Review Paper
Neural Tube Biology With Emphasis on Early Neurulation; A Narrative Review

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ABSTRACT

Neurulation, as the formation of the basis of the nervous system, is the earliest and crucial stage of embryonic development, affecting the development of other parts of the embryonic body. During neurulation, the neural plate is formed through morphological changes. At the end of this stage, the neural tube is established and the central nervous system could be formed in the future. Although this embryonic process occurs morphologically, the precise study of nervous system evolution can be considered by different gene mutations in rodent embryos. Genetic assessments of embryos can finally cause the accurate discovery of the role of genes in embryo development, the stages of nervous system development, and possible associated diseases. Explanation of new findings in the field of neurulation with emphasis on genetics can be helpful in future embryonic studies, abnormalities, and treatments. Thus, the study of neural plate formation can play an important role in increasing the insight of embryological researchers in this field. In this review article, we aimed to collect basic embryonic data in rodent neurulation to provide important information for more laboratory investigations in this field.

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1. Introduction

Artificial mutation in rodents, especially in neurulation components, is a reliable technique for investigating the central nervous system (CNS) development. These transgenic animals can also clarify the side effects following the elimination of some important exogenous agents, such as folic acid on neural tube (NT) occurrence [1]. Thus, by the use of this procedure, various molecular routes have been recognized as involved in mammalian neurulation. Some signaling pathways, including planar cell-polarity [2], involved in NT closure, and sonic hedgehog (Shh) [3], involved in neural plate (NP) folding, are two examples of important molecular routes. The knowledge of neurulation can accurately describe NT defects (NTDs) and neurological diseases. Thus, better treatment procedures can be selected by the physicians. As a primary CNS predecessor, NT formation occurs during a morphological process called neurulation. The non-neural surface of ectoderm (a specialized type of dorsal ectoderm) forms bilateral neural folds. These lateral folds ascend and converge together in the midline, forming NT, which is then enveloped by future epidermal ectoderm [4]. Despite a deep background in neurulation in developmental research, the mechanisms of NT closure (NTC) and its clinical anomalies need more investigation. Although the physiological phases of neurulation are thoroughly characterized, the exact molecular pathways of NT biology are now unknown. Besides, molecular programming of neural crests (NC) and specific neuronal populations in CNS are well understood. The rising publications of genetically mutant rodents with NTDs have provided opportunities for in-depth examination of neurulation. Approximately less than 100 genetic variants are found to have an impressive effect on the neurulation process. Also, the localized NTDs (brain or spine) fluctuate across the variants, representing that the neurulation-related gene expression is associated by region. In this review study, we aimed to gather some novel genes involved in neurulation. This paper can help future studies in exploring the genetic basis of NTDs.

Types of neurulation

During the neurulation in vertebrate embryos, the CNS is one of the first organs formed. With further development of neurulation, the NT is established. NT splits into two main parts: A rostral component, which expands into the brain, and a caudal part, which develops into the spinal cord. Three principal brain swellings are located at the rostral part, including the forebrain, midbrain, and hindbrain, with further swelling subdivision occurring along the rostro-caudal length of the NT named neuromeres [4].

Neurulation is divided into two early (or primary) and late (or secondary) phases. During early neurulation, three distinct stages occur: 1) NP is generated from the epiblast layer, 2) The NP is then shaped, expands in length, and restricted in diameter, and 3) The NP bends to generate a neural groove (NG) bordered by bilateral neural folds (NFs). The edges of the NFs converge and merge in the dorsal midline to form the NT in the last phase [5]. Various processes are also involved in late neurulation; for example, a compact cluster of cells (named medullary cord) originating from the tail bud develops. The medullary cord cavitates, which forms numerous lumina. These lumina merge into a unique lumen, which is confined by the walls of the secondary NT. NT develops distinct rostro-caudal levels as a result of early and late neurulations. The whole brain and most of the length of the spinal cord (cervical to lumbosacral level) are formed by early neurulation, whereas the tailmost section of the spinal cord is developed by late neurulation [6].

Early neurulation

During gastrulation, the epiblast cells located in the rostral part of Hensen's node, as well as the cranial section of the primitive streak, totally respond to multiple extracellular signals [7]. The epiblast cells develop into apico-basal hypertrophy to form an NP. NP is wide medio-laterally and narrow rostro-caudally. Once the epiblast is committed to a neural destiny, the NP creates independently than Hensen's node or non-neural ectodermal cells. The process in which the NP develops narrow transversely and extends rostro-caudally is NP molding. NP is concurrently elongated rostro-caudally and narrowed transversely. Also, during the molding process, the NP thickens apico-basally [8].

In NP shaping, this structure also begins to fold. The cranial portion is the first segment to be affected, followed by the spinal cord formation. The midline of NP also stays in a constant position during folding, forming a median hinge point (MHP) along with the rostro-caudal axis [9]. The lateral aspects of the NP gradually elevate, creating the NG and NFs. NP then bends even more towards its contact with the epidermal ectoderm, establishing two dorsolateral hinge points (DLHPs) [10]. This may be observed at the future of cranial levels and the extreme caudal end of the prospective spinal cord area. The MHP is anchored to the prechordal plate mesoderm and notochord, whereas the DLHPs are anchored to the neighboring surface ectoderm of the NFs. As a result, the NP is stabilized during folding by hinge points [11]. Folding around the DLHPs induces the final NFs to

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converge, guiding their tips medially until they meet in the dorsal midline. DLHPs are not generated more in the spinal cord, and bending occurs around the MHP, providing the apical surfaces of the neuroepithelial cells into apposition to each other. The spinal canal is temporarily occluded as a result of this event. One of the primary distinctions between neurulation at the cranial and spinal cord levels of the neurulation is the absence of DLHPs, and hence the NFs convergence in the spinal cord [12].

The NFs, which contain the intersection of the NP with the surrounding epidermal ectoderm, are positioned near the lateral edges of the NG. As the NP folds over the MHP, the primary NFs develop, and the final NFs emerge later as the folding around DLHPs [13]. Each NF is made up of two layers: An internal neuroepithelial and an external epidermal ectodermal stratums. During NF development and morphogenesis, four critical processes occur: Epithelial ridging, twisting, delamination, and apposition [14]. Ridge formation at the potential outer epidermal–inner neuroepithelial transition zone is known as epithelial ridging. It is caused by the height difference between epidermal ectoderm (EE) and neuroepithelial (NE) cells, causing the development of NFs. The heights of the NE cells elevate, whereas those of the EE cells shrink. Epithelial twisting is the next phase, described as creating a concave curvature centered at the potential EE–NE contact. The key characteristic is the changing cell appearance within the primary NFs; the cells are inverted into wedge-shaped with constricted bases and extended apical ends [15]. Epithelial delamination is the third event, which is described as the splitting of epithelium into two different layers. Finally, this process culminates in creating a linear contact among two epithelial layers at the EE–NE transition zone. Delamination is caused by cavitation and deposition of extracellular matrix at the contact with this transitional zone. Then, the cells rotate radially to form intercellular junctions with either neighboring EE cells or nearby NE cells [16]. Epithelial apposition is the final process in NF morphogenesis. The medio-lateral growth of the NE layer and an apico-basal flattening of the EE layer are prominent characteristics of this stage of NF development. The level of epithelial apposition along the rostro-caudal position varies by region. Apposition is severe where the DLHPs are generated, and the NFs converge in the forebrain and midbrain levels. Epithelial apposition is absent where the real DLHPs do not develop, such as at rostral spinal cord levels [17]. The NG closing is the ultimate stage of early neurulation. In the dorsal midline, NF edges are brought into apposition with each other during the fusion. NG closure begins in the projected midbrain area and extends rostrally to the forebrain, then caudally to

the hindbrain and spinal cord [18]. The rostral and caudal endpoints of the NT are momentarily open due to this event, known as rostral and caudal neuropores, respectively. At the most rostro-caudal levels, the epidermal ectoderm covers neuro-epithelium at the apex of each NF. Following NF apposition, two epidermal ectodermal layers come into touch, leading to NF fusion. The newly created epidermal-ectoderm layer delaminates from the neuro-epithelium as fusion continues. Since these layers of neuro-epithelium provide neuro-epithelium fusion, the NF fusion is defined as a twofold fusion involving two epithelial layers [10].

Cellular-based tissue forces during early neurulation

NP is formed by cell accumulation, which is apico-basal thickening caused by cell elongation. The NP is made up of a pseudostratified columnar epithelium with two main cell types of spindle-shaped (or fusiform) and wedge-shaped (or flask-shaped) cells. The activity of paraxial microtubules oriented along with the cellular longitudinal axis is responsible for the rise in height of neuroepithelial cells during NP development [19]. Other mechanisms, like cell packing and cell–cell adhesion alterations, have minor roles in NP thickness.

The convergent-extension displacements induced by cells of NP are substantially responsible for NP shaping. Neuroepithelial cell remodeling and directed or nonrandomized cell division account for this movement during NP formation [20]. In neurulation, the neuroepithelial cells undergo various rounds of rearrangements of cell–cell intercalation, reducing the NP width. The interkinetic nuclear migration and cell protrusive activity probably cause the cellular forces behind the process. Oriented neuroepithelial cell division also contributes to the NP extension. Neuroepithelial cells represent 2-3 cell divisions in 24 hours. Since the daughter cells are located on the long axis of the NP, a rostro-caudal extension can be resulted [14].

Two main events in NP bending are NP furrowing and folding. The creation of longitudinal furrows at three morphological hinge points (one MHP and two DLHPs) is known as NP furrowing. Changes in neuroepithelial cell morphologies at the hinge sites cause furrowing. During furrowing, many neuroepithelial cells at the MHP and DLHPs positions become wedge-shaped [21]. As a result, neuroepithelial cell wedging causes furrowing at the hinge sites. Both apical constriction and basal extension of neuroepithelial cells cause neuroepithelial cell wedging. During interkinetic nuclear migration, both processes are presumably mediated by the contrac-

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tion of apical bands of microfilaments and translocation of cell nuclei to the bases of the cells, respectively. The underlying notochord provides the molecular signal for MHP furrowing [22].

NP folding is mediated by lateral non-neuroepithelial tissues, including epidermal ectoderm, mesoderm, endoderm, and extracellular matrix underneath the NP. Cell flattening, directed cell division, and cell–cell intercalation cause epidermal ectoderm folding [23].

Early neurulation is triggered by intrinsic and extrinsic tissue forces

Based on the various studies, there are many intrinsic and extrinsic factors causing neurulation. NP shaping and furrowing are caused by intrinsic forces such as neuroepithelial cell activities (changes in cell form, location, and quantity). Extrinsic forces are generated outside the neuroepithelium responsible for NP folding and NG closure [24]. The epidermal ectoderm creates a major extrinsic motive force for NP folding [14]. First, following the separation of the NP from the epidermal ectoderm, the NP is shaped and furrowed with no folding. Second, NP deletion while keeping the epidermal ectoderm causes medial expansion of the epidermal ectoderm [25]. Thus, it is concluded that the epidermal expansion is oriented medially. Third, after epidermal ectoderm deletion, while keeping the underlying mesoderm, it prevents folding, and mesoderm and endoderm deletion cause the resume of folding [24].

Molecular concepts of early neurulation

Progress in the molecular basis of early neurulation has been made following the assessment of neural induction and shaping/bending of NP. In neural induction, the NP is recognized as the default state of ectoderm, and NP induction entails preventing epidermal ectoderm growth [26]. Approximately 100 mutations in mice provided the insight into specific genes involved in both normal and abnormal neurulations [27]. Because neurulation is triggered by changes in cell behavior, it is not unexpected that NTDs are caused by mutations in cytoskeletal, extracellular matrix/cell adhesion, cell cycle, and cell death genes [28]. Neurulation is a carefully choreographed morphogenetic activity involving several tissues [29].

Shaping and bending of neural plate

Convergent-extension and planar-cell polarity pathways

As previously stated, convergent extension is an important factor in neurulation [30]. The Wnt (wingless) signaling system regulates convergent extension [2]. Epithelial layers become polarized in the apico-basal plane of the epithelium. The planar-cell polarity (PCP) pathway is involved in the epithelium polarization [31]. The PCP pathway is responsible for the determination of wing hair direction. This pathway is essential for correct stereociliary bundle orientation in the outer hair cells of the mouse inner ear, as well as convergent extension during gastrulation and neurulation in vertebrates [32]. PCP pathway in Drosophila is made up of several core proteins working together to convert an extracellular polarity into specific cytoskeleton changes [33]. These essential proteins were recognized as Wnt signaling pathway components [31]. Thus, loss-of-function mutations of the cytoplasmic protein disheveled (type I and II) in Xenopus and its two orthologs in mice prevent convergent extension during gastrulation and neurulation [34]. There are canonical and non-canonical Wnt pathways [35]. The PCP route induces a noncanonical pathway using Wnt11 (known as frizzleds) [31]. For correct signaling and proper convergent-extension mechanism, many additional proteins, like dishevelled, must interact in this route. In addition to the double dishevelled 1 and 2 mutants, the circle tail [36], crash [37], spin cycle [38], and loop-tail [39] are four mouse mutants with convergent-extension anomalies. The strabismus/van Gogh-like gene (Vangl1, Vangl2) [31], which produces a transmembrane protein interacting with disheveled, is mutated in loop-tail mice. A mutation in the Celsr1 homologue of the Drosophila protocadherin flamingo gene is seen in both crash and spin cycle mice. Flamingo is essential for PCP signaling in Drosophila. A mutation in the circletail mouse's homologue of the Drosophila scribble gene has been discovered (Scrib). Strabismus interacts with scribble.

Apical constriction and actin-binding proteins

NTDs are caused by genetic ablation of many actin-associated proteins in mice. For example, the actin-binding protein shroom has been extensively studied [40]. Apical constriction is caused by over-expression of shroom protein in cultivated epithelial cells. Shroom produces apical constriction by modulating the establishment of a contractile actomyosin network linked with apical intercellular connections and shifting the distribution of F-

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actin to the apical side of epithelial cells. When shroom is inactivated in Xenopus embryos, hinge point formation is severely disrupted, and NTC is prevented, adding to the growing body of evidence that cell shape alterations play a role in creating crucial intrinsic forces for neurulation [41].

2. Conclusion

Neurulation is a multifaceted process involving numerous cell behaviors inside the neural plate and surrounding tissues. Fundamental cellular processes, such as changes in cell form, location, and quantity, result in differential development, and coordinated morphogenetic motions induce these behaviors. Neural tube abnormalities might be caused by genetic or environmental growth disturbance inside or outside the neural plate during crucial phases of development. This idea is supported by many animal models with neural tube abnormalities. Thus, elucidating the molecular processes governing cell growth during normal neurulation, the impact of dietary fortification and depletion on such growth, and the changes in cell growth that precede the creation of neural tube abnormalities is an important future endeavor.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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