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Development of the Nervous System - Characteristics and Methodological Approaches to The Study Using Monoclonal Antibodies

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Abstract

Recently, the term "molecular topography of the brain" has been used in neuromorphology. Many researchers have shown that the molecular topography often coincides with the topography of the morphological formations of the nervous system. In addition, the commonality of patterns of genes of the human nervous system with similar patterns of rats has been established, which makes it possible to extrapolate the data obtained in experiments on animals to humans. Each stage of ontogenesis is characterized by sequential activation of certain genes that provide molecular specialization of a specific morphological structure of the spinal cord and brain.

The goal of this study is to present a thorough understanding of ectoderm development and how it affects various cell stages. Certain biomarkers are variably identified, impacting various biochemical and physiological processes, from stem cells in the ectoderm layer through progenitors of each tissue. These molecules have countless linkages and crossings, and we can begin to profit from fields like regenerative medicine by having a better knowledge of these intricate networks.

Keywords: nervous system; biomarkers; ectoderm; stem cell; gastrulation

Molecular genetic aspects of early neurogenesis

Recently, the term "molecular topography of the brain" has been used in neuromorphology. Many researchers have shown that the molecular topography often coincides with the topography of the morphological formations of the nervous system. In addition, the commonality of patterns of genes of the human nervous system with similar patterns of rats has been established, which makes it possible to extrapolate the data obtained in experiments on animals to humans. Each stage of ontogenesis is characterized by sequential activation of certain genes that provide molecular specialization of a specific morphological structure of the spinal cord and brain (Ghanavatineja et al.,).

The molecular division of the central nervous system begins at the stage of the neural plate, before morphological differences between its regions appear. Various transcription factors and genes encoding the morphogenesis of spinal cord and brain structures are expressed uniformly or in gradients within the posterior and dorsoventral neuroectoderm, usually symmetrically about the midline (Kumar and Prabhakar, 2012).

Each structure develops under the influence of an increase or decrease in the level of expression of certain genes, as well as epigenetic remote intercellular signaling (Purves D, Augustine GJ, Fitzpatrick D, 2001).

All these phenomena are included in the concept of “patterning”. Planar, or horizontal, neuronal patterning occurs by propagation of signals within the ectoderm itself (neuroepithelium and adjacent neural ectoderm, usually in a limited spatial range), while vertical patterning is provided by signals that emanate from tissues adjacent to the nerve bud, i.e., mesoderm derivatives. or endoderm. Thus, for example, inducing stimuli for the development of the forebrain come from the anterior visceral endoderm.

Studies suggest that the early specialization of different regions and subregions of the neural plate and neural tube often correlates with a certain level of so-called "developmental competence". The state of competence implies a partial differentiation of the tissue, in which, although many of the alternative ways of its specialization are no longer possible, others are still possible (Kumar and Prabhakar, 2012).

Thus, developmental competence is the ability of a tissue under normal conditions to form a specific morphological object at a certain stage of ontogenesis.

The path of cell development according to their molecular specification can be determined already at the blastula stage. The expression of a particular

gene, or a whole group of them, indicates the path of subsequent developmental competence. Differences in cyto-, myelo-, and chemoarchitectonics between different brain structures appearing in the process of ontogenesis are already secondary in relation to the molecular specialization of the early stages of development (Purves D, Augustine GJ, Fitzpatrick D, 2001).

As the neural germ progresses through successive stages, following more and more diverse epigenetic pathways, the structure that emerges from it becomes more and more differentiated.

The most dynamic changes occur in the early stages of ontogenesis, when the sensitivity to various influences (intercellular integration, composition of the intercellular environment) is maximum, then the process stabilizes and proceeds more slowly.

The genetic identity of each locus, formed with the participation of local epigenetic processes, affects all aspects of histogenesis: proliferative properties, differentiation of neurons and glial cells, cell adhesiveness, composition of the extracellular matrix, features in cell migration, axonal navigation, and synaptogenesis (Kumar and Prabhakar, 2012).

The results of scientific research in recent decades indicate that there is a plan for differentiating areas of the central nervous system common to all vertebrates.

This is provided by the similarity of the combination of genes that are responsible for the specialization of neuroepithelial cells. As a result of the expression of these genes in various living organisms, similar morphogenetic structures are formed up to certain stages of developmental competence. This phenomenon is called the "field of homology" (Purves D, Augustine GJ, Fitzpatrick D, 2001).

During prenatal ontogenesis, certain genes are activated. The proteins encoded by them have the ability to penetrate into the nucleus of a nerve cell, interact with DNA and regulate further transcription to RNA. These are the so-called "developmental genes", the dysfunction of which leads to profound disorders in the development of the nervous system.

These genes are not associated with neuronal and glial differentiation, since the latter practically do not affect regional morphogenesis.

In the neural plate, the maximum gene expression is observed among the neuroblasts of the longitudinal ventrodorsal region and, for the most part, the caudal region.

At this stage of ontogenesis, activation of such cell proliferation genes as Nkx, ENC-1, Wnt, Six, Otlx2, En, Irx, Pax, Zic, and a number of others is observed. Moreover, on the dorsal part of the plate, the expression of those genes that control the differentiation of the ventral zone is noted.

The bending of the axis of the neural plate leads to the formation of the neural tube and the activation of a number of genes necessary for the further development of the nervous system (Kumar and Prabhakar, 2012).

Homeobox genes play an important role in the development of the nervous system. Homeobox is a DNA sequence found in genes encoding transcription factors that tend to switch cascades of other genes. The homeobox consists of approximately 180 base pairs and encodes a 60 amino acid long protein domain (homeodomain) that can bind DNA.

Nkx gene. Belongs to the family of homeobox genes. One of the mechanisms by which Nkx can carry out cell-specific programs is transcriptional activation.

In addition to Nkx, homeobox genes also include Lhx, which encodes a cysteine-rich zinc-binding LIM protein that acts as a transcription regulator.

The homeobox ***gene Dbx*** is a transcription factor gene that plays a key role in the differentiation of interneurons in the ventral spinal cord. During the first weeks of pregnancy in rats, Dbx expression is restricted to the telencephalon, diencephalon, dorsal midbrain, and spinal cord. In later pregnancy, Dbx expression extends to the midbrain, diencephalon, and cerebellum. All regions expressing Dbx contain a high proportion of proliferating cells.

ENC-1 gene. Encodes actin-associated proteins that play an important role in oxidative stress reactions by regulating the Nrf transcription factor.

Six3 gene. When the neural tube closes under the influence of activation of the Six3 gene, the rostromedial region is limited. This area will serve as the rudiment for the formation of the forebrain, which includes the telencephalon, septum, eye vesicles (the rudiment of the eyeballs) and the hypothalamus. The Six3 gene is a transcription factor that controls the activity of the Wnt1 gene, which ensures the development of the forebrain and establishes the correct anterior-posterior identity in the mammalian brain. By blocking Wnt1 activity, Six3 is able to prevent abnormal invagination of the back of the brain into the anterior. Suppression of Six3 expression leads to growth retardation of the forebrain and midbrain dysmorphogenesis. During retinal formation, Six3 has been shown to play a key role in the activation of Pax6, a major regulator of eye development. In addition, Six3 is involved in the maturation of the lens (Kumar and Prabhakar, 2012).

Otx2 gene. Encoded by the Otx2 gene, the protein acts as a transcription factor and plays a role in brain, craniofacial, and sensory development. It also influences the proliferation and differentiation of dopaminergic neuronal progenitor cells during mitosis. Mutations in this gene cause syndromic microphthalmia and combined pituitary hormone deficiency. This gene is also thought to play an oncogenic role in medulloblastoma. Otx2 expression is expressed in the tagma of the brain up to the caudal border of the midbrain, although some rostral regions of the forebrain repress Otx2.

Irx1 gene. The Irx1 gene encodes proteins involved in the development of the vertebrate nervous system during embryogenesis. The activity of this gene is observed in the brainstem and midbrain up to the intrathalamic region.

Genes En1 and En2. En1 and En2 gene signals reach the rostral border of the midbrain. They encode proteins involved in the foliation of cortical structures, including the cerebellar cortex.

Wnt gene. Growth factors encoded by Wnt play a key role in maintaining pluripotency, reprogramming, determination, and differentiation of developing cells. Expression of the Wnt gene is observed mainly in the caudal part of the midbrain.

The Pax genes are a family of genes encoding tissue-specific transcription factors. Pax proteins play a key role in the segmentation of the body of the embryo during embryogenesis. The expression of the Pax5 and Pax6 genes is especially important for neurogenesis.

BMP genes encode bone morphogenetic proteins (BMPs; bone morphogenetic proteins). This group of extracellular growth factors (also sometimes referred to as cytokines) act on cells through specific receptors on their surface called BMP receptors (BMPRs). They play an important role in the formation of the anterior-posterior axis of the body of the embryo during embryogenesis. As a result of the interaction of BMP and its inhibitor

chordin, the neural tube is formed from the dorsal ectoderm epithelium (Purves D, Augustine GJ, Fitzpatrick D, 2001).

The Zic genes encode transcription factors that can both directly bind to DNA and indirectly affect transcription by interacting with other proteins. Expression of the Zic genes is observed during embryogenesis in the dorsal hindbrain and in the periotic mesenchyme, adjacent to the developing inner ear. Zic-encoded proteins act in the neuroepithelium or mesenchyme itself, controlling the production of pattern-forming signals, but, in addition, the development of the inner ear is also associated with Zic-controlled changes in the expression of the Wnt and BMP genes(Ghanavatineja et al.,).

Usually, in the process of histo- and morphogenesis, the radial migration of neuroblasts to the lateral mantle zone predominates. Strands of nerve cells thus extend from the cavities of the developing ventricles of the brain to the surface of the neural tube. This phenomenon is especially characteristic of screen-type cortical structures (Kumar and Prabhakar, 2012).

Nevertheless, in some cases, maturing nerve cells migrate to a sufficiently large distance from the initial zone of their origin and colonize one or more ectopic zones of the neural tube.

An example is the migration of a population of inhibitory interneurons from ganglionic eminences to overlying pallidar structures. Most neurons in the olfactory bulb also come from other histogenetic regions via a rostral migration route.

As a result of molecular specialization and differentiation, "vesicles" and "segments" form in the neural tube. Vesicles are usually formed by longitudinal zones of neuroblast migration, while segments are transverse. Adjacent segments and vesicles with similar developmental competence form a tagma.

The developing neural tube during embryogenesis is divided into several regions. First of all, these are morphological objects – vesicles, neuromeres, lobes, convolutions, elevations, depressions, but they can also be characterized as patterns of gene expression.

More intensively growing regions of the neural tube compress or deform morphogenetically less expansive neighboring regions, which leads to their tangential expansion or contraction, changes in thickness, and formation of projections and invaginations. This probably explains the shape of various parts of the brain.

In the course of ontogenesis, histochemical examination shows an increase in the activity of dehydrogenase enzymes, including aldehyde dehydrogenase, in brain structures. A clear increase in the activity of dehydrogenases from the 10th to the 20th day of postnatal development in rats correlates well with the functional maturation of the brain, with a known activation during the same period of energy metabolism enzymes, especially rat brain pyruvate dehydrogenase, which is the most important source of endogenous acetaldehyde in the brain.

The nervous system, which includes sensibility, conduction, and responsiveness, serves as the body's primary regulatory network. In summary, it collects sensory input, transmits it over a complex network, evaluates it, and then reacts by delivering motor impulses to glands and muscles. The conductance is given by nerve cells, which convey electrochemical impulses via axons together with releasing neurotransmitters at synapses.

An individual's nervous system is made up of both a central nervous system (CNS) and a peripheral nervous system (PNS). The brain and spinal cord make up the CNS, while the PNS consists of the nerves that act as a connection bridge between the CNS and other bodily regions. PNS is divided as the enteric nervous system, sympathetic and parasympathetic ganglia. Finding successful intervention techniques for neurological illnesses will be easier if we fully grasp how the nervous system grows (Ghanavatineja et al.,).

The neural system is the first embryonic system to form and the last to be finished after birth. The three major layers (ectoderm, mesoderm, and endoderm) organize the creation of various tissues and organs following gastrulation (Purves D, Augustine GJ, Fitzpatrick D, 2001). Gastrulation is caused by the inward migration of cells from outside to the inner section of the blastula, which produces the gastrula. The nerve system and epiderm are formed by the ectoderm. The mesoderm gives rise to somites. The endoderm creates the epithelium of the respiratory and digestive systems, as well as associated organs including the liver and pancreas.

The neural crest, neural tube, and surface ectoderm are the three components that make up the ectoderm, the outermost of the three germ layers, which eventually gives rise to the neurological system, tooth enamel, epidermis, subcutaneous gland, and carotid body, to mention a few (Henry E Young and Asa C Black, 2014).

Since ectoderm specialization is extremely complicated, a wide range of methods, such as computational biology, micro-RNA studies, proteomics, immunohistochemistry, immunoblotting, and immunofluorescence methods, have been used to identify tissue-specific biomarkers involved in the numerous cell signaling pathways (Honardoost et al., 2015). Cell and molecular biologists frequently employ immunohistochemical labeling to track the development and positioning of protein biomarkers that are differently expressed in various tissue regions (M.-S. Jami et al., 2014a). It is done by inducing certain antibodies versus antigenic markers, and when such antibodies are coupled to a colorimetric enzyme, the antigenic site undergoes a process that produces color (Ramos-Vara, 2005). Western blotting is a more statistical investigative technique that may isolate individual proteins from complicated protein complexes produced from cells (Mahmood and Yang, 2012).

Neural crest

Depending on their distinct cell forms and migratory patterns, the neural crest is composed of four distinct groups. According to those melanocytes, sensory ganglia, parasympathetic ganglia, and the head's cartilage and bone are all developed by the cranial neural crest, which first arises in the embryo's anterior region. The aorticopulmonary septum, conotruncal cushions, and aortic arch smooth muscle are developed by the cardiac neural crest, a component of the cranial neural crest. The enteric nervous system (ENS) is derived from the vagal neural crest. At last, the skin's melanocytes and peripheral nervous system are developed by the trunk neural crest (Crane and Trainor, 2006).

Pluripotency indicators including the homeobox protein NANOG (NANOG), POU domain, class 5, transcription factor 1 (POU5F1), and the transcription factor SOX-2 are expressed by human neural crest cells (hNCCs) . Some endodermal indicators, including transmembrane 4 superfamily member 2 (TM4SF2), hepatocyte nuclear factor 3-beta (FOXA2), glypican-1 (GPC1), and C-X-C chemokine receptor type 4 (CXCR4), have also been found in vitro in hNCCs, highlighting the possibility of neural crest cells to lend credence to extra non-physiologic descendants (Thomas et al., 2008).

The pluripotent cells in mouse cardiac neural crest cells can transform into those melanocytes, chondrocytes, smooth muscle, connective tissues, and sensory neurons, but a few of the above cells only lend credence to certain cell types, like smooth muscle cells, chondrocytes, and Schwann cells, and some stem cells only produce smooth muscle cells or just melanocytes. This finding suggests that cardiac neural crest cells include multipotent, unipotent and pluripotent stem cells. Only 1-3 percent of neural crest cells are absolute pluripotent stem cells, although a broad range of neural crest groups,

including those in adult organs including the heart, hair follicles, stomach, and peripheral nerves, are multipotent or unipotent (Crane and Trainor, 2006).

Central nervous system

The neural tube is the embryonic tissue that gives birth to the CNS. The neural tube is formed in two stages: primary neurulation and secondary neurulation. Primary neurulation begins when cells on the neural plate's edge move along the midline and fuse in the middle of the neural fold. Secondary neurulation results in the formation of a hollowed neural tube in the middle of the neural plate. The neural tube eventually gives birth to the brain (Prosencephalon, Mesencephalon, and Rhombencephalon) and spinal cord(Ghanavatineja et al.,).

The gut tumor suppressor gene adenomatous polyposis coli (Apc) is the primary indicator found at the commencement of oligodendrocyte maturation, followed by reticulon-4 (Nogo-A) and MBP as adult oligodendrocyte protein indicators. The appearance of activated transcription factor 3 distinguishes ependymal cells (ATF3) (Mladinic et al., 2014).

BLBP, neuregulin, and astrotactin have neural guiding roles during migration (Parnavelas and Nadarajah, 2001). Furthermore, during prenatal mouse brain development, radial glial cells respond to the granulocyte colony-stimulating factor receptor (G-CSFR) (Kirsch et al., 2008). They eventually lose nestin (RC2, RAT401) and vimentin expression while acquiring GFAP expression when radial glial cells differentiate to astrocyte cells (Parnavelas and Nadarajah, 2001). This evidence implies that radial glial cells have multipotent properties and are important in therapeutic medicine research.

Aside from particular biomarkers that characterize cell type in the CNS, various aspects of the CNS have distinct expression styles that correspond to their activity. Basal ganglia, for example, are made up of dopaminergic neurons (DA) (Jami et al., 2015; M. Jami et al., 2014b). Folate receptor alpha (FolR1) is a dopaminergic neuronal progenitor marker in the midbrain, while CD166 antigen (Alcam), SUN domain-containing ossification factor (Ch1), immunoglobulin superfamily member 8 (Igsf8), and GDNF family receptor alpha (GFra) are DA indicators. Likewise, the LIM homeobox transcription factor 1-alpha (Lmx1a) midbrain dopaminergic lineage marker is found throughout prenatal murine growth (Gennet et al., 2016). EphrinA5 is a biomarker for the maturation of the telencephalon (Hegarty et al., 2013).

Moreover, the dorsal telencephalon has strong representation of the paired box protein Pax-6 (Pax6), while the intermediate telencephalon has upregulation of GS homeobox 2 (Gsh2) and the central telencephalon has higher activity of NK2 homeobox (Nkx2) and oligodendrocyte transcription factor 2 (Rallu et al., 2002).

Peripheral nervous system

PNS establishes a link between outside stimulus and interior reactions. Motor neurons provide the signal back to the organs, muscles, and glands after being received by the central nervous system from sensory neurons. The somatic nervous system and the autonomic nervous system are two divisions of motor neurons. The somatic nervous system carries messages from the brain to the muscles and is in charge of controlling intentional activity. In contrast, the autonomic nervous system contributes to the sympathetic and parasympathetic nervous systems by sending impulses to smooth muscle and glands. PNS typically consists of satellite glial cells (SGSs), Schwann cells, and neurons (Janig and Habler, 2000).

Sensory neurons contain transcription proteins like POU-domain (Crane and Trainor, 2006). However neuronal nuclei (NeuN) antigen is not significantly expressed in γ-MNs, GDNF family receptor alpha-1 (Gfr1) and estrogen related receptor gamma (Err3) are highly showed. Osteopontin (OPN) and NeuN strikingly distinguish α-MNs. OPN is in charge of establishing elongated axons with a fast rate of transmission speed and maturing neurons. Furthermore, it has been shown that synaptic vesicle glycoprotein 2A (SV2A) is a recognized marker of slow motor neurons, whereas chondrolectin (Chodl) provides a sign for rapid motor neurons (Misawa et al., 2012). SGCs that enclose nerve cell bodies are also identified by proteins including glutamine synthase (GS) and S100 in the sensory, sympathetic, and parasympathetic ganglia. S100 is not a particular indicator of SGCs since it is also expressed by a subset of sensory neurons and Schwann cells, making GS the best indicator for distinguishing SGCs. Glial fibrillary acidic protein (GFAP) can also identify SGCs following axonal damage (Hanani, 2005).

The markers 217c (Ran-1), A5E3, GFAP, and neural cell attachment protein (NCAM) can be used to identify non-myelinated Schwann cells, even though as myelin sheet thickness increases, these proteins become less active. P0, myelin-associated glycoprotein (MAG), and myelin basic protein (MBP) are displayed by myelinated Schwann cells, but in the embryonic stage, underdeveloped non-myelinated Schwann cells express the paired box protein Pax-6 (AN2) (Jessen et al., 1990). Modern studies have shown that AN2 appearance is decreased at the final phases of myelination when the cells induce myelin genes, (Schneider et al., 2001).Because of AN2 activity is relatively low in chemically specified cells, it is possible that axonal contact is required in addition to neural growth factors for AN2 expression.

In contrast, adult non-myelinated and myelinated Schwann cells contain S100, neurotrophin receptor 75 (p75NTR), and E3 SUMO-protein ligase EGR2 (Krox20), which are not found in the initial phases. It's noteworthy to mention that Sox2 and Sox10 activity amounts are constant throughout the cell cycle, which restricts the use of these proteins as indicators for the neural phase. POU domain, class 3, transcription factor 1 (Oct6), which is found in greater than 80% of Schwann cells, and NCAM, which is substantially conveyed by Schwann cells, are additional appropriate indicators for Schwann cells. Contrarily, the GAP43 molecule has baseline activity in young and non-myelinated Schwann cells, suggesting its ability as a protein biomarker, but is not found in adult myelin-forming Schwann cells. In all stages of Schwann cell maturation, MPZ and BMP are displayed; however, the activity rates rise during differentiation (Z. Liu et al., 2015b).

While protein kinase C iota type (PRKCi), negative elongation factor E (NELF), vascular endothelial growth factor (VEGF), and pleiotrophin (PTN) are abundantly displayed in the motor Schwann cells and are regarded as accurate biomarkers, they are also markedly displayed in the sensory Schwann cells. The transduction and myelination of motor Schwann cells are regulated by the above proteins PRKCi and NEFL, while NEFL also plays a role in microtubule assembling and axon supporting. Especially, PRKCi promotes cell survivability, microtubule dynamics, intercellular connectivity, and axonal supporting. Axonal signaling is absent in neural development, migration, and proliferation, where PTN level is weaker than expected (Jesuraj et al., 2013).

Dorsal root ganglion

DRG is the collective term for the specialized cells of pseudo unipolar nerve cells, which communicate information from the PNS to the CNS. Schwann cells of the dorsal root ganglia show Ran-1 and S100. Parallel to this, fibroblasts are identified by fibronectin-1 and Thy-1 membrane glycoprotein (Thy-1) (Fields et al., 1978).

Enteric nervous system

Initial specialization of neurons is defined by the proteins neuromodulin (GAP43) and embryonic lethal, aberrant vision, Drosophila-like protein2/4 (Elavl2/4), whereas glial cell maturation is defined by the protein fatty acid-binding protein (Fabp7). Moreover, upregulation of the proteins

dihydropyrimidinase-related protein 3 (Dpysl3), collapsin response mediator protein 1 (Crmp1), and neuropilin-1 (Nrp1) demonstrate premature migration and axon elongation. VIP and cocaine- and amphetamine-regulated transcript protein (CART) can identify neurons as they near the conclusion of specialization. The unique activity of fibroblast growth factor receptor 2 (FGFR2) in the postnatal ENS ganglia has been well described, and it is notable that stathmin2/3 (Stmn2/3), neuronal migratory protein doublecortin (Dcx), and S100b are indicators of glial cell differentiation (Heanue and Pachnis, 2006).

Sympathoadrenal (SA) system

Three kinds of cells make up the SA system: chromaffin cells, neurons, and small intense fluorescence cells (SIF). Tetrasialogangliosid A2B5 and neurofilament (NF) are present in (SA) progenitors. Final phases of the development of non-neural cells show down-regulation of these indicators, but neurons continue to produce them. Peripherin is also present at elevated levels. Significant levels of nitric oxide synthase (NOS) are found in SIF cells. Prominent SIF cell indicators include the tyrosine hydroxylase (TH), dopamine beta-hydroxylase (DBH), nucleotide sugar epimerase (NSE), PGP9.5, NCAM, and chromogranin-A (CGA) proteins. Chromaffin cells are particularly marked by SA1-5 antibodies. Throughout the course of development, these antigens initially form in the cytoplasm and then progressively travel to the cell membrane (Huber, 2006).

Carotid bodies

The carotid arteries' fork contains a collection of chemo sensitive cells known as carotid bodies. The 3 types of cells that make up the carotid body are glomus cells (types 1 and 2), sustentacular cells, and nerve terminals. (Kumar and Prabhakar, 2012). Tuj1, PGP9.5, TH, and NPY can identify glomus cells and sympathetic neurons.

Melanocyte

M4, M5, and M6 antigens are melanocyte maturation indicators. In prenatal and neonatal melanocytes, spindle shape and mild pigmentation are seen. Moreover, the M9 and M10 proteins are final indicators of melanocyte maturation that correlate to dendritic architecture and complete pigmentation, defining mature melanocytes. Despite modest rates of tyrosinase activity in the early and intermediate stages of specialization, the final stage of development is distinguished by strong tyrosinase expression (Houghton, Alan N. Eisinger, Magdalena. Albino, Anthony P. Cairncross, J Gregory. Old, 1982).

Meninges

The Dcx protein, which is extensively conveyed across the meninges, is a major protein indicator for the meninges. There is also information that excitatory amino acid transporter 1 (EAAT1), IL-13R2, and brain-lipid binding protein (BLBP) can be employed as glial endfeet layer indicators. Stage-specific embryonic antigen-4 (SSEA-4) and chitinase 3 like 1 (YKL-40) are also found in leptomeningeal cells and the end foot glial cell layer. Indeed, the YKL-40 protein is highly identified in the pia-arachnoid tissue, but the collagen-1 protein is found primarily in the pia mater, and claudin-11 and connexin 43 (Cx43) are found specifically in the arachnoid mater (Bifari et al., 2015).

Furthermore, the leptomeningeal cells include a fraction of cells that express neural progenitor identifiers such as Sox2, nestin, and vimentin. This information implies that the meninges are a source of neural progenitor cells during both embryonic and adult differentiation. Likewise, upregulation expression of growth factors like epidermal growth factor receptor (EGFR), fibroblast growth factor receptor 1 (FGFR1), and homing chemotactic agents like SDF-1 in the leptomeninges region suggests that the CNS is in a cellular dynamic state(Bifari et al., 2015).

Dental pulp

The pulp is a connective tissue made up of blood vessels and nerve fibers which is called odontoblasts. Stromal cell surface marker-1 (STRO-1) and CD146 are markers for dental pulp cells (Wei et al., 2007), while CD51/CD140 is a particular marker for dental stem cells that can create both odontoblasts and chondroblasts. Another biomarker, CD271, is certainly an ideal marker which is best for isolating oral mesenchymal stem cells (Alvarez et al., 2015). The discovery of indicators for DPSCs is gaining pace due to their favorable properties and promising discoveries on their usage in cell therapy.

Inner ear

Pro-neural cells, non-sensory cells, and pro-sensory cells develop from internal ear stem cells. Sox2 and Neurog1 are required for the development of pro-neural cells from progenitor cells. Jagged1, Notch1, SOX2, BMP-4, FGF, and IGF-1 are required for the development of pro-sensory cells. Brn3c, Espin Barhl1, Myosin VI, VIIA, and XV are necessary for hair cell final specialization, maintenance, and survival (Liu et al., 2014). Brn3c is necessary for inner ear hair cell development and persistence (Liu et al., 2014).

Myosin VII-A, Espin, parvalbumin alpha 3, and AchR9 have been identified as distinct indicators of hair cells (Li et al., 2003). Furthermore, the most well-known hair cell identifiers include parvalbumin alpha3, Pou4f3 (Brn3c), unconventional myosin-XV (MyoXV), Espin (Q. Liu et al., 2015a), Eya1-Six1, protein atonal homolog 1 (Atoh1), Sox2, and MyoVIIA (Ahmed et al., 2012; Mahmoudian-Sani et al., 2018). Atoh1, Jagged2, and Delta1 guide the maturation mechanism toward hair cells. Calb2, Calm1, Nhih1, and Otof are substantially more abundant in inner hair cells compared in outer hair cells. Whereas Lmod3, Ptgir, and Ptprq are significantly abundant in outer hair cells compared in inner hair cells (Liu et al., 2014)

BETA2/Neurod1, Jagged2 are important controllers of cell fate (Wang et al., 2010; Zine et al., 2000) .Notch Signaling and cdk inhibitors (p27kip1, p19Ink4d, and Rb) also interact during hair cell maturation and create assisting cell fate during the maturation procedure (Devarajan et al., 2011; Liu et al., 2014). Pro-sensory progenitors give rise to all these hair and supporting cells. (Liu et al., 2014). Components Influencing Transcription Hes1-5 promotes to the formation of supporting cells by suppressing the expression of Atoh1. TGF-, on the other hand, stimulates the trans differentiation of supporting cells into hair cells (Liu et al., 2014).

Conclusion

According to all reports and based on validated results, cell-type-specific antibodies were employed to track the formation of neurons and glia in the developing nervous system. Antibodies against neurofilament protein were used to identify differentiated neurons, whereas antibodies against glial fibrillary acidic protein (GFEP) were used to identify glial cells.

In this study, we offered a complete description of biomarkers that may be used to identify neurons and glial cells at early stages of brain development and may be valuable tools in situations when functional identification is challenging.

The use of biomarkers to assess cellular and molecular alterations in the human body, medication reactions, and the efficacy of therapeutic intervention tactics has immense promise. Likewise, biomarkers may be employed to monitor and assess cell growth and differentiation processes.

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