JORNAL DA SOCIEDADE DAS CIÊNCIAS MÉDICAS DE LISBOA

DOI: https://doi.org/10.57849/ulisboa.fm.jscml.0000010.2025

PFIZER RESEARCH AWARDS 2024

BASIC RESEARCH

Retinal Study Reveals Non-Canonical Neuronal Migration Modes that Orchestrate Concomitant Growth and Differentiation

Caren Norden [1]

[1] Head of Cell Biology of Tissue Morphogenesis Lab. Gulbenkian Institute of Molecular Medicine, Oeiras, Portugal

Scientific Background

This coordination between growth and differentiation is a hallmark of organogenesis in diverse settings, including the pancreas, liver, heart, and many others. Disruptions in these processes can lead to developmental disorders and structural abnormalities of organs.

This coordination is particularly evident during brain formation, where neuronal migration is a key event, ensuring that newly born neurons reach their correct positions to establish functional circuits. This is necessary, as most neurons are born away from the place where they ultimately function. Neuronal migration in all areas of the brain must be tightly coordinated with concurrent tissue growth and differentiation. Extensive research has been conducted on the role of neuronal migration for cell positioning and circuit formation, mainly in the developing neocortex. Furthermore, many of the cytoskeletal drivers and molecular cascades that guide neuronal migration have been revealed. However, how neuronal migration might contribute to tissue-wide morphogenesis during periods of rapid growth and differentiation is not as well understood. Specifically, it was unknown how migrating neurons and proliferative progenitors avoid spatial competition, ensuring both the establishment of functional architecture and the continued expansion of the tissue.

We used the vertebrate retina, with its conserved architecture across species, as a powerful model to study neuronal migration in the context of overall tissue development. We focused on cone photoreceptor cell migration, as these cells are

born relatively early in development, when the tissue is still undergoing substantial proliferation. At the same time, these cells are instrumental for light perception in all vertebrates, including humans. Our model organism of choice was the zebrafish, as this model allows for studying neuronal migration *in vivo,* while it happens, where it happens. Zebrafish have small, transparent embryos that can be generated in large numbers daily and feature many transgenic lines to mark different cell populations and intracellular components. Another significant advantage of this system is their rapid development, chemical and genetic manipulability. Findings can be generated in a depth hardly possible for any other vertebrate and, in turn, be compared to the human system, either in the form of donated human tissue or newly arising human brain and retinal organoids. We took full advantage of this cross-species comparison in our study, the main findings of which are outlined below.

Research Project

Our study investigated photoreceptor (PR) migration during retinal development in zebrafish, human fetal retinas, and retinal organoids derived from induced pluripotent stem cells (iPSCs). We used advanced imaging techniques, mainly light-sheet microscopy, to track PR movements and analyze the cytoskeletal mechanisms underlying their migration, which, to our initial surprise, was bidirectional.

Overall, this comprehensive approach provided critical insights into how neuronal migration ensures the coexistence of growth and differentiation, offering potential implications for understanding neurodevelopmental disorders and retinal repair strategies. The following key findings were made:

1. As photoreceptors are born at the same location where they later function, we were surprised to find that these cells actually do not remain stationary after their birth but instead migrate basally before returning apically to their final position. We noted that these movements occur with different kinetics, basal movement being much faster and more directed than apical movement.
2. The finding that basal and apical movements show different kinetics made us explore the underlying cytoskeletal elements responsible. We found that basal movements depend on stabilized microtubules, while apical movement relies on actomyosin contractility driven by Rho-ROCK signaling. This led us to realize that distinct cytoskeletal systems coordinate these directional movements in a highly specialized manner, which is interesting from a cell biology perspective, as this has not been shown within one particular neuronal cell type.
3. Using zebrafish, human fetal retinas, and retinal organoids, we realized that this bidirectional photoreceptor migration pattern is conserved across species. This led us to propose that this bidirectional movement is a fundamental mechanism for correct retinal development.
4. It is important to note that during the time photoreceptors emerge, the retinal tissue is still highly proliferative. From diverse previous studies, we know that progenitors need to divide at apical positions; otherwise, tissue integrity is not ensured. Interestingly, when we disrupted photoreceptor migration in zebrafish using genetic interventions targeting the microtubule cytoskeleton, we found that apical congestion by photoreceptors occurs. This, in turn, leads to improper progenitor cell divisions and lamination defects. This led us to conclude that neuronal migration is not only about positioning cells but also about orchestrating the delicate balance of growth and differentiation in developing tissues.

Together, this study shows that photoreceptor migration is a conserved and essential mechanism for orchestrating retinal tissue growth and differentiation, relying on distinct cytoskeletal systems to prevent spatial congestion, safeguard progenitor divisions, and ensure the coordinated formation of retinal architecture. Importantly, this phenomenon is conserved across species, from fish to humans, showing its overall impact and significance

Future Implications for Research

The findings revealed in our study have significant implications for future research on neuronal migration and its role in tissue morphogenesis in the retina and beyond. The discovery that photoreceptor migration prevents spatial competition and orchestrates growth and differentiation highlights a previously underappreciated function of neuronal movements in ensuring correct and timely morphogenesis of neural tissues. This phenomenon most likely extends beyond the retina. This means that, with the basic knowledge generated here, the investigation of similar phenomena in other regions of the central nervous system and across different organ systems can start.

From a cell biological point of view, the identification of distinct cytoskeletal mechanisms that drive basal and apical migration opens avenues for targeted research into how microtubules and actomyosin interact to coordinate complex cellular movements during neuronal migration and other cell migration phenomena. As most cells in our body are born at different locations than where they later function, this is of outstanding developmental relevance but also crucial for understanding homeostasis. In the retinal context, future studies can now aim to dissect the upstream molecular signals that initiate and regulate these directional migrations, focusing on how the change in directionality is sensed and achieved by the cell.

Another critical direction for future research is the investigation of how disruptions of neuronal migration processes, in the retina and other areas of the brain, could contribute to neurodevelopmental disorders. By understanding the consequences of apical congestion and defective lamination at a mechanistic level, it might be possible to identify potential intervention points to mitigate the impact of such disruptions on neural tissue architecture and function.

The conservation of photoreceptor migration across zebrafish, human fetal retinas, and human organoids also underscores the utility of retinal organoids as models for studying human neurodevelopment when the work is based on strong in vivo findings. Future work should leverage organoid systems to explore how migration dynamics are altered under pathological conditions, such as in inherited retinal diseases or neurodevelopmental disorders, to identify therapeutic strategies using the extensive knowledge that can be gathered in the zebrafish system.

In conclusion, our study highlights the dual roles of neuronal migration in cell positioning and, new and non-canonically, tissue morphogenesis. This work sets the stage for research aimed at understanding and potentially manipulating these processes to address developmental anomalies and support regenerative approaches in neurobiology.

PAPER DISCUSSED

Rocha-Martins M, Nerli E, Kretzschmar J, et al. Neuronal migration prevents spatial competition in retinal morphogenesis. *Nature.* 2023;620(7974):615-624. doi:10.1038/s41586-023-06392-y

Know more.
See the promotional video.