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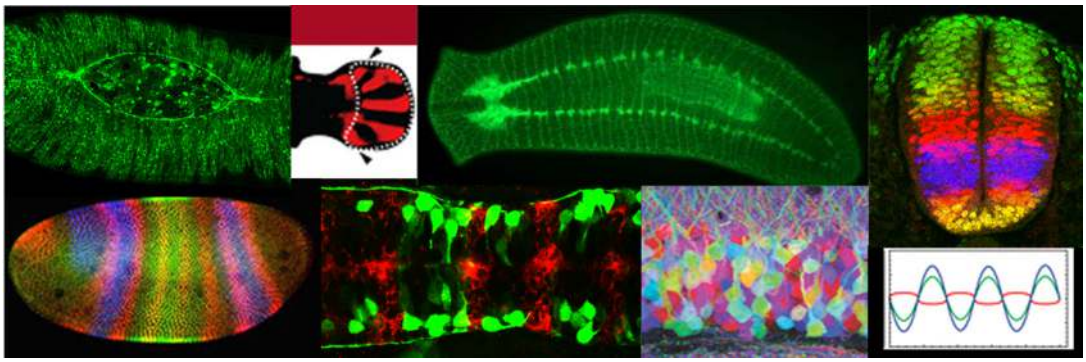

XXVIII DEVELOPMENTAL BIOLOGY MEETING

Date: November 18th 2016

Location: Sala Prat de la Riba, Institut d'Estudis Catalans,
C/ Carme 47, Barcelona

Organized by the Section of Developmental Biology of the SCB

Coordinator:
Francesc Cebrià (UB)

Collaborators:
Teresa Adell (UB)
Berta Alsina (UPF)
Eva Jiménez (CRG)

Secretariat of the SCB:
Mariàngels Gallego
Maite Sánchez

Sponsored by:

Institut d'Estudis Catalans

Societat Catalana de BIOLOGIA

XXVIII JORNADA DE BIOLOGIA DEL DESENVOLUPAMENT
SOCIETAT CATALANA DE BIOLOGIA

Friday November 18th 2016

8:30-9.00 Arrival and Registration at Sala Prat de la Riba
9:00 Welcome by the Coordinator of the Section of Developmental Biology

9.10-10.00 **Invited speaker: Montserrat Corominas (Universitat de Barcelona)**
"Transcriptional regulation during development and regeneration"

Short talks
10.00-10.20 Alfonso Ferrández-Roldán *"Deconstructing the chordate genetic toolkit for cardiac development"*
10.20-10.40 Berta Terré *"GEMC1 is a critical regulator of multiciliated cell differentiation and spermatogenesis"*
10.40-11.00 Joana Silva *"EXD2 is a regulator of cellular metabolism and aging"*

11.00-11.30 Coffee break

Short talks
11.30-11.50 Josefa Cruz *"FGF signalling promotes proliferation of tracheal adult progenitors in Drosophila"*
11.50-12.10 Nídia de Sousa *"Hippo signaling controls cell death, cell cycle and differentiation in planarians"*
12.10-12.30 Lara Barrio *"Boundary Dpp promotes growth of medial and lateral regions of the Drosophila wing"*
12.30-12.50 Neus Martínez-Abadías "*Hearts and limbs in Apert syndrome: genetic and morphometric insights"*
12.50-13.40 **Invited speaker: Manuel Irimia (Centre de Regulació Genòmica)**
"Evolution of a network of alternative exons involved in embryo morphogenesis"

13.45-15.00 Lunch

Short talks
15.00-15.20 Eudald Carreras *"Smed-bs is a novel secreted peptide that controls cell number in planarians"*

15.20-15.50 Esteban Hoijman *"The role of cell dynamics in neuronal specification: a quantitative 4D analysis in the zebrafish inner ear"*

15.50-16.10 Haritz Plazaola *"The role of glial ionic homeostasis in glia-neuron communication"*

16.10-16.30 José Ignacio Rojo-Laguna *"Wnt5-Ror and Slit-RoboC signaling generates a mutually dependent system to position the CNS along the medio-lateral axis in planarian"*

16.30-16.50 Elena Atienza *"The nervous system of Xenacoelomorpha: a genomic and developmental perspective"*

16.50-17.00 Present your Poster

17.00-18.00 Coffee break and Poster session

18.00-18.50 **Invited speaker: Marco Milán (Institut de Recerca en Biomedicina)**
"The other side of genomic instability in tumorigenesis: a fly view"

18.50 Concluding remarks

INVITED TALKS

Montserrat Corominas (University of Barcelona)

Transcriptional regulation during development and regeneration

Cell type–specific transcriptional regulation is crucial not only for development but also to maintain cell identity throughout the lifetime of organisms. Yet, it must be flexible enough to allow for responses to endogenous and exogenous stimuli. Genetic experiments using model organisms have identified many control genes that are critical for pattern formation and cell fate specification during development. A large fraction of these genes are not only conserved throughout evolution and deregulated in human diseases such as cancer, but also re-used in other cellular processes like tissue regeneration. The correct temporal and spatial expression of genes during these processes is likely to be regulated by genomic enhancers and promoters recruiting specific combinations of sequence-specific DNA-binding proteins (i.e. transcription factors, cofactors) as well as chromatin changes. Using Drosophila as a model system the ultimate goal of our research is to understand how gene expression is regulated during development and regeneration.

Manuel Irimia (Center for Regulative Genomics, CRG)

Evolution of a network of alternative exons involved in embryo morphogenesis

A major challenge in evolutionary biology is to identify the origin and nature of genomic changes underlying morphological novelties. Since such structures are mainly built during embryogenesis, it is thus crucial to understand how basic developmental processes operate and have evolved across lineages. Among these processes, epithelial-mesenchymal interactions and transitions are essential for the development of multiple organs and adult structures; therefore, unraveling conserved and derived molecular tools involved in the identity of these tissues and their interplay is key for understanding morphological evolution. In this talk, I will focus on the developmental role of the *Epithelial Splicing Regulatory Protein* (ESRP) gene family, which regulates an extensive alternative splicing program associated with epithelial-to-mesenchymal transitions in human cell cultures and cancer, and is essential in mouse organogenesis. We investigated both the developmental role and transcriptomic impact of ESRP splicing factors during embryogenesis of vertebrates and their close invertebrate relatives. Our results demonstrate that, while ESRP proteins are involved in similar basic developmental processes associated with epithelial-mesenchymal interplays, they have often been coopted for the development of clade-restricted structures through regulation of largely lineage-specific exon targets.

Marco Milán (Institute of Research in Biomedicine, IRB)

The other side of genomic instability in tumorigenesis: a fly view

Despite the proposed role of chromosomal instability (CIN) as a source of mutability in human cancer, CIN is highly deleterious for the cell. CIN-induced lagging chromosomes cause DNA damage and chromosomal rearrangements, and the resulting aneuploidy - abnormal number of chromosomes or parts of them- compromises cell fitness. *Drosophila* epithelial tissues have provided a useful model system to unravel a general and rapid tumorigenic potential of CIN. Whereas aneuploid cells are removed from the tissue by apoptosis through the activation of the stress-response JNK pathway, maintenance of aneuploid cells by apoptosis inhibition induces JNK-dependent tumourigenesis. We found that multiple mechanisms buffer the deleterious effects of CIN in proliferating epithelial tissues, including re-setting of dosage compensation mechanisms, DNA-damage repair, activation of the p38 signaling pathway, and induction of cytokine expression to promote compensatory cell proliferation. Remarkably, compromising the activity of these buffering mechanisms enhances the tumourigenic response of the tissue to CIN and interfering with the existing whole-chromosome dosage compensation mechanism phenocopies CIN-induced tumourigenesis. Altogether, our results unravel a pivotal contribution of genome-wide stoichiometric imbalances to CIN-induced programmed cell death and tumourigenesis in epithelial cells. I will discuss these and other ongoing projects on the role of CIN in tumorigenesis.

SELECTED TALKS

ST1

Deconstructing the chordate genetic toolkit for cardiac development

Alfonso Ferrández-Roldán, Marcos Plana-Carmona, Alba Almazán-Almazán, Anna Moncusí, Paula Bujosa, Miriam Diaz-Gracia, Josep Martí-Solans, Brad Davidson, Ricard Albalat, Cristian Cañestro

Department of Genetics, Microbiology and Statistics, University of Barcelona

Recent increase in genomic data reveals that gene losses are abundant in metazoans. Little is known, however, about how gene loss can impact the evolution of the mechanisms of development. As a case study, we investigate how gene losses affected the cardiogenetic toolkit in the chordate *Oikopleura dioica*. After the first description of the heart in 1903 by Saliensky, our work provides the first modern atlas of its development and describes the cell lineage fate map of all cardiac progenitors up to tailbud stage. Our data reveals that cardiac precursor cells derive from the most anterior muscular cells and migrate from the tail into the trunk, very similar as in ascidians. In *O. dioica*, however, precursor cells finally migrate and fuse to form the heart primordium in the left side of the animal, rather than in the midline as in ascidians. Our exhaustive *in silico* survey for all cardiogenic factors conserved in other chordates reveals important differences in *O. dioica* regarding its early signaling pathways as well as cardiac transcription factors involved in migration, differentiation and cardiogenesis. Thus, our work reveals that despite the highly similar process of early heart development between *O. dioica* and ascidians, the former appears to have pushed its mechanisms of heart development to their functional limits, deconstructing its cardiac genetic toolkit with several gene losses, absence of cardiac expression and lack of action of developmental signaling pathways that are fundamental to make a heart in other chordates.

ST2

GEMC1 is a critical regulator of multiciliated cell differentiation and spermatogenesis

Berta Terré Torras[1], Gabriele Piergiovanni[2], Sandra Segura-Bayona[1], Camille Stephan Otto-Attolini[1], Michaela Wilsch-Brauninger[3], Marko Marjanovic[1,4], Lluis Palenzuela[1] Wieland B. Huttner[3], Vincenzo Costanzo[2], Travis H. Stracker[1]

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[2] FIRC Institute of Molecular Oncology, Milan
[3] Max Planck Institute of Molecular Cell Biology and Genetics, Dresden
[4] Dufer Boskovic Institute, Zagreb

The characterization of mice lacking GEMC1, a protein that has been implicated in DNA replication control, revealed its crucial role in regulating two differentiation programs in mammals, multiciliogenesis and spermatogenesis. *Gemc1*-deficient mice are growth impaired, develop hydrocephaly and are infertile due to defects in the formation of multiciliated epithelial cells in the brain, respiratory tract, oviducts and efferent ducts. Although no patients harboring GEMC1 mutations have been identified to date, we believe that *Gemc1* is a good candidate for the rare mucociliary clearance disorder RGMC. This hypothesis is supported by the evidence that GEMC1 shares high similarity with MCIDAS, a previously identified as RGMC gene, and it also controls MCIDAS expression. The generation of these animal models has provided new insights into the molecular functions of these proteins in different tissues and expanded our knowledge of the etiology of pathologies associated with rare human diseases.

ST3

EXD2 is a regulator of cellular metabolism and aging

Joana Silva[1], Suvi Aivio[1], Andreu Casali[1], Maria Vinaixa[2], Laura Bailey[3], Isabel Garcia-Cao[1], Philip A. Knobel[1], Pablo Perez[1], Aidan Doherty[3], Acaimo Gonzalez-Reyes[4], Oscar Yanes[2], Travis H. Stracker[1]

[1]Institute for Research in Biomedicine (IRB Barcelona)
[2]Centre for Omic Sciences, Universitat Rovira I Virgili- CIBERDEM
[3]Genome Damage and Stability Centre, School of Life Sciences, University of Sussex
[4]Centro Andaluz de Biología del Desarrollo, Universidad Pablo de Olavide, Sevilla

The uncharacterized protein, Exonuclease 3'-5' domain like 2 (EXD2), exhibits strong homology to WRN, deficient in Werner's syndrome progeria. As WRN is characterized by chromosomal instability and increased cancer predisposition and EXD2 has been implicated in recombination and DNA damage sensitivity, we sought to understand its cellular functions. EXD2 localized to mitochondria and its depletion resulted in lower oxygen consumption, defects in metabolism and reduced mtDNA. Impairment of *Drosophila* EXD2 led to a significant increase in female lifespan accompanied by decreased fecundity, and depletion of germ stem cells (GSCs), that could be rescued with antioxidants. EXD2 does not appear to associate with known replication proteins and its depletion does not affect mtDNA replication. In contrast, we find that its tandem CxxC motif is required to maintain mtDNA levels and affinity purification identified a number of OXPHOS components as EXD2 interactors. We hypothesize that EXD2 directly optimizes mitochondrial oxidative metabolism to prevent ROS accumulation and current results from ongoing efforts to define its precise cellular role will be presented.

ST4

FGF signalling promotes proliferation of tracheal adult progenitors in *Drosophila*

Cristina de Miguel Vijandi, Josefa Cruz, David Martin, Elena Casacuberta, Xavier Franch-Marro

Institute of Evolutionary Biology IBE UPF-CSIC PRBB, Barcelona

The fibroblast growth factor (FGF) pathway plays a major role in several biological processes, like cell migration, axis specification and mesoderm formation. In vertebrates, FGF signalling also has a role in the control of cell proliferation and its deregulation is observed in many cancer types. In contrast, in Drosophila, FGf signalling plays a role in cell migration of mesoderm and tracheal cells without any direct mitogenic effect. The Drosophila tracheal system is remodeled during metamorphosis by populations of adult progenitor cells that divide under control of the transcription factor *cut*. These cells, late in development, migrate upon activation of FGF signalling to form the adult trachea network. Here, we show that, contrary to previous reports, the tracheal adult progenitor proliferation depends on the activation of FGF signalling. Thus, overexpression of the FGF ligand *branchless* induces adult progenitor over-proliferation whereas inactivation of the pathway blocks cell division. Moreover, we show that the FGF mitogenic effect is mediated by the transcription factor Pointed. Finally, we demonstrate that the expression of *cut* in adult progenitors is only required to modulate FGF action by maintaining the proliferative fate of these cells. Altogether, our results show a dual role of FGF signalling during tracheal remodelling, first inducing the proliferation of cut-expressing adult progenitor cells and then inducing the migration of these cells once *cut* expression is switched off.

ST5

Hippo signaling controls cell death, cell cycle and differentiation in planarians

Nidia de Sousa, Heura Cardona, Emili Saló, Teresa Adell

Department of Genetics, Microbiology and Statistics, University of Barcelona and Institute of Biomedicine of the University of Barcelona (IBUB)

Growth control is an open basic question in developmental biology. The Hippo signaling emerges as an essential pathway in the organ size control for its unique ability to simultaneously regulate cell proliferation and apoptosis, and thus to enable a balanced stem cell versus post-mitotic cell compartment. Although the core of the signaling pathway is well understood, the downstream transcriptional regulation and the main biological processes regulated remain still obscure since they are highly context-dependent. We have studied the function of the Hippo elements in Planarians, which stem cell based plasticity provides us an ideal scenario to approach the role of the pathway in the different cell compartments. Our results show that Hippo silencing in Planarians does not lead to an increase of organ size but to the formation of overgrowths that are not the result of an increase in cell number but rather to a problem in cell differentiation. Cellular analysis demonstrates that in Planarians Hippo regulates the mitotic division in stem cells and the apoptosis and maintenance of cell differentiation in pots-mitotic cells.

ST6

Boundary Dpp promotes growth of medial and lateral regions of the *Drosophila* wing

Lara Barrio, Marco Milán

Institute for Research in Biomedicine (IRB Barcelona)

The gradient of Decapentaplegic (Dpp) in the *Drosophila* wing has served as a paradigm to characterize the role of morphogens in regulating patterning. However, the role of this gradient in regulating tissue size is a topic of intense debate as proliferative growth is homogenous. Here we combined the Gal4/UAS system and a temperature-sensitive Gal80 molecule to induce RNAi-mediated depletion of *dpp* and characterise the spatial and temporal requirement of Dpp in promoting growth. We show that Dpp emanating from the AP compartment boundary is required throughout development to promote growth by regulating cell proliferation and tissue size. Dpp regulates growth and proliferation rates equally in central and lateral regions of the developing wing appendage and reduced levels of Dpp affects similarly the width and length of the resulting wing. Our data are consistent with a permissive role of the Dpp gradient in regulating final size and number of cells.

ST7

Hearts and limbs in Apert syndrome: genetic and morphometric insights

Neus Martínez-Abadías[1,2,3], R. Mateu[1,2,3], J. Sastre[1,2,4], A. Robert-Moreno[1,2], J. Swoger[1,2], L. Russo[1,2], J. Richtsmeier[5], J. Sharpe[1,2,6]

[1] Center for Genomic Regulation (CRG), Barcelona
[2] Universitat Pompeu Fabra (UPF), Barcelona
[3] Universitat de Barcelona, Barcelona
[4] Universidad de las Islas Baleares (UIB), Palma de Mallorca
[5] Pennsylvania State University, University Park (PA), USA
[6] Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona

Despite great progress in developmental biology research to understand how organs are formed and how disease can affect normal developmental process, a highly accurate methodology to pinpoint how, when and which processes of development are altered during embryonic development to produce birth malformations is still not available. To overcome this issue we combined 3D imaging and shape analysis tools, Optical projection tomography (OPT) microscopy and Geometric Morphometrics (GM), on a mouse model for Apert syndrome that carries a mutation in Fgfr2 (Fibroblast growth factor receptor 2) that causes skull, limb and heart malformations. OPT imaging of embryos labelled for Whole-mount in situ hybridization successfully revealed in a 3D framework the expression patterns of Dusp6 and Hand2 within whole embryos at embryonic days 10.5 and 11.5. Statistical comparative analyses of Fgfr2+/P253R control and mutant littermates showed significant differences in the size and shape of the limbs and the hearts, as well as their associated gene expression domains. Our results demonstrate that our method combining OPT and GM is an accurate and insightful tool to compare normal and disease-altered patterns of variation and to reveal how the genotype translates into the phenotype. Precise embryonic phenotyping of Apert syndrome mice helped us to pinpoint that altered Fgf/Fgfr signalling has direct consequences on target genes that contribute to limb and heart malformations as early as E10.5. These results will help us further understand the origins of abnormal limb and heart morphogenesis in Apert syndrome.

ST8

Smed-bs is a novel secreted peptide that controls cell number in planarians

Eudald Pascual-Carreras[1], Nidia de Sousa[1], Marta Marín[2], Kay Eckelt[1], Emili Saló[1], Teresa Adell[1]

[1] Department of Genetics, Microbiology and Statistics, University of Barcelona (UB) & Institute of Biomedicine of the University of Barcelona (IBUB)
[2] Norwich Research Park, UK

The final size of animal bodies depends on the size and number of their cells. Cell number relies on the tight balance between cell death and cell proliferation. The control of cell size seems largely dependent on nutrient conditions. The molecular mechanism underlying both processes and their tight relationship during development remains largely unknown. The striking plasticity of planarians, which allows them to regenerate any missing part and to continuously change their body size, offer us an ideal scenario to approach this question. Here we report the finding of a novel secreted peptide, *Blitzschnell* (*Smed-bs*), whose inhibition produces an acceleration of the regenerative response, and an increase in the total cell number in homeostatic planarians, eventually leading to overgrowths. The phenotype comes with a higher rate of proliferation and a decrease of cell dead, while cell differentiation appears unaffected. Interestingly, the increase in cell number never produces bigger planarians but a decrease in cell size in starved animals, while feeding allow the faster growth of planarians. These findings suggest that only under energy supply the increase in cell number is translated to an increase in body size.

ST9

Role of cell dynamics in neuronal specification of the zebrafish inner ear

Esteban Hoijman, Laura Fargas, Berta Alsina

Department of Experimental and Health Sciences, Universitat Pompeu Fabra

Neural patterning is established by secreted morphogens that regulate positional information mechanisms. The signals that influence these patterns have been extensively studied. Recently, cell movements were also implicated in the refining or progression of these patterns. Specifically, the role of cell behavior in neural specification is still unknown. Here, we use the establishment of a neurogenic domain in the zebrafish inner ear as a model to evaluate contributions of cell dynamics to neuronal specification. Until now, otic specification was conceived to occur in a static tissue. Single cell quantitative 4D imaging allows us to analyze how otic primordium morphogenesis is coordinated with expression of the proneural gene neurog1. We identify a group of migrating cells that express neurog1 outside the organ and ingress into the primordium, becoming the first otic neuronal progenitors. After ingression, other cells of the primordium express neurog1 and this pool is expanded by apical symmetric divisions. Laser ablation of the ingressing cells revealed that they also play an instructive role by promoting the specification of the resident cells of the domain. Finally, tracking of photoconverted nuclei indicate that FGF signaling regulates ingression of these cells. We propose a novel view for otic neurogenesis integrating cell dynamics whereby FGF-dependent ingression of pioneer cells instruct local neuronal specification.

ST10

The role of glial ionic homeostasis in glia-neuron communication

Haritz Plazaola[1], Qi Zhu[1] , Héctor Gaitán-Peñas[2], Raúl Estévez[2], Marta Morey[1]

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[2]Unitat de Fisiologia II, Campus Bellvitge, Facultat de Medicina, Universitat de Barcelona.

The importance of glia-neuron communication during development and adulthood is becoming evident. Deregulation of this interaction can result in leukodystrofy, that is vacuolization and edema of the brain due to disruption of the myelin sheath. The CLCN2 chloride channel has been related to some types of leukodystrofy. Analysis of *CLCN2* mutant mice suggests that leukodystrophy is a result of impaired ionic glial homeostasis early in development. However, the consequences of this ionic impairment on glial function, and the secondary effects on neurons are still unknown. We turned to Drosophila since the intimate relationship between glia and photoreceptors early in development of the visual system allows studying the role of this channel in glia-neuron interactions. We have detected expression of the CLCN2 *Drosophila* homolog gene *ClC-a* in glial cells in the developing brain. Mutant *ClC-a* animals show defects in photoreceptor axon guidance during development and RNAi depletion of ClC-a transcripts exclusively in glia phenocopies the guidance defects. The glia-photoreceptor interaction in the early development of the visual system is mediated by Slit/Robo signaling. Slit secretion from glial cells is necessary for the correct guidance of photoreceptors. *ClC-a* mutant glia is morphologically wild type and transcribes *slit*. Together with the genetic interaction observed between *ClC-a* and *slit*, these results suggest that ClC-a mediated glial homeostasis regulates Slit secretion. Our hypothesis is that impairment of ionic homeostasis in glia might be causing defects in secretion of molecules important in glia-neuron communication events.

ST11

WNT5-ROR2 and SLIT-ROBO-c signals generate a mutually dependent system to position the CNS along the medio-lateral axis in planarians

José Ignacio Rojo-Laguna[1], María Almuedo-Castillo[2], Thileepan Sekaran[3], Kerstin Bartscherer[3], T Adell[1]

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The acquisition of bilateral symmetry was a key evolutionary step, allowing the development of a centralized nervous system. However, the developmental signals that position bilateral symmetric structures in relation to the midline remain poorly understood. Planarian plasticity demands continuous positional information to maintain body proportions and axis information during regeneration and homeostasis. This ability offers an ideal context to study the signals required to position the CNS in relation to the midline. Our results demonstrate that *Wnt5* and *Slit*, which are expressed in complementary domains respect to the CNS, are axon repulsive cues in planarians. We identified ROR2 and ROBO-c as WNT5 and SLIT receptors, respectively. Their co-expression in neurons suggests that both signals cooperate to guide the axonal path in relation to the midline. Furthermore, *ror2* and *robo-c* are also expressed in muscular cells that express *slit* and *wnt5*, respectively, suggesting a regulatory relationship between both signals. We are currently exploring the hypothesis that WNT5-ROR and SLIT-ROBO-c signals could conform a self-regulated system to define their expression boundaries in addition to guide the axonal path. In conclusion, WNT5-ROR2 and SLIT-ROBO-c are axon repulsive cues that define the medio-lateral position of the CNS in planarians. Their domains of expression could be mutually regulated, allowing the self-maintenance of the medio-lateral positional information.

ST12

The nervous system of Xenacoelomorpha: a genomic and developmental perspective

Elena Perea-Atienza[1], Brenda Gavilán[1], Pedro Martínez[1,2]

[1]Department of Genetics, Microbiology and Statistics, University of Barcelona
[2]Institució Catalana de Recerca i Estudis Avançats (ICREA)

Phylogenetic studies maintain that acoelomorph flatworms (acoels and nemertodermatids) constitute a sister group of Xenoturbellida, forming the monophyletic phylum Xenacoelomorpha. Given the relative phylogenetic positions of its constituent three clades, with Xenoturbella as the earliest branch followed by the split of Nemertodermatida and Acoela, Xenacoelomorpha has becomes an interesting animal group for studying evolutionary trends (whether genomic or morphological). The major aim of our research group is to understand the structure, evolution and development of nervous systems. Since the members of the clade Xenacoelomorpha present different degrees of "cephalization", analyzing the nervous system development inside this phylum could provide us with insights about the early organization of the bilaterian nervous system and the origin and formation of 'cephalized' nervous systems (brains). Recently, the involvement of several research groups (included ours) in sequencing several xenacoelomorph genomes has allowed us to initiate molecular evolutionary studies of some specific gene families. We have characterized three gene families involved in several aspects of the nervous system's formation: the basic helix-loop-helix (bHLHs), G protein-coupled receptors (GPCRs) and Wnts. We have focused our analysis in the acoel *Symsagittifera roscoffensis* and the xenoturbellid *Xenoturbella bocki* (the most complete genomes we have). How their evolutionary history is reflected in the progressive degree of 'cephalization' seen in the phylum constitutes the target of our study. In parallel, several new techniques have been developed in the lab to better map the detailed structures of the nervous tissue in these organisms.

POSTERS

P1

Tail elongation and muscle development in Oikopleura dioica. A chordate evolutionary knockout for retinoic acid signalling

Alba Almazán-Almazán, Marcos Plana-Carmona, Alfonso Ferrández-Roldán, Anna Moncusí, Josep Martí-Solans, Miriam Díaz-Gracia, Enya Durán, Paula Bujosa, Natalia Rojas, Cristian Cañestro, Ricard Albalat

Department of Genetics, Microbiology and Statistics, University of Barcelona

A characteristic feature of vertebrates and cephalochordates is an obvious segmented body plan made of repetitive muscular units that develop by a complex process of somitogenesis. Retinoic acid (RA) and Fgf are two of the main signaling pathways that regulate the temporal and spatial formation of somites in an anterior-to-posterior direction. In urochordates, however, tail muscle consists of an array of muscle cells, but no obvious structural somites are observed. The evolutionary origin of somitogenesis remains unknown, and whether the formation of the array of muscle cells of urochordates shares some of the signaling pathways that underlie somitogenesis remains unclear. To address this issue, our group investigates the mechanisms of development of the tail muscle in *Oikopleura dioica*, a larvacean urochordate species that does not suffer a drastic metamorphosis as ascidians and preserves its tail throughout their entire life. We have performed an exhaustive in silico survey to identify several muscular gene markers, many of which have suffered extensive gene duplications during larvacean evolution. Comprehensive analyses of their expression patterns revealed an unexpected anterior-posterior molecular regionalization that correlated with their cell lineage origin. We are now investigating the role of Fgf signaling in muscle development and tail elongation in the absence of RA, a signaling pathway that has been lost during *O. dioica* evolution due to the high propensity of this species to lose genes.

P2

Smed-egfr-1 controls gut progenitor differentiation during planarian regeneration and homeostasis

Sara Barberán, Francesc Cebrià

Department of Genetics, Microbiology and Statistics, University of Barcelona and Institute of Biomedicine of the University of Barcelona (IBUB)

The activation and regulation of differentiation programs in stem cells is a fundamental process during animal development and regeneration, required for proper tissue and organ formation and maintenance. Freshwater planarians are an excellent model to study the behavior of stem cells *in vivo* as they possess a population of pluripotent stem cells called neoblasts. Neoblast are a heterogeneous population containing many different lineage-specific progenitors, identified by the expression of particular transcription factors. However, little is known about how these lineage-committed neoblasts differentiate into mature cell types. The EGFR signaling pathway has been shown to play an important role during key steps of cell differentiation and organogenesis in all studied model systems. Previous studies have showed that *Smed-egfr-1* is required for pharynx and eye pigment cells regeneration and maintenance. Here we show that *egfr-1*, which is expressed in the digestive system, is additionally essential for correct gut regeneration and homeostasis, as *Smed-egfr-1(RNAi)* animals fail to regenerate new gut branches and dramatically lose the pre-existing ones during homeostasis. Moreover, their gut has a very reduced lumen, aberrant tissue organization, and significantly less gastrodermal cells. Importantly, the loss of gut cells in *Smed-egfr-1(RNAi)* animals is not due to an increase in apoptotic levels in the gastrodermis, suggesting that the gut-associated phenotype is likely caused by defects in gut cell differentiation. This is further corroborated by the reduced number of newly differentiated gut EdU+ cells after silencing *Smed-egfr-1*. Remarkably, double labeling indicates that *Smed-egfr-1* is co-expressed with the gut progenitor markers *gata4/5/6* and *hnf4* in the mesenchyme around the gut. After silencing *Smed-egfr-1* the number of *hnf4*- and *gata4/5/6*-positive cells increases in the mesenchyme. Overall, our results indicate that the defects observed in the regeneration and maintenance of the gut could be caused by the failure of those progenitors to differentiate into mature gut cells. Therefore, the EGFR pathway would have a key role regulating the differentiation of gut cells from their specialized progenitors. This work reports for the first time the role of the EGFR signaling pathway in the differentiation of planarian neoblasts.

P3

No drama in the aftermath of extensive Wnt losses in urochordates

Miriam Diaz-Gracia[1]*, Josep Martí-Solans[1]*, Alfonso Ferrández-Roldán[1], Alba Almazán-Almazán[1], Enya Duran-Bello[1], Paula Bujosa[1], Natalia S. Rojas-Galván[1], Ildiko Somorjai[2], Cristian Cañestro[1], Ricard Albalat[1]

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[2]Gatty Marine Laboratory, Scottish Oceans Institute, University of St Andrews, St Andrews (UK).
*Equal contribution.

The bloom of Genomics is revealing a new perspective of gene loss as a pervasive evolutionary source of genetic variation that can influence the evolution of the mechanism of development of animal species. Our group, focuses how the evolution of the Retinoic Acid, Wnt and Fgf signaling pathways has been affected by gene losses during the evolution of urochordates, and how these losses have impacted the evolution of the mechanisms of development of this chordate subphylum. Results revealed, for instance, how the loss in ascidians of particular Wnt genes related with anterior-posterior axial determination in other chordates has been accompanied by the recruitment of other Wnt genes to provide equivalent functions. Our work in the larvacean *O. dioica* reveals also extensive losses affecting most Wnt families in this species accompanied by the dismantling of the RA-signaling, a morphogen classically linked to anterior-posterior axial pattering of chordates. Our results in *O. dioica* illustrates, therefore, how the identification of patterns of gene co-elimination can be a useful strategy to recognize developmental gene network modules associated to distinct embryonic functions, and how the identification of survival genes can help to recognize neo-functionalization events and ancestral functions. Interestingly, the extensive loss of Wnt gene families and of the RA genetic machinery in *O. dioica* does not translate in drastic changes of its chordate body plan, providing a paradigmatic example of the inverse paradox of Evo-Devo, that is, how similar structures at the morphological level are build despite important differences in their developmental genetic toolkits.

P4

A comprehensive pipeline for identifying lincRNAson the basal-branching chordate Amphioxus

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Among the numerous classes of RNAs, long non coding RNAs (lncRNAs) are similar in terms of expression and gene structure to the mRNAs but lack the potential to encode proteins. Over the last years, lncRNAs have been proven to play important roles in gene regulation, and have shown to be involved in many key developmental processes. However, the low sequence conservation of lncRNAs has hindered the identification of deep orthologues among distantly related species, hence the evolutionary dynamics of lncRNAs has been scarcely studied, and few data are known at evolutionary key-nodes of animal evolution. We aim to identify the lncRNA complement in the cephalocordate amphioxus, the best proxy to the key evolutionary node of the origin of chordates and vertebrates. For this, we used strand specific RNA-seq data from several adult tissues and developmental stages of Branchiostoma lanceolatum. We used first the CPAT software in order to assess the coding potential of each canonical transcript, then a selection of probably non coding, multiexonic gene structures (at least 2 exons) and a minimum length of 300 nucleotides. Transcripts were blasted using blastx against the non-redundant protein database, and the ones that did not had a significant hit were filtered again with hmmer searches to eliminate the ones with similarity to conserved protein domains upon 6-frame translation. This yielded around 1700 transcripts that were classified according to their relative position among coding genes into intergenic, antisense, intragenic or overlapping. Using the intergenic portion (lincRNAs) we have developed the scripts for finding conserved microsynteny between Branchiostoma lanceolatum, Homo sapiens, Danio rerio, and Strongylocentrotus purpuratus, and more organisms will follow soon. This approach pointed at some candidates that are being tested right now. Some of the current and future work includes In Situ Hybridization and, if possible, knock-outs with CRISPR.

P5

ROS-induced JNK and p38 signaling is required for unpaired cytokine activation during Drosophila

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The study of tissue repair in Drosophila imaginal discs has shed light into the identification of many signaling pathways activated in healing and regenerative growth. Upon apoptotic stimuli, epithelial cells compensate the gaps left by dead cells by activating proliferation. This has led to the proposal that dying cells signal to surrounding living cells to maintain homeostasis. Whether Reactive Oxygen Species (ROS) emerge from dead cells and what is the genetic response triggered by ROS is pivotal to understand Drosophila imaginal disc regeneration. To explore this issue, we genetically induced cell death, monitored the production of ROS and analyzed the signals required for repair. We found that cell death generates a burst of ROS that propagate to the nearby surviving cells. Propagated ROS activate p38 and induce tolerable levels of JNK, which results in the expression of the cytokines Unpaired (Upd). The JAK/STAT signaling activated by Upd has a key role triggering regeneration. Our findings demonstrate that this ROS/JNK/p38/Upd stress responsive module restores tissue homeostasis. This module is not only activated after cell death induction but also after physical damage and reveals one of the earliest responses for imaginal disc regeneration.

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