J Cell Signal. 2025;6(3):119–121.

Journal of Cellular Signaling Editorial

A Renewed Interest in Bioelectric Signaling: Unveiling an Epigenetic Layer of Neural Stem Cell Self-renewal and Differentiation

Chun-Chih Tseng[1,*]

[1]Department of Developmental Neurobiology, St. Jude Children's Research Hospital, Memphis, TN 38105, USA

[*]Correspondence should be addressed to Chun-Chih Tseng, charles.tseng@stjude.org

Received date: September 01, 2025, **Accepted date:** September 04, 2025

Citation: Tseng CC. A Renewed Interest in Bioelectric Signaling: Unveiling an Epigenetic Layer of Neural Stem Cell Self-renewal and Differentiation. J Cell Signal. 2025;6(3):119–121.

Keywords

Bioelectricity, Brain development, Neural stem cells

Editorial

Neural stem cells (NSCs) are the foundation of brain development, giving rise to the vast diversity of neurons and glial cells that form the central nervous system. In the embryonic cerebral cortex, radial glia arise from primitive neuroepithelium and act as the main source of NSCs and progenitors of other glial cells that balance self-renewal with differentiation in a spatially and temporally regulated manner [1,2]. Neural stem and progenitor cells can also be found in the neural crest during development, the subgranular zone (SGZ) of the dentate gyrus in the hippocampus, and subventricular zone (SVZ) of the lateral ventricles in the adult brain [3,4]. The precise orchestration of NSC lineage progression underlies the layered architecture of the cerebral cortex and the functional connectivity of the adult brain [5,6]. Dysregulation in NSC behavior can result in developmental abnormalities, impaired cognition, or predisposition to disease [7].

While transcriptional and epigenetic regulations at the chromatin level have been extensively studied during neural development, emerging evidence highlights a renewed interest in bioelectricity, one of the most basic and intrinsic properties of cells, as a key layer of control influencing NSC proliferation and differentiation [8,9]. Bioelectricity is fundamental to all cell types and established through the differential distribution of ions and charged particles across the plasma membrane by the modulation of expression and activity of ion channels, transporters, gap junctions, and pumps [9]. Nearly all animal cells maintain a conserved ionic asymmetry, where intracellular potassium ion (K^+) concentration is higher and sodium ion (Na^+) level is lower compared to the extracellular environment. This gradient is upheld by the Na^+/K^+-ATPase ion pump and underlies critical functions such as cellular volume regulation [10]. The resting membrane potential reflects a balanced state of ions, chemicals, and charged molecules between the extracellular and intracellular spaces and contributes to each cell type's unique physiology [9].

Gap junctions (GJs) are formed by direct docking of two GJ hemichannels, with 6 connexin or pannexin isoforms on each apposing side, between adjacent cells or cell-cell contact sites [11]. GJs are multifaceted mediators on the plasma membrane capable of coordinating rapid electric and chemical coupling of a large group of cells through GJ formation. They can also perform GJ-independent functions as hemichannels, adhesion molecules, and modulators of intracellular signaling pathways [12]. Studies have found that GJ subunits are widely expressed in the developing brain and participate in neurogenesis, migration of postmitotic cells, and chemical synapse formation [13]. Connexin 43 (Cx43) has been shown to regulate the fate of human neural progenitor cells (hNPCs) [14]. Silencing of Cx43 shifts their differentiation balance, promoting a neuronal phenotype while reducing a glial phenotype, through GJ-independent and β-catenin-mediated transcription of pro-neuronal genes. Notably, studies in an E16-17 rat model reveal that Cx43 hemichannels serve as key initiators of radial glial calcium waves, and that disruption of this activity compromises neurogenesis in the ventricular zone [15]. Similar findings have been observed in mouse embryonic stem cell–derived neural progenitors, where connexin 43-mediated electrical coupling drives the activation of voltage-gated Ca^{2+} channels, which in turn leads

to the generation of Ca^{2+} oscillations, ultimately enhancing progenitor proliferation and contributing to cortical layer development [16]. It was also reported that GJ communication mediated by Cx43 and Cx45 in rat fetal (E10.5) NSCs is essential for their survival and proliferation [17]. Taken together, these studies underscore critical roles of GJs in shaping cortical development [18].

Various ion channels have also been reported during the proliferation and/or differentiation of neural stem and progenitor cells. Emerging evidence indicates that hNPCs derived from fetal midbrain progressively acquire functional voltage-gated sodium and calcium channels as they mature into neurons *in vitro*, which are essential for the generation of action potentials, while proliferating hNPCs engage transient receptor potential (TRP) channel-mediated calcium entry during neurogenesis [19,20]. Notably, store-operated calcium ion influx mediated by calcium release-activated channel (CRAC) also plays important roles in embryonic and adult NPC proliferation *in vitro* and *in vivo* [21]. In glial progenitor cells, blockage of K^+ channel activity resulted in accumulation of cyclin-dependent kinase inhibitors, p27(Kip1) and p21(CIP1), and cell cycle arrest at the G1 phase, linking electrical states to cell cycle progression [22]. In the postnatal and adult mouse hippocampal dentate gyrus, the Na^+-K^+-$2Cl^-$ (NKCC1) cotransporter is a central regulator of chloride homeostasis that preserves neural stem cell quiescence, thereby ensuring life-long neurogenesis [23]. Moreover, Piezos are mechanically activated and nonselective cation channels localized on the plasma membrane [24]. They convert mechanical forces such as stretch, stiffness, and shear into lineage cues via integrin, ERK1/2 MAPK, Notch, and WNT pathways, linking extracellular mechanics to stem cell fate [25]. In E10.5 mouse embryos, Piezo1 regulates neural stem cell proliferation, differentiation, and cholesterol metabolism [26], while in traumatic brain injury models, its inhibition directs the differentiation of hippocampal NSCs toward neurons [27]. Extending this biology into biomaterials, human neural stem and progenitors cultured on piezoelectric scaffolds differentiated into β-III tubulin-positive neuronal cells even without inductive factors [28]. Together, these findings highlight Piezo1 as a hub of mechano-bioelectric regulation and underscore piezoelectric materials as powerful tools for neural tissue engineering.

Lastly, electrical stimulation has been shown to drive embryonic stem cells toward neuronal lineages through calcium-dependent mechanisms and to increase fetal NSC proliferation and differentiation [29,30]. These findings suggest that incorporating electrical modulation into pluripotent stem cell-based brain organoids could provide an exciting opportunity to enhance their developmental precision and functional relevance. Key challenges include capturing the dynamics of membrane potentials at single-cell resolution and clarifying how bioelectric signals interface with cell-cell/cell-extracellular matrix interactions, intracellular signaling, transcriptional regulation, and chromatin regulators. Innovative tools such as optogenetics, piezoelectric biomaterials, and nanotechnology-based voltage modulators hold promise for experimental dissection and therapeutic translation. Collectively, these advances position bioelectricity as a frontier in developmental neurobiology with the potential to redefine models of brain development and open new avenues for regenerative medicine.

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