Biomechanical analysis of in vivo directional collective migration

Reporting

Project Information

**VIVO_MECH_COLL_MIGRA**
Grant agreement ID: 658536

Funded under
EXCELLENT SCIENCE - Marie Skłodowska-Curie Actions

Total cost
€ 183 454,80

EU contribution
€ 183 454,80

Coordinated by
UNIVERSITY COLLEGE LONDON
United Kingdom

Start date: 2 February 2016
End date: 1 February 2018

Periodic Reporting for period 1 - VIVO_MECH_COLL_MIGRA (Biomechanical analysis of in vivo directional collective migration)

Reporting period: 2016-02-02 to 2018-02-01

Summary of the context and overall objectives of the project
Directional cell migration is important in physiology and pathology. Molecular mechanisms regulating directional migration are largely studied; but the role of mechanical cues and their interplay with biochemical signals during directional migration is poorly understood. To address this I used Neural Crest (NC) cells, a highly migratory embryonic cell population. Evidence about how chemical cues regulate NC migration has accumulated, but nothing is known about the interaction among these cells and their mechanical environment. This proposal focused on understanding how NC interacts with the mechanical cues from its environment during directional migration in vivo, as well as understanding the molecular nature of this interaction. The aims I developed here were: Aim 1) to study the role of mechanical cues in vivo and their interplay with chemical signals during in vivo NC migration. Aim 2) identify the molecular mechanism by which the mechanical properties of the substrate are sensed and translated as signals into the NC, and to test the role of Nedd9 as a key component of this process.

After developing several methods to measure and modify mechanical cues in embryos I discovered that the tissue underneath the neural crest called mesoderm stiffens towards the onset of its migration and that this stiffening triggers the migration of the neural crest. Hence, results from this project provided the first demonstration that collective migration is mechanically triggered in vivo and that embryonic tissues interact in a mechanical level to ensure correct morphogenesis. The neural crest cells migrate all over the embryo to differentiate in a large number of embryonic tissues and any deficiency on its migration may lead to congenital defects, i.e. intestinal aganglionosis and craniofacial malformations. Hence, these results are relevant to understand aetiology of neural crest-related congenital disorders by introducing mechanical cues as new aspects to be considered when studying the biology of these defects. Additionally, as neural crest and cancer cell migration are highly similar, our data is also relevant to our understanding of the mechanical microenvironment of cancer cells. This reveal that our project had an impact not only in the scientific community but also in human health.

Finally, this grant was a great experience – it provided me with multidisciplinary collaborations, a complete toolbox to address new scientific questions, and it gave me managerial and leadership skills that I will use to obtain funding and lead my own research group.

Work performed from the beginning of the project to the end of the period covered by the report and main results achieved so far

Workpackage 1. I tested the ability of mechanical cues to promote NC migration and their interplay with chemical signals in vivo.

Milestone 1.1. Mechanical properties of the neural crest and its surrounding tissues were effectively measured.
Milestone 1.2. The role of mechanical cues in directional NC migration in vivo was determined.
Milestone 1.3. I partially determined the interplay between mechanical and biochemical cues during directional NC migration. In vivo experiments pending.

Work package 2. Identified part the molecular mechanism by which the mechanical properties of the substrate are sensed and translated as signals into the NC and analysed the role of Nedd9 as a key component of this process.
Milestone 2.1. I tested the potential of Nedd9 as a force-transducer in the NC. Additionally I showed that the NC uses Integrin, Vinculin, and Talin as sensors.
Milestone 2.2. Further experiments are required to fully understand the mechanism mediating the transduction of signals from the focal adhesions into the nucleus of NC cells.

For images supporting this findings and a more detailed story, please read Tech PartB Report; Barriga et al., Nature (doi:10.1038/nature25742); or http://thenode.biologists.com/mechanical-cues-developmental-pacers-orchestrate-morphogenesis/research/.

--Dissemination:

The results of this grant were disseminated as follow:

--Research articles:

Results from work packages 1 and 2 are published in:


Barriga and Mayor, 2018: “Adjustable viscoelasticity allows for efficient collective cell migration” Seminars in Cell and Dev Biol, in press.

Results from Milestone 1.3 and 2.3 are in preparation for submission. This action will be appropriately acknowledged in future publications.

--Conferences:

Results from Milestones 1.1 1.2 and 2.1: Abercrombie Meeting, Oxford, 2017; EMBO network meeting 2017; Developmental-Biology Symposium, Chile, 2018; Tissue Self Organisation: Challenging the systems, EMBL, 2018; and 18th Meeting of the International Society for Developmental Biology, Singapore, 2017.

Unpublished results from milestones 1.3 and 2.2 will be presented as a poster in the “Mechanobiology of Polarised Cells Meeting, France 2018”.

--Additional publications:

Kotini & Elias H. Barriga &... and Mayor. Gap Junction protein Connexin-43 is a direct transcriptional regulator of N-cadherin in vivo. (201X). Nature Communications. & these authors contributed equally.


-Highlights, Press, and Social media:
Disseminated results have been highlighted in web resources, social media, and Press. Very importantly this research was recommended by the F1000. This ensure that my research can outreach and have an impact in the non-scientific community.

–Highlights:

F1000 recommendation: https://f1000.com/prime/732661919


–Press:


LongRoom: https://www.longroom.com/discussion/893188/tissue-mechanics-essential-for-cell-movement

–Social Media:
https://twitter.com/the_Node/status/976858911394365440
https://twitter.com/uclnews/status/964101552658092032
https://www.facebook.com/theNodedevbio/posts/2155659747822821

Progress beyond the state of the art and expected potential impact (including the socio-economic impact and the wider societal implications of the project so far)

The neural crest cells migrate all over the embryo to differentiate in a large number of embryonic tissues and any deficiency on its migration may lead to congenital defects, i.e. intestinal aganglionosis and craniofacial malformations. Hence, these results are relevant to understand aetiology of neural crest-related congenital disorders by introducing mechanical cues as new aspects to be considered when studying the biology of these defects. Additionally, as neural crest and cancer cell migration are highly similar, our data is also relevant to our understanding of the mechanical microenvironment of cancer cells. This shows that this project had an impact not only in the scientific community but also in human health.

Last update: 1 April 2021