIGIN OF CELL DIFFERENTIATION IN ANIMALS

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Over the past two decades, studies of the unicellular relatives of animals have greatly advanced our understanding of the origins of animal complexity, including cell differentiation and development. For instance, it was shown that some transcription factors involved in embryonic development predate the emergence of animals. In this study, we use the ichthyosporean Abeoforma whisleri as a model to explore the origins of cell differentiation in the animal lineage. Abeoforma exhibits a morphologically diverse non-linear life cycle. Using microscopy, culture manipulation, bulk RNA sequencing, and single-nuclei RNA sequencing, we identify and characterize its distinct life stages. Notably, we describe, for the first time, a highly polarized cell morphology with a complex cytoskeleton and vesicular infrastructure. These cells form at a specific time point and environmental cues, and carry the function of motility and dispersion. After performing their task, the cells die. This is reminiscent of the terminal cell differentiation in animals, the phenomenon previously undocumented in unicellular organisms. Our findings suggest that the unicellular ancestor of animals had a complex life cycle regulation involving animal-like molecular factors and with prerequisites to cell differentiation. This highlights the evolutionary principle of co-opting existing genes and pathways into new functions and physiological processes, highlighting this important mechanism in the evolution of animals.

ROS-MEDIATED PTEN INACTIVATION REGULATES REGENERATION IN *DROSOPHILA* GUT AND WING IMAGINAL DISC

Iván Sopena-Majós[1], José Esteban-Collado[1], Joan Vallhonrat-Pinell[1], Montserrat Corominas[1], Florenci Serras[1]

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Tissue damage generates early signals that trigger damage response in the surrounding cells. Reactive oxygen species (ROS) produced by apoptotic cells activate the nutrient-dependent Insulin pathway. Akt is the core kinase downstream the Insulin pathway that phosphorylates Ser^{83} of MAP3K Ask1, a necessary event for p38 signalling activation during regeneration. Furthermore, nutrient restriction has been described to impair wound healing. We demonstrate that ectopic activation of Akt rescues regeneration after nutrient restriction, proving that Insulin pathway plays a key role in early tissue damage response. We recently found that Akt phosphorylation is ROS-dependent. Here we explore how the ROS produced by apoptotic cells target the neighbouring cells activating PI3K/Akt to drive regeneration. Phosphatase and tensin homolog (Pten) antagonises PI3K-Akt. It has been suggested in mammalian cells that Pten undergoes a ROS-dependent reversible inactivation by formation of a disulphide bond between two Cys nearby the catalytic domain. To explore if Pten is operating as a ROS sensor in regeneration we used *Drosophila* wing imaginal disc and adult midgut, both epithelial tissues with well described regenerative capacities. We observed that after ectopic activation of Pten, regeneration was impaired. However, applying oxidative stress rescued regeneration. To demonstrate that ROS targets Pten, we mutated by amino-acid substitution its residues Cys^{79} and Cys^{132} to block the ROS-dependent inactivation of the phosphatase activity but not the phosphatase activity itself. We show here that oxidative stress was unable to rescue regeneration in these mutant backgrounds. In addition, ROS-dependent activation of Akt and p38 after expression of *wild-type* Pten was abolished in $Pten^{C79A}$. Altogether, our findings indicate that ROS target Pten during regeneration, providing new insights into the molecular mechanisms underlying tissue repair. This study contributes to our understanding of how early signals trigger the regenerative response and may have implications for developing targeted therapies to enhance tissue regeneration.

SMED-CDK-17 REGULATES EYE SIZE DURING PLANARIAN REGENERATION AND HOMEOSTASIS

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During embryonic development and regeneration, the growth of any organ must be tightly regulated in order to achieve their optimal final size and become fully functional. Freshwater planarians, with their remarkable ability to regenerate any part of their body based upon the presence of adult pluripotent stem cells, provide an ideal model to study how the final organ size is regulated, in a regeneration context. Also, the fact that they are constantly growing and degrowing depending on culture conditions, allows us to study how the size of the different organs is determined under those homeostatic conditions. Here, we investigate the role of *Smed-cdk-17*, a cyclin dependent kinase that belongs to the PCTAIRE subfamily of CDKs, which still remains poorly understudied. Functional analyses show that *Smed-cdk-17* silencing results in bigger eyes both in intact and regenerating planarians. Planarian photoreceptors consist in two cell types: sensory photoreceptors and a pigmented eye-cup. The increase in eye size is associated to an increase of the number of both progenitor and differentiated eye cell types. Phototaxis behavioral assays reveal that *Smed-cdk-17* RNAi planarians exhibit an increased sensitivity to light. In addition, the absence of *cdk-17* disrupts the normal proportions of the cephalic ganglia. Overall, these findings highlight *Smed-cdk-17* as a key regulator of eye size and neural patterning in planarians.

STAU2 COORDINATES METABOLISM AND RNA REGULATION IN EARLY HUMAN NEUROGENESIS

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RNA-binding proteins (RBPs) are central to post-transcriptional gene regulation during neurogenesis. Here, we dissect the role of the double-stranded RBP STAU2 in early human cortical development using single-cell transcriptomics, gene regulatory network (GRN) inference, and cerebral organoids derived from STAU2 knockout (KO) iPSCs. STAU2 loss profoundly affected neuroepithelial cells, accelerating neuronal differentiation. STAU2 coordinated downregulation of RNA-processing and translation pathways, alongside upregulation of glycolysis, oxidative phosphorylation, and cholesterol biosynthesis, indicating premature metabolic activation. GRN analysis identified CHD2 and ARID3A as downstream mediators of STAU2 function, linking its loss to altered chromatin and transcriptional regulation towards a neurogenic fate. In parallel, STAU2 deficiency disrupted miRNA host gene expression (including MIR9-1HG and SLIT2), reinforcing combined transcriptional and post-transcriptional control. Functionally, STAU2 KO organoids showed impaired progenitor expansion, disorganized architecture, and accelerated neuronal differentiation. Together, these results position STAU2 as a key integrator of metabolic, transcriptional, and post-transcriptional programs governing early human neurogenesis.

FATTY ACID β-OXIDATION COUPLES METABOLISM TO EPIGENETICS TO ORCHESTRATE EPITHELIAL GROWTH

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Developing tissues integrate multiple intrinsic and extrinsic cues to successfully grow and differentiate. Tissue growth is regulated by several well-known mechanisms, including morphogenetic signals (such as WNT and TGFβ), mechanical cues (like cellular tension), and systemic endocrine hormones. However, the direct impact of nutritional uptake and its further metabolism, in coordinating growth remains poorly understood. *Drosophila* wing disc has been a fundamental model in building our understanding of tissue growth and development. Here, using this model, we unravel how tissue-intrinsic metabolism controls growth and development. First, we performed a genetic screening to dissect the differential contribution of various metabolic pathways in growth and development. We present evidence that Fatty Acid β-Oxidation (FAO) is required preferentially over glycolysis for proliferative growth. In absence of FAO, epithelial cells can switch their metabolic state and consequentially utilize available dietary glucose as an alternative metabolite, highlighting the plasticity of the tissue to adapt to other metabolic pathways to ensure growth. Interestingly, we found that the effects on tissue growth upon FAO depletion is independent of ATP production. Next, we found that FAO is crucial for maintaining an epigenetic state permissive to tissue growth by maintaining a pool of acetate required for histone acetylation. In the absence of FAO, histone acetylation is compromised, and subsequently nascent transcription is affected. Impaired transcription ultimately affects protein translation, and here, we propose a novel intermediary role of Myc in doing so. Thus, our results elucidate the direct impact of metabolism on epigenetics and hence in coordinating transcription and translation and ultimately facilitating growth.

POSTERS

P1. METABOLIC CONTROL OF PLANARIAN REGENERATION: THE ROLE OF DIET

Talia Fundora Barrios and Cristina González Estévez

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Planarians, particularly *Schmidtea mediterranea*, are powerful models for studying regeneration due to their extraordinary ability to regenerate complete body structure, including the brain, from small tissue fragments. This process depends on neoblasts, a population of adult stem cells capable of differentiating into all cell types. Remarkably, planarians retain robust regenerative capacity even under prolonged starvation, suggesting a tight link between metabolism and stem cell function. Recent studies in other model systems have identified metabolism as a key regulator of stem cell behavior, affecting quiescence, activation, and differentiation, as well as the modulation of gene expression and of signaling pathways such as mTOR, AMPK, and Wnt/β-catenin. While glycolysis and oxidative phosphorylation have been widely studied in stem cell biology, emerging evidence highlights a crucial role for lipid metabolism, particularly fatty acid oxidation, in stem cell maintenance. In planarians, dietary conditions such as caloric restriction influence regenerative outcomes, yet the metabolic mechanisms that initiate regeneration remain poorly understood. In this project, we aim to investigate how metabolic changes regulate the initiation of regeneration in planarians, focusing on the interplay between nutrient availability, neoblast behavior, and the activation of genetic cascades required for a successful regenerative response. This ongoing work is expected to provide new insights into the metabolic control of regeneration and may inform future strategies in regenerative medicine and stem cell-based therapies.

P2. DNA REPAIR GENES SHAPING EMBRYONIC DEVELOPMENT

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DNA is constantly undergoing damage from both endogenous and external sources and DNA repair mechanisms work to repair this damage. DNA damage and repair failure are key contributors to neurodegeneration and dementia, yet the precise mechanisms linking DNA repair defects to neuronal decline remain poorly understood. Neurons, with their high metabolic activity and long lifespan, are particularly vulnerable to DNA lesions, making them highly dependent on efficient repair systems. Dysfunctional DNA repair has been implicated in several neurodegenerative disorders, including dementia with Lewy bodies (DLB), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS). Among the major DNA repair pathways, nucleotide excision repair (NER) is crucial for removing bulky lesions caused by UV light, chemical mutagens, and reactive oxygen species (ROS). Defective NER is associated with oxidative stress, mitochondrial dysfunction, and chromatin reorganization, leading to neuronal cell death and cognitive decline. Despite these associations, the molecular mechanisms by which NER failure drives neurodegeneration remain unclear, largely due to the lack of in vivo models that allow precise control over DNA damage.

Defects in NER in humans are linked to a disease called xeroderma pigmentosum (XP). XP is characterized by extreme sensitivity to UV light, leading to a 2000x higher incidence of skin cancer. Patients may also suffer from neurodegenerative or neurodevelopmental symptoms. We are investigating the role of the XPA and XPC proteins, both implicated in XP disease, in embryonic development in Drosophila melanogaster. The XPA protein acts as the central hub for the NER excision complex, while the XPC protein recognizes DNA damage before the complex is assembled. During embryonic development, sources of DNA damage are primarily endogenous. These include reactive oxidative species and errors in DNA replication. Embryonic cells are rapidly dividing and differentiating, and defects in gene expression can result in developmental abnormalities.

P3. EXPLORING ORGANELLE DYNAMICS IN SUBCELLULAR BRANCHING

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Cell shape is intrinsically connected with cell function in tissues and organs, varying enormously throughout nature. Branched cellular networks are a common feature of multicellular animals and underlie the formation and function of numerous tissues and organs, including the nervous system, respiratory system, vasculature, and many internal glands. The production of branched structures by single cells, known as subcellular branching, involves complex organelle and cytoskeletal remodelling events. We aim to better understand single-cell branching beyond the dynamics of the cytoskeleton. Previous research from the Araújo laboratory showed that centrosomal and acentrosomal cytoskeletal changes affect subcellular branching in tracheal cells. We are now exploring how organelle dynamics can influence single-cell branching and identify the molecular partners involved. Ribosomes, involved in protein synthesis, have a homeostatic effect on cells during development. Since rapid protein transition is important for local stimuli response, ribosome localization and composition are expected to be important for single-cell branching. Additionally, protein synthesis, cell movement, and cytoskeletal dynamics are necessary for cell branching and require high ATP production. Mitochondria dynamics play a role in transporting mitochondria into axons and dendrites for neuronal activity. Yet, we do not know the function and effect of mitochondria and ribosomal localization on the subcellular branching of tracheal terminal cells.

We are using three different branched cell types as models: sensory and motor neurons and tracheal terminal cells, and focusing on the influence of organelles, such as the mitochondria and the ribosomes in the single-cell branching process. By analysing these cellular models in parallel we will be able to find common/shared mechanisms of subcellular branching as well as the specific mechanisms involved in each of these cell types.

P4. SPATIOTEMPORAL COORDINATION OF INJURY-INDUCED CELLULAR STATES DURING PLANARIAN TAIL REGENERATION

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Tail regeneration in bilaterian animals requires the coordinated re-establishment of body patterning and tissue growth. While key signaling pathways are well-studied, how injury-induced cellular states dynamically organize the regenerating tissue remains poorly understood. We investigated the cellular dynamics of posterior blastema formation in *Schmidtea mediterranea* through single-cell sequencing of posterior wounds from 0 to 96 hours post-amputation. We identified cell clusters corresponding to muscle, parenchymal, and phagocytic cells that adopt transient, regeneration-specific states. Functional study of genes expressed in these populations such as *fascin* and the E3 ubiquitin-ligase *ARI2/3* demonstrates their requirement for proper tail regeneration. Our study provides evidences that the triggering of regeneration-specific transcriptomic signatures in specific cell types is required for mounting a successful regeneration response.

P5. CHARACTERIZATION OF CG6398, A NEW CLAUDIN-LIKE PROTEIN, DURING EPITHELIAL DEVELOPMENT IN DROSOPHILA MELANOGASTER.

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During embryonic development different tissues undergo extensive remodelling. In relation to this, their adhesion structures must be strictly regulated, becoming flexible enough to enable the dynamic movements but also strong enough to maintain tissue integrity. Our lab previously identified the adhesion protein Sidekick (Sdk), as a key component of tricellular Adherens Junctions (tAJs, points where three or more cells meet). Our analysis indicated a crucial role of Sdk in regulating cell rearrangements during tissue remodelling. To better understand the molecular mechanisms of Sdk activity we carried out a a TurboID-based proximity labeling assay aimed at uncovering potential interactors. One of the identified proteins was CG6398. CG6398 belongs to the claudin family. Claudins typically localize at Septate Junctions (SJs, functionally analogous structures to the Tight Junctions in vertebrates) with a key role in sealing the paracellular space.

We observed an atypic subcellular distribution of CG6398 as despite being a claudin it was found at tAJs where it colocalized with Sdk at early stages of development. We also observed that CG6398 display a highly dynamic pattern of subcellular localization, spreading from a pattern in the junctional region to an enrichment at the apical cortex across developmental stages. Besides, our results indicate a consistent colocalization with the actin cytoskeleton.

Given these distinctive characteristics, we are currently investigating the functional role and the cellular mechanisms of CG6398 using available tools and the ones we have generated for this study. We are analyzing the effects of CG6398 loss-of-function and overexpression conditions, in combination with subcellular localization analyses.

P6. TGFB/BMP-DEPENDENT CONTROL OF HUMAN EMBRYONIC ALVEOLAR DIFFERENTIATION BY IGFBP3 AND ITS LINK TO STEM CELL STATES IN THE ADULT LUNG

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Alveolar differentiation during human lung development depends on the controlled transition from progenitor states to differentiated alveolar cells. Among the genes potentially involved in this process, we identified insulin-like growth factor binding protein 3 (*IGFBP3*), a key modulator of growth factor signaling through IGF-dependent and independent mechanisms. We observed that *IGFBP3* expression was progressively downregulated during the human pseudoglandular stage (8-12 weeks) and during human lung embryonic organoid differentiation. This pattern suggested a role for *IGFBP3* in epithelial differentiation, but the signaling pathways underlying its function remained unclear. To investigate this, we analyze the role of *IGFBP3* in human embryonic tip-derived lung organoids, focusing on TGFβ-related signaling pathways. siRNA-mediated silencing of *IGFBP3* induced an alveolar-like differentiation, characterized by morphological changes and the formation of alveolospheres. This process was associated with a significant downregulation of stem cell markers (*SOX2*, *OCT4*, *NANOG*) and a marked upregulation of AT2 and AT1 markers, including *SFTPB*, *SFTPC* and *SFTPD*. To explore the molecular mechanisms involved, we analyzed the phosphorylation status of key proteins related to the TGFβ pathway. *IGFBP3* silencing resulted in a marked inhibition of canonical TGFβ signaling, evidenced by decreased phosphorylation of SMAD2, together with activation of BMP signaling, indicated by increased phosphorylation of SMAD1. These changes correlated with the repression of TGFβ target genes associated with stemness and the activation of BMP-responsive alveolar differentiation markers. Furthermore, *IGFBP3* expression was found to be significantly higher in adult lung tissue-derived organoids compared to paired normal tissue, suggesting a potential role in adult lung stem cell regulation and possibly in tumor-associated epithelial states. Together, our results identify *IGFBP3* as a regulator of alveolar differentiation during human lung development by modulating the TGFβ/BMP signaling balance and suggest a potential role for *IGFBP3* in epithelial stem cell regulation beyond embryonic development. Funded by Marató TV3 202524-10.

P7. TRANSCRIPTIONAL PROFILE OF PLANARIAN SENESCENT CELLS

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Cellular senescence is traditionally associated with aging and degeneration; however, increasing evidence suggests that senescence-associated programs can positively influence tissue regeneration. Despite this, the molecular mechanisms linking senescence to regeneration remain poorly understood. Planarians are an excellent model system for studying regeneration, as they possess adult stem cells that enable them to regenerate almost any part of their body within a few days.

Here, we will investigate the role of senescence-associated pathways during planarian regeneration by comparing stem cell populations that differ in senescence burden. Specifically, we will analyze SPiDER-Gal–positive (spider^{+}) and SPiDER-Gal–negative (spider^{-}) cell populations. Using bulk RNA sequencing, we will define transcriptional differences between spider^{+} and spider^{-} cells to identify gene expression programs associated with elevated senescence. Transcriptomic analyses will be used to identify candidate genes and pathways enriched in the spider^{+} population.

Based on these data, we will perform a targeted RNA interference (RNAi) screen to functionally test whether specific genes enriched in the spider^{+} population are required for planarian regeneration. By assessing the effects of gene knockdown on senescence markers, regenerative capacity, and stem cell biology, this approach will allow us to directly link senescence-associated transcriptional programs to functional outcomes. Together, these studies will establish a framework for identifying molecular drivers of senescence and testing their causal roles in regulating regeneration.

P8. EFFECTS OF CBP-3 RNAI ON CELL TYPE PROPORTIONS AND GENE EXPRESSION IN SCHMIDTEA MEDITERRANEA

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Their regenerative capabilities have made planarians a well-established model organism for stem cell research: Leveraging an abundant population of adult pluripotent stem cells, the so-called neoblasts, planarians can re-generate any part of their body upon injury. Recent findings have shown that the neoblast population does not constitute a heterogeneous group of pluripotent stem cells, but rather a heterogeneous population of stem cells ranging from pluripotent to more specialized cells closer, and potentially pre-committed, to certain differentiated cell types. The exact mechanisms regulating maintenance and differentiation of neoblasts, however, remain poorly understood.

Here, we present our findings from RNAi perturbation experiments to knock down, in regenerating and intact planarians, *Smed-cpb-3*, a transcriptional co-activator that regulates gene expression by several means, including acetylating histones and other proteins. This perturbation results in the formation of a normal-sized blastema, but fails the regeneration of eyes, neurons and other terminal differentiated cell types. Instead, these blastemas are enriched in neoblasts. Thus, we postulate that *cbp-3* is essential for terminal differentiation of progenitor cells.

To elucidate which cell types are affected and through what *cbp-3* target genes, we performed RNA-seq (bulk and single-cell) in *cbp-3* RNAi animals. Here, we present our findings regarding over- and under-represented cell types/populations and (cell type specific) differential gene expression analyses.

P9. MODELLING TYROSINE HYDROXYLASE DEFICIENCY USING PATIENT-DERIVED IPSCS HUMAN BRAIN ORGANOIDS

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Biallelic mutations in the tyrosine hydroxylase (TH) gene cause tyrosine hydroxylase deficiency (THD), an ultra-rare neurometabolic disorder characterized by impaired dopamine (DA) synthesis during brain development. Given the critical role of DA in neurodevelopment, affected individuals typically present in early infancy with motor symptoms, including hypokinesia, tremor, and postural instability, along with cognitive and behavioral impairments. Currently, no disease-modifying therapies are available for patients with the severe form of THD (THDB) who are unresponsive to first-line L-dopa treatment, representing a significant unmet medical need.

To characterize disease-specific cellular impairments and elucidate the role of dopamine in THD during brain development, we generated ventral midbrain organoids (vmOs) and cortical organoids (COs) from a THDB patient-derived iPSC line and its corresponding isogenic control. VmOs faithfully recapitulated key features of the human midbrain. Protein-level, morphological, and functional analyses revealed multiple cellular defects, including a reduced population of TH^+ dopaminergic neurons, impaired DA release, and decreased neurite complexity. GCaMP-based calcium imaging further demonstrated reduced spontaneous neuronal activity and desynchronized network dynamics in mature THDB vmOs. Notably, several of these phenotypes were rescued in the gene-corrected isogenic iPSC line.

Moreover, early treatment with tetrahydrobiopterin (BH4), the TH enzymatic cofactor and a clinically repurposed therapy, normalized neuronal morphology and restored neuronal activity. To further investigate early cortical developmental alterations resulting from dopamine depletion, preliminary analyses in COs revealed an expanded progenitor pool and a reduced neuronal population in THDB-derived organoids. These findings suggest that impaired DA signaling disrupts the transition from neuronal progenitors to mature cortical neurons, potentially contributing to the cognitive deficits observed in patients.

Together, these results establish THDB vmOs and COs as robust human models of severe THD and neurodevelopment, highlighting their utility as platforms for mechanistic studies and therapeutic screening in dopamine-deficiency disorders.

P10. CHARACTERIZING GENES ASSOCIATED WITH POSTERIOR REGENERATION IN *SCHMIDTEA MEDITERRANEA*

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Proper gene program activation in specific cell types is needed for a successful regeneration. The wnt-βcatenin pathway is the main signal required for proper posterior patterning during planarian regeneration. Inhibition of key proteins associated with this pathway leads to problems in the appropriate polarization of the body, forming "*tailless*" or *"two-headed"* animals. This project aims to study four different genes upregulated during posterior regeneration in regeneration-specific cell types: *fascin, ari2/3, sorcin* and *smed-2850*. The aim is to characterize their spatial expression, and their involvement in triggering cell proliferation at early timepoints (12h and 48 h after the cut). We will also test whether the polarity of the animals is properly established after their RNAi inhibition though the analysis of anterior and posterior markers. Through this study we will have a better understanding of the role that regeneration-specific cell types could have in triggering the regenerative response.

P11. DIFFERENT CELLULAR AND MOLECULAR MECHANISMS OF CHITIN DEPOSITION CONTRIBUTE TO THE SPECIFICITY OF THE TWO CHITIN SYNTHASES IN *D. melanogaster*

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Chitin, a key aminopolysaccharide, is a major component of arthropod extracellular matrices, such as the exoskeleton and midgut peritrophic matrix, playing essential roles in insect development, growth, and survival. Beyond its biological significance, chitin has also received a lot of attention in medicine and biotechnology due to its exceptional physicochemical and mechanical properties as a biopolymer. Chitin is synthesized and deposited extracellularly by chitin synthases. Most insects encode two types of chitin synthases, type A primarily associated with exoskeleton formation, and type B, linked to peritrophic matrix production. However, the factors controlling the specificity of these enzymes remain unclear. Using *Drosophila melanogaster* as a model system, we investigated the mechanisms and functional roles of Kkv (Chitin synthase A) and Chs2 (Chitin synthase B). We demonstrated that Chs2 is expressed and required in the larval proventriculus, a region responsible for producing chitin in the peritrophic matrix. Additionally, we explore whether these chitin synthases can substitute for each other, examine their subcellular localization in various tissues, and assess their ability to deposit chitin alongside auxiliary proteins. Our findings reveal that Kkv and Chs2 are not functionally interchangeable and employ distinct cellular and molecular mechanisms for chitin deposition. We propose that the specificity of insect chitin synthases underpins the production of chitin polymers with unique properties, which in turn confer diverse physiological functions to extracellular matrices.

P12. THE ROLE OF THE RETINOIC ACID PATHWAY IN PLANARIANS REGENERATION.

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Retinoic acid (RA), a metabolite of vitamin A (retinol), is one of the most conserved morphogens across Metazoa and plays a crucial role in embryonic development, body axis patterning, and organogenesis. In this study, we investigate the conservation of the retinoic acid signaling pathway in *Schmidtea mediterranea* (Tricladida, Platyhelminthes), focusing on its core components and the effects of pathway inhibition following experimental manipulation.

This pathway has been extensively studied and is classically associated with the heterodimer formed by the nuclear receptors RAR and RXR. While chordates show a RAR/RXR module, protostomes rely primarily on RXR and co-regulators to maintain retinoic acid sensitivity, highlighting the flexibility and evolutionary plasticity of this ancestral signaling system. In *S. mediterranea*, no RAR genes have been identified, consistent with observations in other protostomes. However, two RXR homologs with conserved DNA-binding and ligand-binding domains are present and, according to 3D simulations, they could be functional. A co-regulators RERE complex, which can act as either a transcriptional co-repressor or co-activator depending on the associated proteins, has also been identified in *S. mediterranea*.

Experimental inhibition of the RA pathway in *S. mediterranea*, achieved through knockdown of key components (ADH, ALDH, RXR, and RERE) as well as through the use of DEAB (competitive inhibitor of ALDH), demonstrates that disruption of this pathway affects regeneration both anterior and posterior regeneration. During anterior regeneration specific defects in the cephalic ganglia and the eyes are observed. During posterior regeneration, inhibition of the pathway produces tailless animals and asymmetric-tails phenotypes.

Although a more in deep analysis if the knockdown phenotypes is required, these findings demonstrate the important role of the RA pathway during planarian regeneration, probably during nervous system differentiation and in posterior identity specification.

P13. DECIPHERING REGULATORY MECHANSIMS DRIVING DRAVET SYNDROME IN BRAIN ORGANOIDS

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Dravet syndrome (DS) is one of the most common developmental epileptic encephalopathies (DEEs), characterized by early onset epilepsy and severe neurodevelopmental impairment. In approximately 80% of cases, DS is caused by mutations in the *SCN1A* gene encoding the Nav1.1 sodium channel subunit, leading to alterations in neuronal excitability. Brain organoids (BOs) enable the recapitulation of developmental processes, molecular mechanisms underlying cell differentiation and mimic the spatial organization and structural architecture of the developing human brain. Furthermore, assembloids, created by integrating different types of organoids, allow the study of interactions driven by distinct genotypes, offering a more comprehensive model of brain development and disease mechanisms. In this project, we aim to identify key regulatory networks involved in cortical development in Dravet syndrome compared to control organoid models.

To achieve this, we developed brain organoids and inter-genotype assembloids using unguided protocols (Lancaster (2014)) to explore how the cellular environment influences epigenetic regulation. BOs were derived from a Dravet induced pluripotent stem cell line (iPSCs) and a human control embryonic stem cell line expressing a mCherry reporter (H9::mCherry) and collected at day 90 of differentiation. Inter-genotype assembloids were dissected prior to fixation into three different regions: the DS14 derived region, the intersection region and the H9::mCherry enriched region. Chromatin accessibility changes were profiled by the ATAC-seq technique and compared across organoids and assembloid regions. Unexpectedly, chromatin accessibility profiles revealed that the intersection region clustered more closely with Dravet organoids than with the Dravet derived region of the assembloid as expected. Consistent with this, a higher number of shared open regions were observed between DS organoids and intersection part compared to DS region in the assembloid. As the DS14 organoid and the intersection region behave similarly, this suggests that the influence of the DS genotype in the assembloid is stronger than of the healthy genotype, indicating that the Dravet genotype may influence the surrounding environment through non cell autonomous mechanisms. Further analyses are required to explore this possibility and better understand the mechanisms underlying this observation.

P14. EARLY EVENTS OF REGENERATION: THE ROLE OF AUTOPHAGY

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Regeneration is a fundamental developmental process that requires coordinated stem cell activation, metabolic adaptation, and preservation of tissue integrity after injury. However, the mechanisms that allow stem cells to sustain rapid proliferation and differentiation during regeneration, particularly under nutrient-limited conditions, remain poorly understood. Autophagy, a conserved intracellular degradation pathway induced by fasting and stress, has emerged as a key regulator of cellular homeostasis, yet its in vivo role during regeneration is still unclear. Here, we investigate the function of autophagy during regeneration using the planarian Schmidtea mediterranea, a classical model of stem cell–based whole-body regeneration. Regeneration is driven by neoblasts, adult pluripotent stem cells that undergo robust proliferative responses after injury while maintaining genomic stability during prolonged starvation. Using an RNA interference (RNAi) screen targeting canonical autophagy (atg) genes, we identify autophagy regulators enriched in stem cells that are essential for regeneration initiation under starved conditions. Inhibition of these genes impairs blastema formation, alters stem cell proliferation dynamics, and leads to DNA damage accumulation and tumor-like overgrowths. These phenotypes are partially rescued by feeding, revealing a tight link between autophagy, metabolic state, and regenerative capacity. Our findings identify autophagy as a critical early regulator linking metabolism to stem cell function during regeneration

P15. iPSCs AND iPSC-DERIVED PPCs AS A HUMAN MODEL OF CERKL-ASSOCIATED RETINAL DEGENERATION

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Mutations in the CERKL (Ceramide Kinase-Like) gene are responsible for retinitis pigmentosa (RP) and cone-rod dystrophy (CRD), two forms of autosomal recessive inherited retinal dystrophies (IRDs) characterized by dysfunction and progressive degeneration of photoreceptor cells, due to alterations in developmental and functional photoreceptor-related pathways, ultimately leading to vision loss and blindness. To date, over 40 pathogenic CERKL mutations have been identified. The CERKL protein is believed to play an essential role in retinal homeostasis through the regulation of mitochondrial dynamics, autophagy, cell metabolism, and oxidative stress response. In this study, we used human induced pluripotent stem cells (iPSCs) derived from a patient homozygous for the CERKL R257X mutation and successfully differentiated them into photoreceptor progenitor cells (PPCs) as a model of diseased-developing photoreceptors. Phenotypic characterization of patient-derived CERKL R257X iPSCs, as well as their differentiated PPCs, revealed altered mitochondrial morphology and function, including a change in mitochondrial major length, form factor and aspect ratio, and in levels of VDAC (a mitochondrial outer membrane protein) and OXPHOS proteins. Under oxidative stress, these cells exhibited enhanced autophagy and activation of ferroptosis pathways (evidenced by reduced FTH1 levels), suggesting impaired mitochondrial homeostasis and a differential stress response due to CERKL deficiency. Overall, our findings reinforce the critical role of CERKL protein in maintaining cell metabolism, mitochondrial integrity, and protection against oxidative stress. Differentiation into PPCs from CERKL-patient's iPSCs constitute a robust in vitro platform for identifying biomarkers of disease progression and exploring novel therapeutic targets for IRDs associated with CERKL dysfunction. Keywords: CERKL, inherited retinal dystrophies, retinitis pigmentosa, iPSCs, photoreceptor progenitor cells, mitochondrial dynamics, autophagy, oxidative stress, ferroptosis.