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Review

The Formation and Development of the Retina retinal neurogenesis and interkinetic nuclear cell migration

Hydar M Khalfa[1], haider L al-msaid[2]

[1]*Department of biology, Faculty of Science, University of kufa, Kufa, Iraq.*

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*Corresponding Author: *Hydar Khalfa, Department of biology, Faculty of s*cience, University of kufa, Kufa, Iraq;
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Email: hydarm.jmaiwai@uokufa.edu.iq

Abstract: This review aims to understand the relationship between retinal neurogenesis and interkinetic nuclear cell migration during mammalian eye formation. Research has shown that certain chemical and physiological changes occur during these two activities during eye formation. Based on recently published articles and documented evidence, this review highlights the complex process of retinal development. The development of the retina involves multiple stages and mechanisms to achieve a healthy retina with the ability to respond to light. Retinal cells develop particular mechanisms during their cell cycle, enabling them to upgrade from retinal progenitor cells to specialized retinal cells. These mechanisms include the inhibition of particular factors and the activation of master regulators to support their proliferation and differentiation. Retinal cells move from layer to another using different migration modes, some of which are supported, while others enable cells to move freely.

Keywords: interkinetic migration, retina, embryonic, neurogenesis.

1.Introduction

The intricate process of cell growth is carefully orchestrated by a variety of growth factors. These factors play a crucial role in guiding the development of the eye, particularly in the retina where light-sensitive neural networks form. These regulatory factors are essential throughout the various stages of eye development, influencing not only the formation of a normal eye but also exhibiting both activating and inhibiting effects on subsequent developmental phases. This review delves into the fascinating process of retinal formation within the human eye, examining the key stages, underlying mechanisms, and the remarkable journey of neurogenesis, where cells divide, migrate, and ultimately reach their designated positions [1].

2. Eye Formation

The formation of the eye is a remarkable feat of developmental biology, involving the intricate interplay of three primary tissue types: the surface ectoderm, the neural ectoderm, and the surface mesoderm. Each of these tissues serves as a starting point, giving rise to distinct components of the eye during embryogenesis. The neural ectoderm, for instance, is responsible for the formation of the light-sensitive retina and the retinal pigmented epithelium, which supports the retina's function. The surface ectoderm, on the other hand, gives rise to the lens, a transparent structure that focuses light onto the retina. Lastly, the mesoderm contributes to the development of the sclera, the tough outer layer of the eye, and the cornea, the transparent front part of the eye that allows light to enter [2].

The process of eye formation involves a series of carefully orchestrated steps. Initially, the developing forebrain extends outward, forming two optic vesicles that make contact with the surface ectoderm. This interaction triggers the formation of the lens placode, a

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thickened region of the ectoderm that will eventually develop into the lens. Simultaneously, the optic vesicles maintain a connection with the developing brain through small stalks that will mature into the optic nerves, responsible for transmitting visual information from the eye to the brain. As development progresses, the lens placode exerts pressure on the optic vesicle, leading to the formation of the optic cup, a double-layered structure that will give rise to the retina and the retinal pigmented epithelium. The outer layer of the optic cup ultimately develops into the mature retina, while the inner layer forms the retinal pigmented epithelium [3].

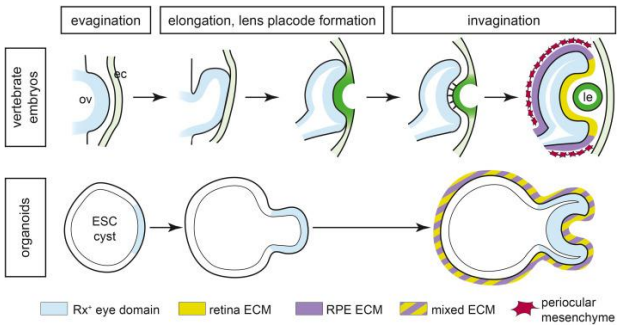


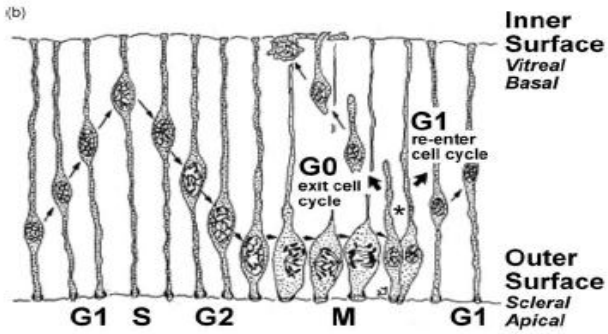
Fig.1. Retinal development and eye cup formation during embryogenesis (casey , 2021)

This description provides a simplified overview of the complex process of eye formation. Numerous intricate stages and mechanisms are involved in achieving the final, fully functional eye. Further exploration of these stages and mechanisms will shed light on the remarkable journey of eye development [4].

3. Retinal cell cycle

The cells in the retina undergo the same cell cycle as described previously. Following the completion of the cell cycle, several stages are involved in the formation of the retina (Sernagor et al., 2006; Martins & Pearson, 2008). The formation of retinal cells takes place between the scleral apical surface and the vitreal basal surface. During this process, cells migrate to their final site through different migration methods. The major stages of retinal cell formation include cell division and migration between the apical surface of the sclera and the vitreal basal surface, as well as cell migration to their final site through various migration methods. A diagram illustrating the cell migration process is provided below [3]..

Fig.2. *Retinal development, (*Sernagor et al., 2006)



Retinal progenitor cells are found in the neural retina, waiting to proliferate and differentiate into specialized retinal cells. When growth signals arrive, signaling cell division, the retinal progenitor cells undergo the cell cycle as described above. During the M phase of the cell cycle, new cells either re-enter the cell cycle or become neurogenic cells [3,4]. The concept of interkinetic migration explains how retinal progenitor cells proliferate and become specialized cells within the neural retina. These cells span the entire space of the neural retina, exploring different environments that enable them to either proliferate or become neurogenic cells. Cells that exit the M phase of the cell cycle explore different environments, where growth factors cause them to undergo further cell division or inhibitory signals suppress them to become neurogenic cells. When cells receive signals to proliferate, the G, S, G2, and M phases of the cell cycle are repeated to achieve further cell division and produce the characteristics of specialized retinal cells. A diagram illustrating interkinetic nuclear migration within the neural retina is provided below [4,5].

4. Inter kinetic nuclear migration

Cells need to migrate to their final location and become specialized, exhibiting specific functions. The neural retina is a proliferative area where newly generated cells undergo proliferation and differentiation [7]. After differentiation, cells need to migrate to their final location to form neural connections and acquire functions. Neural cells migrate between the inner limiting membrane and the outer limiting membrane through different migration methods. Different retinal cells adopt different migration methods; for example, rods, bipolar cells, and Müller glia migrate through the guidance of glial cells, whereas cones, amacrine, horizontal, and ganglion cells move freely through the

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unconstrained cell migration mode. The different modes of cell migration are highlighted below [8].

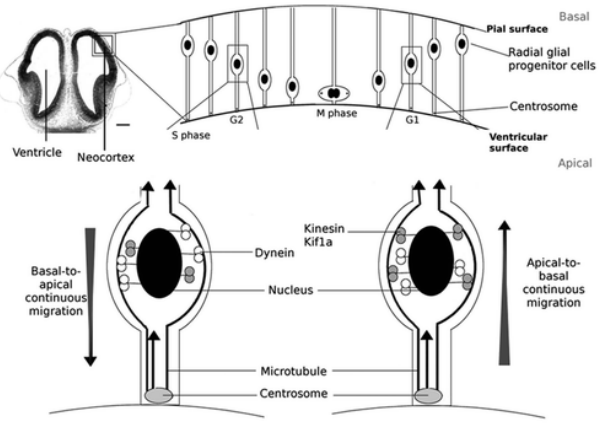


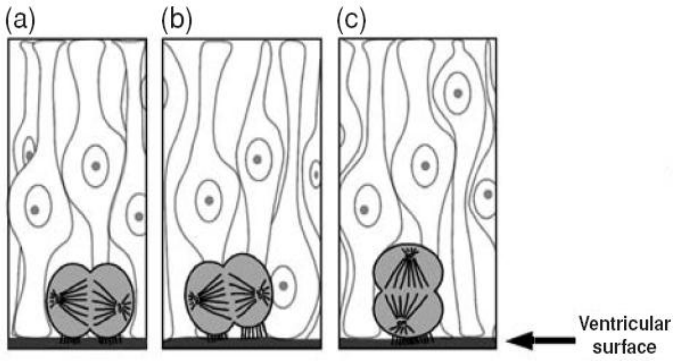
Fig..3. Interkinetic cell migration during retinal neurogenesis showing the movement of cells at different cell cycle phases with time, (Kulikova ., et al, 2011).

This method of cell migration involves post-mitotic cells growing a cytoplasmic process that extends to the inner limiting membrane. The cells form a contact with the outer limiting membrane and grow the cytoplasmic process, extending away from the outer limiting membrane. The cell then moves down the cytoplasmic process by translocation on the generated process until the correct position is achieved. When the cells reach their final location, suited for their phenotype, the cytoplasmic process degenerates, and the cell is allowed to fix its final location [9].

5. Cell migration modes

During the cell cycle, the formation of spindle fibers inside the cell enables the chromosomes to attach, ensuring the correct genetic material is acquired in each cell. When the cell cycle reaches the G2 phase, there is a checkpoint in which chromosomes are examined by the cell for accuracy. The M phase is the stage in which the cell undergoes the division process through cytokinesis. There are two ways in which a retinal cell can divide and give rise to new cells: symmetric and asymmetric division [10]. The two methods are associated with the orientation of the plane of cleavage to the ventricular surface. Symmetric division produces cells that are proliferative, which become differentiated at a late stage, whereas asymmetric division produces cells that are neurogenic, which do not differentiate. Retinal progenitor cells undergo symmetric division at an early stage, in which both cells reenter the cell cycle, increasing the pool of progenitor cells [9,10]. At a later stage, the retinal progenitor cells undergo asymmetric division, where one daughter cell exits the cell cycle and differentiates, and the other becomes a neurogenic cell. Furthermore, retinal progenitor cells reach a final stage where they undergo a final symmetric division and lose their mitotic activities, becoming neurogenic cells; this stage is known as the terminal. The orientation of the plane of cleavage determines the mode of division and the resulting cells [11]. If asymmetric division occurs, then neurogenic cells are produced, which are undifferentiated and controlled by NOTCH, which controls their undifferentiated state. If, however, symmetric division occurs, then proliferative cells are produced, enabling cells to differentiate and become specialized cells. A diagram showing the two modes of division is provided below [11].

Fig..4. *Diagrammatic illustration* showing the two modes of division (purves , 2004)



Conclusion

The development of the retina involves many stages and mechanisms to achieve a healthy retina with the ability to respond to light. Retinal cells develop particular mechanisms during their cell cycle, which enables them to upgrade from retinal progenitor cells to specialized retinal cells. Such mechanisms include the inhibition of particular factors and the activation of master regulators to support their proliferation and differentiation. Retinal cells move from layer to another using different migration modes, some of which are supported, while others enable cells to move freely. The ability of cells to migrate to different regions in the retina enables the developing cells to explore and acquire growth signals from different environments. Retinal cells develop at different stages during the growth of an embryo, enabling the concept of retinal neurogenesis to provide a

precise timescale of the birth of retinal cells.

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Author's Contributions

All authors had an equall contribution in the preparation and of the manuscript.

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