© 2023. Published by The Company of Biologists Ltd | Development (2023) 150, dev202086. doi:10.1242/dev.202086

MEETING REVIEW

Development, regeneration and aging: a bizarre love triangle

Luisa Cochella[1,*] and Zayna Chaker[2,*]

ABSTRACT

The Jacques Monod Conference on 'Growth and regeneration during development and aging' was organized by Claude Desplan and Allison Bardin in May 2023. The conference took place in Roscoff, France, where participants shared recent conceptual advances under the general motto that developmental processes do not end with embryogenesis. The meeting covered various aspects of how development relates to fitness, regeneration and aging across a refreshing diversity of evolutionarily distant organisms.

Introduction

The Station Biologique de Roscoff provided a spectacular backdrop for the Jacques Monod Conference on 'Growth and regeneration during development and aging'. The meeting had a friendly and open-minded atmosphere, triggering stimulating scientific discussions. Here, we provide an overview of the conference's main themes, including how developmental events shape regeneration and aging trajectories, how aging affects regeneration and the development of offspring, and the molecular mechanisms that are at play in these three inter-related processes. The work presented spanned investigations ranging from molecular and cellular levels, to organismal and population scales.

Transcriptional control of development

Transcriptional regulation is at the heart of development, and several talks discussed novel insights into how transcription factors and chromatin regulation achieve the necessary precision to control gene expression in space and time.

Mounia Lagha's lab (University of Montpellier, France) investigates how transcription is first activated in the *Drosophila* zygote. Combining genetics, imaging and mathematical modeling, the Lagha lab has generated quantitative models describing the dynamics of RNA synthesis and translation to ultimately understand how reproducible cell fate decisions can arise in the face of variability and noise (Bellec et al., 2022; Dufourt et al., 2021; Pimmett et al., 2021). Olivier Hamant (ENS Lyon, France) also discussed the importance of buffering or filtering transcriptional heterogeneity to ensure reproducible development. Starting with the question of how multicellular organisms grow to reproducible forms despite variability in growth at the level of individual cells, he showed that loss of POLYMERASE ASSOCIATED FACTOR 1 (PAF1) in *Arabidopsis thaliana* causes increased transcriptional variability across adjacent cells that ultimately seems to lead to local growth conflicts and increased variability in organ shape. A concept that emerged from this talk was how evolution favors robustness at the expense of performance or optimality (Trinh et al., 2023).

Temporal aspects of transcriptional control were also discussed. Gantas Perez-Mockus from Jean-Paul Vincent's lab (The Francis Crick Institute, UK) addressed how the *Drosophila* hormone ecdysone can have opposite effects on proliferation at different developmental stages. They proposed a mechanism by which accumulation of ecdysone over developmental time generates a temporal concentration gradient resulting in activation of gene targets with different sensitivity to hormone levels (Perez-Mockus et al., 2023 preprint). Wolfgang Keil (Institut Curie, Paris, France) discussed the mechanism by which orthologs of circadian rhythm genes program transcriptional dynamics to drive post-embryonic development in *Caenorhabditis elegans*. Intriguingly, they find that transcription of microRNA genes specifying temporal identity is driven by two orthologs of the mammalian circadian transcription factors REV-ERB and ROR. These transcription factors exhibit antagonistic functions in other organisms, but they act cooperatively in worms and are only co-expressed during a short temporal window between larval molts. This generates sharp pulses of microRNA transcription that mediate larval developmental progression (Kinney et al., 2023).

Lionel Christiaen's lab (Michael Sars Centre, University of Bergen, Norway) studies cardiopharyngeal development in the tunicate *Ciona*. In these ascidians, cell diversification is coupled with stereotypic cell divisions, meaning that transcriptome changes along different developmental trajectories can be followed using single-cell RNA sequencing and mapped relative to each mitosis (Wang et al., 2019). As in other systems, the progenitor that gives rise to cardiac and pharyngeal lineages is 'multi-lineage primed', expressing genes related to both fates, but its two descendants become transcriptionally asymmetric in a manner that depends on both extrinsic signaling and cell division. This raises exciting mechanistic questions about how mitosis is coupled to regulation of transcription and ultimately cell fate. By contrast, the cardiopharyngeal lineage of mammals has been challenging to study because it is inaccessible in the embryo, but Fabienne Lescroart (Aix-Marseille Université, France) presented a mouse gastruloid system that recapitulates formation of cardiopharyngeal mesoderm and its differentiation into cardiac and muscle lineages. This provides an exciting system in which to study further the parallel differentiation of cardiac and skeletal muscle in mammals (Argiro et al., 2023).

The power of ascidian embryos as models with stereotypic development has been expanded by the lab of Patrick Lemaire (CRBM, Montpellier, France). Using light-sheet whole-embryo imaging and computational reconstruction of single-cell dynamics, they have shown that homologous cells are found in similar spatial locations across all individuals of a species and even between distantly related species. This is a powerful model in which to study how morphological stability can be maintained despite large genetic diversity (Fiuza and Lemaire, 2021).

[1]Department of Molecular Biology and Genetics, The Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA. [2]Biozentrum, University of Basel, 4056 Basel, Switzerland.

*Authors for correspondence (mcochel1@jhmi.edu; zayna.chaker@unibas.ch)

L.C., 0000-0003-4018-7722

Development (2023) 150, dev202086. doi:10.1242/dev.202086

Clockwise from top left: View of the Île de Batz from the coast of Roscoff during high tide; aquarium room in the marine biology research station (the sign above the doorway states 'Science has neither religion nor politics'); view of the spring flowers found along the coast of Roscoff; looking back on the mainland from the Pont de Roscoff.

The changing structure of chromatin during development is also a crucial determinant of transcriptional activity at different loci, and it is tightly linked to the concentration of various metabolites. Alice Davy (Centre de Biologie Intégrative, Université de Toulouse, France) presented work on the role of DHFR, a key enzyme in the one-carbon metabolism pathway that is highly expressed in the developing mammalian neocortex. Among other metabolites, this pathway is essential for producing SAM, the methyl donor in most cellular methylation reactions. Decreasing DHFR reduced the global levels of SAM and of methylated H3K4 (a mark associated with active transcription) in neural progenitors. Heterozygous mutation of *Dhfr* resulted in defects in neocortex development, likely caused by the deregulation of gene expression associated with these chromatin changes (Saha et al., 2023).

Post-transcriptional control of development

Post-transcriptional layers of regulation are also essential for correct execution of developmental programs. Dan Ohtan Wang (New York University Abu Dhabi, UAE) works on the role of the mRNA modification m6A in neurodevelopment. This mark is recognized by a class of 'reader' proteins that includes YTHDF3, which has been reported to affect mRNA translation but also decay. Her lab showed that loss of YTHDF3 function specifically in mouse excitatory neurons causes significant changes in spine morphology and density, highlighting the importance of properly controlled mRNA metabolism for spine development (Madugalle et al., 2020).

Luisa Cochella's lab (Johns Hopkins University, USA) works on microRNA-mediated regulation of gene expression during development. She presented their efforts to dissect the function of miR-100, which has been conserved since the origin of Eumetazoa (Dexheimer et al., 2020). Working with *C. elegans*, they have shown that this microRNA acts in a dose-dependent manner during embryogenesis, most likely to tune the properties of the extracellular matrix and enable correct morphogenesis. Excitingly, targets of this microRNA family seem to be conserved between *C. elegans* and various vertebrate species.

Generating neuronal diversity, one cell at a time

Recent research has raised the exciting hypothesis that neurodegenerative disorders may stem from neurodevelopmental defects. Highlighting this convergence between development, aging, and possibly regeneration, several talks offered a deep cellular understanding of temporal control of fate choice and neuronal wiring during brain development.

Robert Johnston (Johns Hopkins University, USA) presented how the human retinal organoid model used in his lab recapitulates various aspects of retinal development, specifically cone specification in the foveola, the high-acuity region of the retina.

Development (2023) 150, dev202086. doi:10.1242/dev.202086

He showed how temporally controlled signaling via retinoic acid and thyroid hormone is necessary and sufficient for the temporally ordered specification of blue and red/green cones. The cone composition balance seems to be highly plastic, which opens promising therapeutic avenues using retinal organoids as a powerful organ-in-a-dish test model (Eldred et al., 2018).

Giselle Cheung from Simon Hippenmeyer's lab (ISTA, Austria) investigates how cell-type diversity is generated in the superior colliculus of the mouse brain, using the very elegant MADM (mosaic analysis with double markers) clonal lineage-tracing model. By combining MADM with single-cell 'patch-sequencing' (MADM-CloneSeq), a hand-based cell-picking method on brain slices, Cheung et al. showed that superior colliculus progenitors are multipotent, with no visible spatial or temporal pattern governing cell fate. Nevertheless, they identified PTEN signaling as a master regulator of adequate excitatory/inhibitory neuron proportions (Cheung et al., 2023 preprint).

Stem/progenitor cells reside in tightly controlled microenvironments called niches, which provide the necessary signaling cues for stem cell maintenance and differentiation. Pauline Spéder's lab (Pasteur Institute, France) is interested in the functional components of the neural stem cell niche in the *Drosophila* brain. Cortex glia are an important part of this niche. It is a complex cell network of syncytial, spatially segregated units, each housing individual stem cell clones. These glial cells can fuse, a property likely modulating signal transmission and crosstalk between stem cell subpopulations over space and time (Rujano et al., 2022). Interestingly, the junctions between cortex glia and stem cells, and between the stem cells themselves, are also important for building the stereotyped architecture of the niche. They also direct the axonal path of newborn neurons and further impact adult behavior (Banach-Latapy et al., 2022 preprint). This talk highlighted a provocative concept of a modular niche, able to physically and functionally segregate distinct stem cell subpopulations, which is worth exploring in the mammalian brain.

Finally, in addition to cell fate determination, neuronal wiring choice is crucial for circuit formation during development. Maheva Andriatsilavo from Bassem Hassan's lab (Paris Brain Institute, France) showed how individuality emerges within *Drosophila* dorsal cluster neurons targeting either the proximal or distal optic lobes. Wiring involves two successive stochastic processes (Andriatsilavo et al., 2022 preprint). The first step involves activation of Notch signaling though lateral inhibition, which restricts growth. In a second step, microtubule growth and stabilization selects a further subpopulation of Notch-OFF neurons that will finally reach the distal target. These temporally restricted, individualized wiring patterns contribute to behavioral differences between individuals.

Does regeneration mirror development?

Regeneration following injury requires cells from surrounding tissue to proliferate and replenish tissues with the correct cell identities in the right pattern. Regeneration seems to make use of many transcriptional regulators and signaling pathways that also specify tissues during development. However, it is unclear how these are deployed to regenerate missing structures, particularly given that the starting point for regeneration is unpredictable. Michalis Averof (IGFL, Lyon, France) has developed a system to study leg regeneration in *Parhyale hawaiensis*. He reported that, despite a large overlap in gene usage during leg development and regeneration, the temporal patterns of gene expression and the underlying mechanisms are different in both processes (Sinigaglia et al., 2022). It will be interesting to explore this further in *Ciona*, in which cardiac development has been studied at single-cell resolution and which Lionel Christiaen reported can completely regenerate their heart, involving cells from non-cardiac lineages. Meanwhile, Roger Revilla-i-Domingo (University of Vienna, Austria) has established the sponge *Suberites domuncula* as a model in which to study regeneration, with a complete genome assembly and single-cell transcriptomes (Revilla-I-Domingo et al., 2018). This not only expands the systems that can be studied for their regenerative capacities, but also provides one with key relevance for evolutionary studies. He showed the successful implementation of transgenesis, promising interesting new insights in the near future.

In a keynote lecture, Peter Reddien (MIT, Whitehead Institute, USA) addressed the enigmatic question of how the correct missing cell types are regenerated after injury/amputation in planarians. Neoblasts are planarian pluripotent stem cells that faithfully replenish the cell-type diversity of missing tissue following injury. Single-cell sequencing revealed that most neoblasts already express distinct fate-specific transcription factors that drive them preferentially to specific cell identities. However, some neoblasts are also able to adapt their fate choice to contextual cues from the wounded tissue. This provides a framework for understanding how intrinsic and extrinsic information is integrated to drive cell-fate choices during regeneration (Reddien, 2018).

Hernán López-Schier (New York University Abu Dhabi, UAE) considered how regenerated cell types acquire the correct tissue pattern. Studying the regeneration of the neuromast, a mechanosensory organ in zebrafish, his lab uncovered how the complex pattern of hair cells within this organ is produced by the combination of local lateral inhibition mediated by Notch and deterministic symmetry breaking mediated by Wnt signaling from surrounding tissue (Kozak et al., 2023; Viader-Llargués et al., 2018).

Agnès Boutet (CNRS/Sorbonne, Roscoff, France) studies the local catshark (*Scyliorhinus canicula*), which can regenerate nephrons throughout life, in contrast to the limited regeneration observed in mammals. This regenerative potential is sustained by slow-cycling nephron progenitor cells retained in the juvenile kidney, which are characterized by low translation levels throughout the catshark's life. The molecular mechanisms underlying the maintenance of these cells will be key to infer possible nephrogenesis reactivation routes in mammals.

Physiological and hormonal regulation of development and regeneration

In ancient Greek times, the word 'physiology' was first used to describe the philosophical inquiry into the nature of things, including living organisms. Faithful to this spirit, Irene Miguel-Aliaga (Imperial College London, UK) sparked thought-provoking discussions following her keynote lecture on the first day of the conference. Her lab investigates sex differences in organ development and maintenance and has demonstrated key differences between male and female gut. Moreover, she discussed the important concept of organ functional crosstalk that occurs through neurons, hormones and metabolites. In *Drosophila*, they have uncovered intricate connections between the intestine and the reproductive system and have shown that male enterocytes are metabolically specified by their proximity to the testis. Altogether, this talk suggested that there is more to sex than sex hormones and that each organ might be 'sexualized' depending on a complex combination of extrinsic and intrinsic factors in distinct

Development (2023) 150, dev202086. doi:10.1242/dev.202086

physiological contexts (Hudry et al., 2019; Hadjieconomou et al., 2020; Stojanović et al., 2022).

Even adult organs with low cell-replacement dynamics, such as the brain, retain stem cells in specialized niches that are sensitive to sex and changing physiological states. Fiona Doetsch (Biozentrum, University of Basel, Switzerland) discussed how the choroid plexus in mice, an epithelial structure floating in the lateral brain ventricles that contributes to the production of cerebrospinal fluid, integrates physiological fluctuations and secretes molecular signals affecting adult neural stem cells in the adjacent ventricular niche. Her lab showed that the choroid plexus can change its secretome over short- or long-time windows, from daily circadian cycles to aging. Its secretome also differs between males and females (Silva-Vargas et al., 2013, 2016).

Zayna Chaker, from the Doetsch lab, presented work on pregnancy that supports an emerging model of regionally distinct adult neural stem cell subpopulations that give rise to specific neuronal or glial cell types in response to physiological or pathological stimuli. She showed how pregnancy recruits restricted pools of adult neural stem cells to generate temporally controlled waves of neurogenesis in the mother's olfactory bulb (Chaker et al., 2021 preprint). These pregnancy-associated neurons are functional during the first week of perinatal care and disappear around weaning. Although transient, this on-demand neurogenesis is behaviorally relevant, as it regulates sensitivity to pup odor and own pup recognition.

The environment is an important regulator of development and regeneration. Abderrahman Khila's lab (IGFL, Lyon, France) studies a case of phenotypic plasticity observed in the males of the water strider *Microvelia longipes*. Male legs are disproportionally long and are used as weapons to dominate egg-laying sites and access to females. Variation in this exaggerated growth is determined by the interaction between genetic variation and environmental factors, such as nutrition (Toubiana and Khila, 2019; Toubiana et al., 2021).

Finally, Guo Huang (UCSF, USA) guided the audience through an elegant evolutionary perspective of heart regeneration across 41 different vertebrate species. Regenerative potential in mammals is known to decrease after a brief perinatal time window, but the molecular mechanisms underpinning this are still not fully understood. The Huang lab's phylogenetic analysis reveals an intriguing relationship between thermogenesis and heart regeneration capability: animals with higher body temperature also have higher metabolic rates and a lower proportion of diploid cardiomyocytes, which negatively impacts regeneration capacity. The Huang lab also identified adrenergic and thyroid hormone signaling, both involved in thermogenesis, as two major regulators in establishing this trade-off between body temperature and heart regenerative capacity in evolution and development (Hirose et al., 2019; Payumo et al., 2021).

Genetic and epigenetic control of aging

Two main theories have been put forward to understand why organisms age. The mutation accumulation theory argues that aging is a consequence of accumulation of near neutral variants that have a negative impact only after reproductive maturity and are thus not efficiently removed from the gene pool. A non-mutually exclusive theory is antagonistic pleiotropy, which posits that positive selection acts on variants that increase reproductive fitness but have detrimental effects later in life. Dario Valenzano (Leibniz Institute on Aging, Jena, Germany) has pioneered the use of turquoise killifish to study aging. Turquoise killifish exist as diverse populations in fragmented habitats and can vary significantly in their lifespan, providing an opportunity to explore signatures of selection. The Valenzano lab's work suggests that mutation accumulation, which is compatible with the nearly-neutral theory of molecular evolution, is the most likely mechanism driving the lifespan differences between killifish populations. This is largely due to their small population size and genetic isolation rendering purifying selection ineffective. Interestingly, the effective human population size is also relatively small and has gone through several bottlenecks. It is tempting to speculate that different human populations may age differently as a result of different rates of mutation accumulation and purification (Cui et al., 2019; Willemsen et al., 2020).

Ants provide another remarkable opportunity to address the epigenetic component of aging. Individuals in an ant colony are essentially identical genetically but display a large diversity of morphology and physiology. Claude Desplan (New York University, USA) is using the jumping ant, *Harpegnathos saltator*, in which the queen lives about ten times longer than the workers. If the queen is removed from the colony, a worker takes its place. This worker changes its behavior, produces eggs and displays a lifespan expansion similar to that of the queen. Intriguingly, the increase in lifespan of these pseudo-queens is accompanied by production of insulin to support egg production; this would be expected to shorten lifespan, not extend it. This has led to the discovery of a mechanism by which the effects of insulin signaling on reproduction and lifespan are uncoupled (Yan et al., 2022).

Other talks focused on cellular functions that decay during aging. Michael Rera (CNRS, INSB, France) explored how loss of intestinal integrity correlates with the probability of death across individuals of different species, over time, giving new insights on the aging process (Tricoire and Rera, 2015). Allison Bardin (Institut Curie, Paris, France) and Benjamin Boumard from her lab focused on genomic integrity during aging and showed that adult tissues become genetically mosaic as a result of mechanisms ranging from mitotic recombination to chromosome loss (Riddiford et al., 2021).

Germ cells have specific maintenance and repair mechanisms to protect their genome integrity. Björn Schumacher (University of Cologne, Germany) showcased the power of *C. elegans* as a system to uncover unexpected mechanisms affecting genome stability in the germline. He showed how somatic stress results in signaling via p38 to the female germline to induce apoptosis, and that impaired signaling results in aneuploidy in the next generation. He also presented striking differences in how maternal and paternal DNA breaks are repaired that could help explain complex inheritance patterns in humans (Soltanmohammadi et al., 2022).

In many species, oocytes must survive for up to a few decades. Oocyte quality, however, declines with maternal age, and several mechanisms have been proposed to explain this deterioration. Elvan Böke (CRG, Barcelona, Spain) discussed how frog and human primordial (non-growing) oocytes minimize damage from reactive oxygen species by drastically reducing protein levels of Complex I of their electron transport chain (a major reactive oxygen species-generating complex) (Rodríguez-Nuevo et al., 2022). Interestingly, loss of Complex I seems to be a recurrent adaptation during evolution (Maclean et al., 2018). The Böke lab also found that assemblies of lysosomes, autophagosomes and proteasomes form in healthy mouse oocytes, sequestering aggregated proteins. These assemblies do not have degradative activity in immature oocytes, but become degradative at the final stages of oocyte growth, possibly providing a mechanism to pass an aggregate-free cytoplasm to the zygote. Interestingly, analogous strategies to

Development (2023) 150, dev202086. doi:10.1242/dev.202086

maintain proteostasis in the eggs exist in other animals, including *Drosophila* and *C. elegans* (Bohnert and Kenyon, 2017; Fredriksson et al., 2012).

Senescence in the context of regeneration: friend or foe?

Cellular senescence is a form of stress-related cell cycle arrest in which cells permanently cease division but still functionally contribute to tissue development, regeneration and aging. Accumulation of senescent cells in a tissue leads to loss of regenerative capacity and to aging. However, transient senescence can be beneficial for development and regeneration. Senescent cell function is thought to be mediated by secretion of various senescence-associated proteins. Bill Keyes (IGMBC, Strasbourg, France) showed that senescent cells can break off large membrane-bound fragments of themselves. These fragments ultimately rupture and 'spill' their contents on neighboring cells, possibly impacting the immune response in the tissue that may contribute to both the positive and detrimental functions of senescent cells (Durik et al., 2023 preprint).

Two speakers discussed senescence during aging. Pura Muñoz-Cánoves (Altos Labs, San Diego, USA and Pompeu Fabra University, Barcelona, Spain) showed that senescent cells emerge in skeletal muscle after an injury. These senescent cells secrete inflammatory and fibrotic factors that are detrimental to muscle regeneration. Reducing the secretion of these inflammatory factors improves regeneration capacity in young and old mice, suggesting that the senescent cells induce cell cycle arrest of muscle stem cells via paracrine signaling (Moiseeva et al., 2023). Camille Lafage, from Sandrine Humbert's group (Université Grenoble Alpes, France) presented how altered neural stem cell physiology in a mouse model for Huntington's disease leads to reduced adult neurogenesis in the subventricular zone. They hypothesized that stem cells carrying the huntingtin mutation enter a senescent state.

Han Li (Pasteur Institute, Paris, France) illustrated a positive role of senescent cells, which are important for muscle cell reprogramming. Her lab showed that muscle can be reprogrammed to awaken stem cells, but this happens only upon injury. This context-specific plasticity is facilitated by proteins secreted by senescent cells (Chiche et al., 2017).

Closing remarks

We are grateful to Claude Desplan and Allison Bardin for putting together an exciting program spanning a diverse palette of model systems and countries. Both the talks and posters were selected to maximize interactions among all participants and foster those between young trainees and established scientists specifically. Looking forward to the next edition!

Acknowledgements

We thank Claude Desplan and Alison Bardin for a stimulating program and the participants for sharing their work, and for their feedback on the manuscript. We apologize to the poster presenters whose work we could not include owing to space limitations.

Competing interests

The authors declare no competing or financial interests.

Funding

Z.C. is supported by the Research Fund for Excellent Junior Researchers, University of Basel (Universität Basel). The Cochella Lab is supported by Career Award 2238425 from the National Science Foundation (NSF).

References

Andriatsilavo, M., Dumoulin, A., Bias Dutta, S., Stoeckli, E. T., Hiesinger, P. R. and Hassan, B. A. (2022). Probabilistic axon targeting dynamics lead to individualized brain wiring. *bioRxiv* 2022.08.26.505432.

Argiro, L., Chevalier, C., Choquet, C., Nandkishore, N., Ghata, A., Baudot, A., Zaffran, S. and Lescroart, F. (2023). Gastruloids as an in vitro model of Cardiopharyngeal Mesoderm specification into skeletal and cardiac muscle lineages. *Arch. Cardiovasc. Dis. Suppl.* **15**, 194. doi:10.1016/j.acvdsp.2023.03.034

Banach-Latapy, A., Rincheval, V., Briand, D., Guénal, I. and Spéder, P. (2022). A corset of adhesions during development establishes individual neural stem cell niches and controls adult behaviour. *bioRxiv* 2022.10.04.510893.

Bellec, M., Dufourt, J., Hunt, G., Lenden-Hasse, H., Trullo, A., Zine El Aabidine, A., Lamarque, M., Gaskill, M. M., Faure-Gautron, H., Mannervik, M. et al. (2022). The control of transcriptional memory by stable mitotic bookmarking. *Nat. Commun.* **13**, 1-14. doi:10.1038/s41467-022-28855-y

Bohnert, K. A. and Kenyon, C. (2017). A lysosomal switch triggers proteostasis renewal in the immortal C. elegans germ lineage. *Nature* **551**, 629-633. doi:10.1038/nature24620

Chaker, Z., Segalada, C. and Doetsch, F. (2021). Spatio-temporal recruitment of adult neural stem cells for transient neurogenesis during pregnancy. *bioRxiv* 2021.07.11.451957. doi:10.1101/2021.07.11.451957

Cheung, G., Pauler, F. M., Koppensteiner, P., Krausgruber, T., Streicher, C., Schrammel, M., Gutmann-Özgen, N., Ivec, A. E., Bock, C., Shigemoto, R. et al. (2023). Multipotent progenitors instruct ontogeny of the superior colliculus. *bioRxiv* 2023.04.16.537059.

Chiche, A., Le Roux, I., Von Joest, M., Sakai, H., Aguín, S. B., Cazin, C., Salam, R., Fiette, L., Alegria, O., Flamant, P. et al. (2017). Injury-induced senescence enables in vivo reprogramming in skeletal muscle. *Cell Stem Cell* **20**, 407-414.e4. doi:10.1016/j.stem.2016.11.020

Cui, R., Medeiros, T., Willemsen, D., Iasi, L. N. M., Collier, G. E., Graef, M., Reichard, M. and Valenzano, D. R. (2019). Relaxed selection limits lifespan by increasing mutation load. *Cell* **178**, 385-399.e20. doi:10.1016/j.cell.2019.06.004

Dexheimer, P. J., Wang, J. and Cochella, L. (2020). Two microRNAs are sufficient for embryonic patterning in C. elegans. *Curr. Biol.* **30**, 5058-5065.e5. doi:10.1016/j.cub.2020.09.066

Dufourt, J., Bellec, M., Trullo, A., Dejean, M., De Rossi, S., Favard, C. and Lagha, M. (2021). Imaging translation dynamics in live embryos reveals spatial heterogeneities. *Science* **372**, 840-844. doi:10.1126/science.abc3483

Durik, M., Gonçalves, D. S., Spiegelhalter, C., Messaddeq, N., Keyes, W. M. and Keyes, B. (2023). Senescent cells deposit intracellular contents through adhesion-dependent fragmentation. *bioRxiv* 2023.01.11.523642.

Eldred, K. C., Hadyniak, S. E., Hussey, K. A., Brenerman, B., Zhang, P.-W., Chamling, X., Sluch, V. M., Welsbie, D. S., Hattar, S., Taylor, J. et al. (2018). Thyroid hormone signaling specifies cone subtypes in human retinal organoids. *Science* **362**, 6411. doi:10.1126/science.aau6348

Fiuza, U.-M. and Lemaire, P. (2021). Mechanical and genetic control of ascidian endoderm invagination during gastrulation. *Semin. Cell Dev. Biol.* **120**, 108-118. doi:10.1016/j.semcdb.2021.08.001

Fredriksson, Å., Johansson Krogh, E., Hernebring, M., Pettersson, E., Javadi, A., Almstedt, A. and Nyström, T. (2012). Effects of aging and reproduction on protein quality control in soma and gametes of Drosophila melanogaster. *Aging Cell* **11**, 634-643. doi:10.1111/j.1474-9726.2012.00823.x

Hadjieconomou, D., King, G., Gaspar, P., Mineo, A., Blackie, L., Ameku, T., Studd, C., De Mendoza, A., Diao, F., White, B. H. et al. (2020). Enteric neurons increase maternal food intake during reproduction. *Nature* **587**, 455-459. doi:10.1038/s41586-020-2866-8

Hirose, K., Payumo, A. Y., Cutie, S., Hoang, A., Zhang, H., Guyot, R., Lunn, D., Bigley, R. B., Yu, H., Wang, J. et al. (2019). Evidence for hormonal control of heart regenerative capacity during endothermy acquisition. *Science* **364**, 184-188. doi:10.1126/science.aar2038

Hudry, B., De Goeij, E., Mineo, A., Gaspar, P., Hadjieconomou, D., Studd, C., Mokochinski, J. B., Kramer, H. B., Plaçais, P.-Y., Preat, T. et al. (2019). Sex differences in intestinal carbohydrate metabolism promote food intake and sperm maturation. *Cell* **178**, 901-918.e16. doi:10.1016/j.cell.2019.07.029

Kinney, B., Sahu, S., Stec, N., Hills-Muckey, K., Adams, D. W., Wang, J., Jaremko, M., Joshua-Tor, L., Keil, W. and Hammell, C. M. (2023). A circadian-like gene network programs the timing and dosage of heterochronic miRNA transcription during *C. elegans* development. *Dev. Cell*. doi:10.1016/j.devcel.2023.08.006

Kozak, E. L., Miranda-Rodríguez, J. R., Borges, A., Dierkes, K., Mineo, A., Pinto-Teixeira, F., Viader-Llargués, O., Solon, J., Chara, O. and López-Schier, H. (2023). Quantitative videomicroscopy reveals latent control of cell-pair rotations in vivo. *Development* **150**, 9. doi:10.1242/dev.200975

Maclean, E. A., Hertle, P. A., Ligas, J., Bock, R., Balk, J. and Meyer, H. E. (2018). Absence of complex I is associated with diminished respiratory chain function in European mistletoe. *Curr. Biol.* **28**, 1614-1619.e3. doi:10.1016/j.cub.2018.03.036

Madugalle, S. U., Meyer, K., Wang, D. O. and Bredy, T. W. (2020). RNA N6-methyladenosine and the regulation of RNA localization and function in the brain. *Trends Neurosci.* **43**, 1011-1023. doi:10.1016/j.tins.2020.09.005

Moiseeva, V., Cisneros, A., Sica, V., Deryagin, O., Lai, Y., Jung, S., Andrés, E., An, J., Segalés, J., Ortet, L. et al. (2023). Senescence atlas reveals an aged-like inflamed niche that blunts muscle regeneration. *Nature* **613**, 169-178. doi:10.1038/s41586-022-05535-x

Payumo, A. Y., Chen, X., Hirose, K., Chen, X., Hoang, A., Khyeam, S., Yu, H., Wang, J., Chen, Q., Powers, N. et al. (2021). Adrenergic-thyroid hormone interactions drive postnatal thermogenesis and loss of mammalian heart regenerative capacity. *Circulation* **144**, 1000-1003. doi:10.1161/CIRCULATIONAHA.121.054846

Pimmett, V. L., Dejean, M., Fernandez, C., Trullo, A., Bertrand, E., Radulescu, O. and Lagha, M. (2021). Quantitative imaging of transcription in living Drosophila embryos reveals the impact of core promoter motifs on promoter state dynamics. *Nat. Commun.* **12**, 4504. doi:10.1038/s41467-021-24461-6

Perez-Mockus, G., Cocconi, L., Alexandre, C., Aerne, B., Salbreux, G. and Vincent, J.-P. (2023). The Drosophila ecdysone receptor promotes or suppresses proliferation according to ligand level. *Dev. Cell*. doi:10.1016/j.devcel.2023.08.032

Reddien, P. W. (2018). The cellular and molecular basis for planarian regeneration. *Cell* **175**, 327-345. doi:10.1016/j.cell.2018.09.021

Revilla-I-Domingo, R., Schmidt, C., Zifko, C. and Raible, F. (2018). Establishment of transgenesis in the demosponge suberites domuncula. *Genetics* **210**, 435-443. doi:10.1534/genetics.118.301121

Riddiford, N., Siudeja, K., Van Den Beek, M., Boumard, B. and Bardin, A. J. (2021). Evolution and genomic signatures of spontaneous somatic mutation in Drosophila intestinal stem cells. *Genome Res.* **31**, 1419-1432. doi:10.1101/gr.268441.120

Rodríguez-Nuevo, A., Torres-Sanchez, A., Duran, J. M., De Guirior, C., Martínez-Zamora, M. A. and Böke, E. (2022). Oocytes maintain ROS-free mitochondrial metabolism by suppressing complex I. *Nature* **607**, 756-761. doi:10.1038/s41586-022-04979-5

Rujano, M. A., Briand, D., Đelić, B., Marc, J. and Spéder, P. (2022). An interplay between cellular growth and atypical fusion defines morphogenesis of a modular glial niche in Drosophila. *Nat. Commun.*, **13**, 4999. doi:10.1038/s41467-022-32685-3

Saha, S., Jungas, T. T., Ohayon, D., Audouard, C., Ye, T., Fawal, M. A. and Davy, A. (2023). Dihydrofolate reductase activity controls neurogenic transitions in the developing neocortex. *Development* **150**, dev201696. doi:10.1242/dev.201696

Silva-Vargas, V., Crouch, E. E. and Doetsch, F. (2013). Adult neural stem cells and their niche: a dynamic duo during homeostasis, regeneration, and aging. *Curr. Opin. Neurobiol.* **23**, 935-942. doi:10.1016/j.conb.2013.09.004

Silva-Vargas, V., Maldonado-Soto, A. R., Mizrak, D., Codega, P. and Doetsch, F. (2016). Age-dependent Niche signals from the choroid plexus regulate adult neural stem cells. *Cell Stem Cell* **19**, 643-652. doi:10.1016/j.stem.2016.06.013

Sinigaglia, C., Almazán, A., Lebel, M., Sémon, M., Gillet, B., Hughes, S., Edsinger, E., Averof, M. and Paris, M. (2022). Distinct gene expression dynamics in developing and regenerating crustacean limbs. *Proc. Natl. Acad. Sci. USA* **119**, 1-28. doi:10.1073/pnas.2119297119

Soltanmohammadi, N., Wang, S. and Schumacher, B. (2022). Somatic PMK-1/p38 signaling links environmental stress to germ cell apoptosis and heritable euploidy. *Nat. Commun.* **13**, 1. doi:10.1038/s41467-022-28225-8

Stojanović, O., Miguel-Aliaga, I. and Trajkovski, M. (2022). Intestinal plasticity and metabolism as regulators of organismal energy homeostasis. *Nat. Metab.* **4**, 1444-1458. doi:10.1038/s42255-022-00679-6

Toubiana, W. and Khila, A. (2019). Fluctuating selection strength and intense male competition underlie variation and exaggeration of a water strider's male weapon. *Proc. R. Soc. B* **286**, 1901. doi:10.1098/rspb.2018.2400

Toubiana, W., Armisén, D., Dechaud, C., Arbore, R. and Khila, A. (2021). Impact of male trait exaggeration on sex-biased gene expression and genome architecture in a water strider. *BMC Biol.* **19**, 89. doi:10.1186/s12915-021-01021-4

Tricoire, H. and Rera, M. (2015). A new, discontinuous 2 phases of aging model: Lessons from Drosophila melanogaster. *PLoS ONE* **10**, 1-14. doi:10.1371/journal.pone.0141920

Trinh, D. C., Martin, M., Bald, L., Maizel, A., Trehin, C. and Hamant, O. (2023). Increased gene expression variability hinders the formation of regional mechanical conflicts leading to reduced organ shape robustness. *Proc. Natl. Acad. Sci. USA* **120**, e2302441120. doi:10.1073/pnas.2302441120

Viader-Llargués, O., Lupperger, V., Pola-Morell, L., Marr, C. and López-Schier, H. (2018). Live cell-lineage tracing and machine learning reveal patterns of organ regeneration. *eLife* **7**, 1-23. doi:10.7554/eLife.30823

Wang, W., Niu, X., Stuart, T., Jullian, E., Mauck, W. M., Kelly, R. G., Satija, R. and Christiaen, L. (2019). A single-cell transcriptional roadmap for cardiopharyngeal fate diversification. *Nat. Cell Biol.* **21**, 674-686. doi:10.1038/s41556-019-0336-z

Willemsen, D., Cui, R., Reichard, M. and Valenzano, D. R. (2020). Intra-species differences in population size shape life history and genome evolution. *eLife* **9**, e55794. doi:10.7554/eLife.55794

Yan, H., Opachaloemphan, C., Carmona-Aldana, F., Mancini, G., Mlejnek, J., Descostes, N., Sieriebriennikov, B., Leibholz, A., Zhou, X., Ding, L. et al. (2022). Insulin signaling in the long-lived reproductive caste of ants. *Science* **377**, 1092-1099. doi:10.1126/science.abm8767