Connexin Connections in Neurogenesis

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Summary

Radial glia-like cells that act as stem cells in the sub-granular zone of the dentate gyrus are involved in adult neurogenesis. The communication between these cells results in their proliferation into neurons and occurs via gap junctions. Connexins 43 and 30 are shown to be significant proteins that form gap junctions, fostering neurogenesis in the brain region linked with learning and memory.

Introduction

In college campuses throughout the world, there comes a time when students sit down in hopes of intensely studying. This time is known to students as finals, a stressful period that consists of demonstrating one's mastery of his or her courses. Repeated exposure to class material in a meaningful manner allows these students to strengthen their neuronal synapses. One way through which this is achieved in the brain is through long-term potentiation, where, similar to physical conditioning in athletics, physical changes occur in the brain cells that strengthen old connections or form new ones that contribute to learning and memory[1,2]. Within the past decade, however, adult neurogenesis-the birth of new neurons in the adult brain—has shown to be another way through which neurons are able to form novel connections. Countering past idea that neurons do not form in the mature brain, adult neurogenesis is a rapidly developing field. A recently published paper on the *Proceedings of the National Academy of Sciences* by Kunze *et al*. bridges the gap in knowledge about the mechanisms through which radial glia-like (RG-like) astrocytes assist in adult neurogenesis[3].

In the brain, astrocytes have been known to be modulators of synaptic transmission and cell growth. More recently, RG-like cells have also been shown to have the unique ability to give rise to both neurons and other RG-like cells. These cells arise in the subgranular zone of the dentate gyrus, which is part of the hippocampus—the region of the brain associated with memory. RG-like precursor cells that arise from these RG-like stem cells have been shown to not receive inhibitory or excitatory neurotransmitter signals, thus provoking Kunze *et al*. to conduct experiments yielding a better understanding of the molecular mechanisms of communication between these precursor cells that ultimately leads to adult neurogenesis and differentiation[3] (Fig 1(A)).

Previously conducted in-vitro experiments have shown that progenitor cells require gap junctions to remain in a proliferative state[4]. Additionally, research has shown that gap junctions coordinate the migration of neurons during embryonic development[5]. This led Kunze *et al.* to hypothesize that the coupling of these RG-like cells via gap junctions serve as the main communication pathway resulting in proliferation and differentiation of RG-like cells to neurons.

In efforts to test their hypothesis of coupling, Kunze *et al.* injected a stain called biocytin and observed its spread via microscopy that would allow scientists to observe multiple layers and confocal z-stack micrographs—an experimental technique dimensions of tissue[3]. They were able to show that the stain in the majority of RG-like cells had spread to an average of 6 to 13 neighboring cells. This indicated that since most RG-like cells were coupled, their membranes contained gap junctions that allowed for the passive diffusion of the cells, potentially serving as the main pathway through which these cells communicate.

In order to gain a better understanding of the molecular components of these gap junctions, Kunze *et al*. conducted experiments to determine the connexin (Cx) isoforms that made up the gap junctions. Past studies have shown that while Cx26 and Cx43 are most prevalent in the prenatal dentate gyrus, connexin expression in the postnatal brain has not been assessed[6]. On the other hand, scientists have demonstrated that Cx43 has been linked to spinal cord neurogenesis as well[7].

To test which connexin isoform is most prevalent in the adult dentate gyrus, Kunze *et al.* harvested the cytoplasm of the biocytin-filled RG-like cells and conducted RT-PCR on them with probes that were specifically designed to amplify Cx43, Cx30 and Cx263. Upon analyzing the results, the scientists concluded that Cx43 (50%) and Cx30 (31%) were most prevalent in these cells, whereas Cx26 was expressed in only about 18% of the cells[3](Fig 1 (B)).

Having shown that RG-like cells are coupled through gap junctions, and that the connexin proteins that form these gap junctions are mainly Cx43 and Cx30, Kunze *et al.* sought to confirm the role that these gap junctions play in enabling communication between the RG-like cells. To accomplish this, the scientists made a knockout mutation of Cx43 and Cx30 in RG-like cells and injected biocytin into the cells to determine if coupling was still present. As anticipated, there was spread in biocytin and hence no coupling seen between these cells[3].

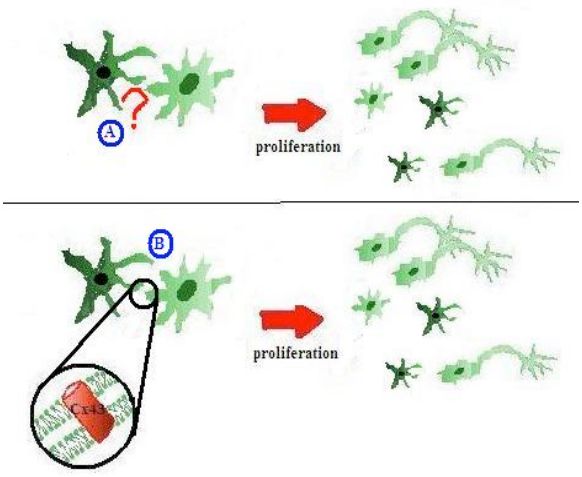

Figure 1: Connexin 43 expression in radial glia (RG)-like precursor astrocytes contributes to adult neurogenesis. (A) RG-like precursor cells proliferate into both granule neurons and more RG-like cells. The mechanisms of communication between these RG-like cells that contribute to proliferation were previously unknown. (B) Kunze et al. demonstrated that RG-like cells communicate through gap junctions mostly composed of connexin 43 (Cx43). When Cx43 is ablated, proliferation of RG-like cells and survival of granule neurons decreases.

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Next, in order to determine if the communication between these neurons were important for proliferation and differentiation of granule neurons, Kunze *et al.* did a before-mutation and after-mutation count of the granule neurons and noticed a 21% decrease in the number of neurons when Cx30 and Cx43 were lacking[3]. To ensure that this decrease in neurogenesis was not due to indirect or developmental defects, Kunze *et al*. performed the same test in juvenile dentate granule neurons and noticed that there was still a decrease in the number of cells. This decrease, however, was less profound, affirming that connexin expression is vital for the generation of new granule neurons in adults.

This paper is one of many recent papers that delve deeper into understanding the pathways and biological environments that best contribute to adult neurogenesis. Kunze *et al*.'s findings will have a significant impact in this field since their experiments provide a comprehensive understanding of one of the main pathways of communication that leads to proliferation of granule neurons. Future experiments should focus on identifying the molecules responsible for inducing proliferation and differentiation of the RG-like precursor cells into neurons in the subgranular zone of the dentate gyrus. These findings also shed light onto understanding the mechanisms through which some of the most debilitating neurodegenerative diseases can potentially be reversed.

References

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