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Review

Protein biomarkers of neural system

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ABSTRACT

The utilization of biomarkers for *in vivo* and *in vitro* research is growing rapidly. This is mainly due to the enormous potential of biomarkers in evaluating molecular and cellular abnormalities in cell models and in tissue, and evaluating drug responses and the effectiveness of therapeutic intervention strategies.

An important way to analyze the development of the human body is to assess molecular markers in embryonic specialized cells, which include the ectoderm, mesoderm, and endoderm. Neuronal development is controlled through the gene networks in the neural crest and neural tube, both components of the ectoderm. The neural crest differentiates into several different tissues including, but not limited to, the peripheral nervous system, enteric nervous system, melanocyte, and the dental pulp. The neural tube eventually converts to the central nervous system.

This review provides an overview of the differentiation of the ectoderm to a fully functioning nervous system, focusing on molecular biomarkers that emerge at each stage of the cellular specialization from multipotent stem cells to completely differentiated cells. Particularly, the otic placode is the origin of most of the inner ear cell types such as neurons, sensory hair cells, and supporting cells. During the development, different auditory cell types can be distinguished by the expression of the neurogenin differentiation factor1 (Neuro D1), Brn3a, and transcription factor GATA3. However, the mature auditory neurons express other markers including βIII tubulin, the vesicular glutamate transporter (VGLUT1), the tyrosine receptor kinase B and C (Trk B, C), BDNF, neurotrophin 3 (NT3), Calretinin, etc.

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1. Introduction

The nervous system represents the main regulatory network in the body, providing sensitivity, conductivity, and responsiveness. In essence, it receives sensory information, conducts this information through an intricate network, and interprets and responds to the information by sending motor signals to muscles and glands. The conductivity is provided by nerve cells where electrochemical signals are transmitted through long fibers called axons that finally release neurotransmitters at the synaptic neuronal junctions (Biology, 1989).

The nervous system consists of two main parts: the central nervous system (CNS) and peripheral nervous system (PNS). CNS includes the brain and spinal cord and PNS includes nerves that mediate the communication network between the CNS to other parts of the body. The cell bodies of neurons are gathered in peripheral ganglions. PNS is also classified as sympathetic, parasympathetic ganglia and enteric nervous system (Frebreg, 2009). Representing an intricate network the neuronal system ensures a delicate balance of perception and response where any malfunction may lead to severe debilitating diseases. Thus, having a full understanding of how the nervous system develops will provide greater possibilities for designing effective intervention strategies for neurological disorders.

Neural system development is the first embryonic system that begins to form and the last one to be completed after birth. As illustrated in Fig. 1, the embryological development of the nervous system entails the formation of three germinal layers or gastrulation. Gastrulation occurs by inward migration of cells from outside the blastula to the inner part that forms the gastrula. During gastrulation, the three primary layers (ectoderm, mesoderm, and endoderm) organize the formation of different tissue and organs (Purves D, Augustine GJ, Fitzpatrick D, 2001). The ectoderm gives rise to the nervous system and epidermis. The mesoderm develops somites, which later differentiate into numerous systems including but not limited to bone, cartilage, blood vessels, and connective tissues. The endoderm forms the epithelium of the respiratory system, digestive systems and also related organs such as the liver and pancreas. The ectoderm, the outer layer of three germ layers, consists of three parts: neural crest, neural tube and surface ectoderm which ultimately develops into the nervous system, tooth enamel, epidermis, subcutaneous gland, carotid body to only mention a few (Henry E Young and Asa C Black, 2014).

As ectoderm differentiation is highly complex a myriad of different approaches have been used to detect tissue-specific protein biomarkers engaged in the various cell signaling processes and pathways including computational biology (Honardoost et al., 2015), micro-RNA studies (Keshavarzi et al., 2017; Mahmoodian Sani et al., 2016; Mahmoudian-Sani et al., 2017; Reza and Ghahfarrokhi, 2017), proteomics (Ahmadinejad et al., 2017; García-Estrada et al., 2013; Kosalková et al., 2012), Immunohistochemistry (Ghasemi-Dehkordi et al., 2015), Immunoblotting and immunofluorescence techniques. Immunohistochemical staining is widely used in cell and molecular biology to understand the propagation and localization of protein biomarkers differentially expressed in different parts of tissue (M.-S. Jami et al., 2014a). It is accomplished by eliciting specific antibodies against antigenic markers where antibodies conjugated to a colorimetric enzyme causes a color-producing reaction at the antigenic site (Ramos-Vara, 2005). A more quantitative analytical approach is represented by Western blotting which has the ability to identify specific proteins from complex protein mixtures obtained from cells (Mahmood and Yang, 2012). Fluorescence immunoassays are also frequently used where antibodies containing fluorescent tags detect specific antigens within complex protein solutions. All these techniques generally involve antibody-antigen interactions to specifically target biomarkers of clinical or research value. The utilization of biomarkers for *in vivo* and *in vitro* research is growing rapidly. This is mainly due to the enormous potential of biomarkers in evaluating molecular and cellular abnormalities in cell models and in tissue, and evaluating drug responses and the effectiveness of therapeutic intervention strategies. Biomarkers are essential tools in terms of basic research and clinical practices and they have the ability to detect variations and/or states of a protein related to a normal or abnormal cellular pathway. In other words, biomarkers act as good indicators of normal biological process, pathogenic processes and/or pharmacological responses to therapeutic interventions (Mayeux, 2004; Tanha et al., 2016). Indeed, biomarkers can be used to track and evaluate cell developmental stages and differentiation processes. To further highlight this the FDA is promoting biomarker discovery for basic and clinical researches (Strimbu and Tavel, 2010).

This review aims to provide a comprehensive view of ectoderm differentiation and how this influences cell stages. From stem cells in the ectoderm layer to progenitors of each tissue, specific proteins are differentially expressed affecting different biochemical and cellular pathways. These proteins have numerous interactions and intersections and only through a greater understanding of these complex networks can we start to reap the benefit towards areas such as regenerative medicine.

2. Neural crest

As the neural folds promote and join cells at the lateral edge or

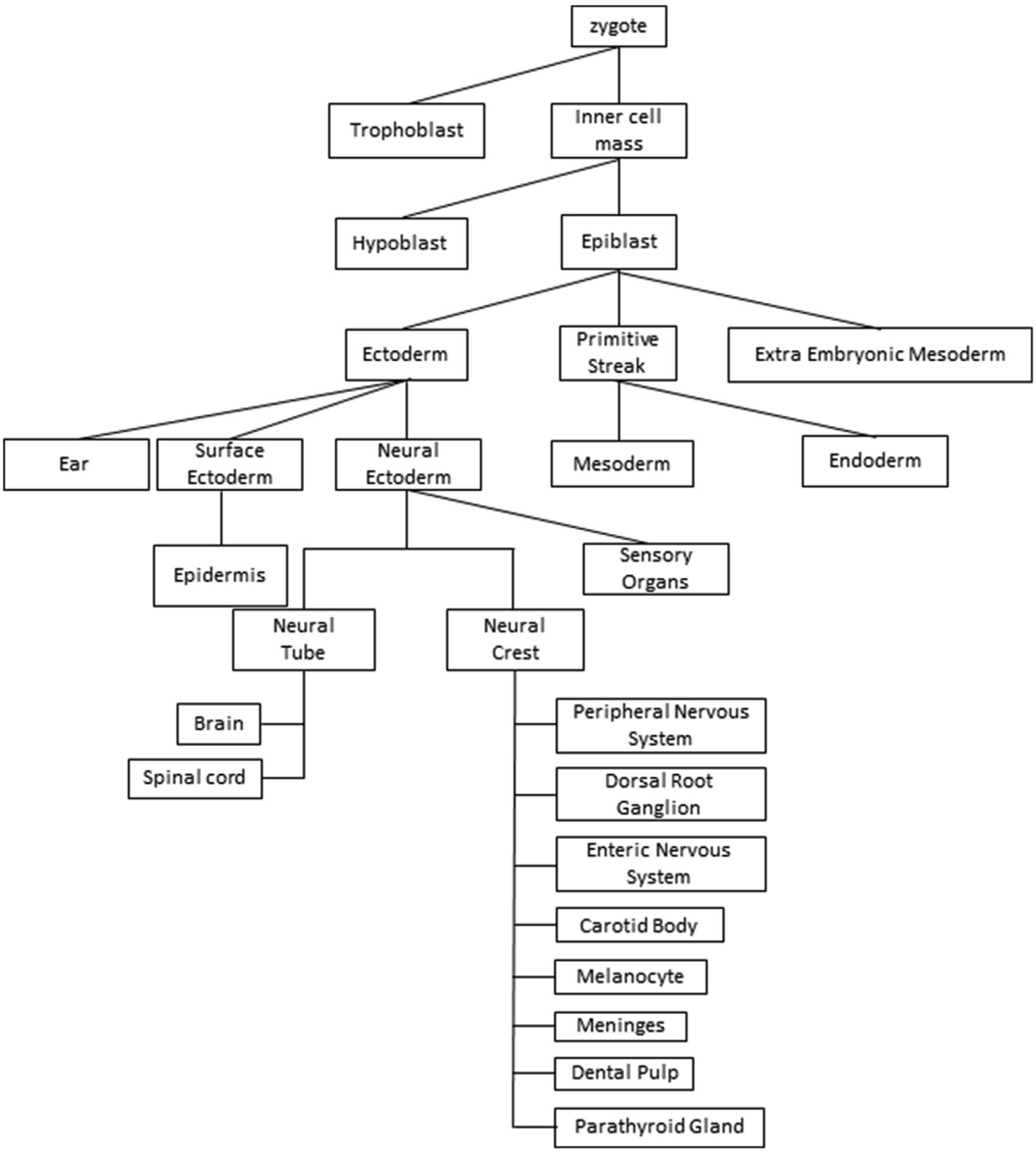

Fig. 1. Zygote develops three germinal layers through gastrulation. Ectodermal derivatives specifically portrayed to provide a schematic overview of divers tissues thrived from Ectoderm layer.

crest the neuroectoderm start to detach from their adjacent cells. The neural crest, then, experiences an epithelial-to-mesenchymal transition, delaminating from the neuroepithelium and migrating through the periphery to enter the basal mesoderm (Disc et al., 2012). The neural crest constitutes four different populations based on their migration pathway and unique cell types. The cranial neural crest appears within the anterior part of the embryo and develops cartilage and bone of the head, melanocytes, sensory ganglia, and parasympathetic ganglia. The cardiac neural crest, which represents a subdivision of the cranial neural crest, develops aorticopulmonary septum, conotruncal cushions, and aortic arch smooth muscle. The vagal neural crest gives rise to the enteric nervous system (ENS). Finally, the trunk neural crest develops the peripheral nervous system and skin melanocytes (Crane and Trainor, 2006).

Neural crest cells can differentiate into a variety of cell types but the pluripotent potential of neural crest is still a matter of controversy. It has been argued that although each cell is pluripotent they may indeed be committed at the outset of migration or shortly thereafter (Crane and Trainor, 2006). What is making this debate challenging is the fact that human neural crest cells (hNCCs) express pluripotency markers such as homeobox protein NANOG (NANOG), POU domain, class 5, transcription factor 1 (POU5F1) and transcription factor SOX-2 (SOX2). Some endodermal markers, like hepatocyte nuclear factor 3-beta (FOXA2), glypican-1 (GPC1), transmembrane 4 superfamily member 2 (TM4SF2), C-X-C chemokine receptor type 4 (CXCR4) have also been detected *in vitro* in hNCCs, which emphasizes the potential of neural crest cells to give rise to extra non-physiologic progeny (Thomas et al., 2008). Mouse cardiac neural crest cells comprise some pluripotent cells that can

differentiate into melanocytes, chondrocytes, smooth muscle, connective tissues, and sensory neurons whereas some of these cells differentiate into limited cell types such as smooth muscle cells, chondrocytes, and Schwann cells and some progenitors give rise to smooth muscle cells or just melanocytes. This observation proposes that there are pluripotent stem cells as well as multipotent and unipotent cells among cardiac neural crest cells, which is shown in Fig. 2. Only 1–3% of neural crest cells are pure pluripotent stem cells yet a wide spectrum of neural crest populations are multipotent or unipotent (progenitors) which can also be found in adult some organs such as heart, hair follicles, gut and peripheral nerves (Crane and Trainor, 2006).

2.1. Peripheral nervous system

The peripheral nervous system (PNS) provides a connection between external stimuli and internal responses. Sensory neurons transfer signals from stimulus receptors to the central nervous system and motor neurons return the signal to organs, muscles, and glands. Motor neurons are subdivided into the somatic nervous system and the autonomic nervous system. The somatic nervous system is responsible for voluntary control of movement and transmits signals from the brain to the muscles. Conversely, the autonomic nervous system transmits signals to smooth muscle and glands and contribute to the sympathetic and parasympathetic nervous system. The sympathetic nervous system represents the "fight or flight" response whilst the parasympathetic system develops the "rest or digest" system. Generally, PNS includes neurons, Schwann cells, and satellite glial cells (SGCs). Each of these cells is recognized by specific protein markers that can also define their function (Janig and Habler, 2000).

Neural crest cells are committed to differentiate towards sensory or autonomic lineages and environmental and transcriptional factors determine their fates toward neurogenesis or glial genesis. Alpha motor neurons (α-MNs) are motor neurons that supply skeletal muscle (the extrafusal muscle fibers) with nerves. α-MNs are located within the gray matter that forms the ventral horn of spinal cord while their axons travel down to muscles fibers to send motor signals via neuromuscular junction which launch muscle contractions. They receive signals from α-MNs that can simultaneously innervate multiple muscle fibers. Small muscles are supplied by low innervation ratio whereas large muscles need higher ratios of innervations of α-MNs that provide more precise control by the CNS (Bear, F Mark. Connors, W Barry. Paradiso, 2007). Containing smaller axons, the gamma motor neurons (γ-MNs) represent another type of lower neurons, residing in the same place of α-MNs though providing a lower rate of velocity. They receive input from the motor cortex and brainstem and innervate intrafusal muscle fibers. Their function is not associated with muscle contraction but rather they contribute to the contraction of muscle spindles, sensory receptors located within muscles that allow communication to the spinal cord and brain. A significant role of γ-MNs is to maintain the tautness of muscle spindles allowing the continued firing of alpha neurons, leading to muscle contraction (Frebreg, 2009).

It is important to differentiate between fast motor neurons, involved in fast and energy demanding movements such as running and leaping, and slow motor neurons that coordinate smaller action potentials for continued resistance to fatigue in actions such as walking or standing (Ritzmann and Zill, 2009).

In terms of protein biomarker, POU domain, class 4, transcription factor 1(Brn-3.0) and POU- domain transcription factors are found in sensory neurons (Crane and Trainor, 2006). Although neuronal nuclei (NeuN) antigen shows low expression levels in γ-MNs, Estrogen Related Receptor gamma (Err3) and GDNF family receptor alpha-1 (Gfrα1) are highly expressed. Osteopontin (OPN) and NeuN remarkably define α-MNs. As shown by Misawa and coworkers, OPN is responsible for neuronal maturation and establishment of long axons with a high rate of conduction velocity. Similarly, it has been demonstrated that Chondrolectin (Chodl) represents a fast motor neuron marker whilst synaptic vesicle glycoprotein 2A (SV2A) is a known marker of slow motor neurons (Misawa et al., 2012). SGCs that envelope nerve cell bodies in the sensory, sympathetic and parasympathetic ganglia and are further defined by protein markers such as glutamine synthase (GS) and S100 (Hanani, 2005). GS is the best marker for identifying SGCs whilst S100 is not a specific marker of these cells because subpopulation of sensory neurons and Schwann cells also express this protein. SGCs can also be detected by glial fibrillary acidic protein (GFAP) after axonal injury (Hanani, 2005).

Schwann cell markers differ due to the myelination state. Non-myelinated Schwann cells can be detected by 217c (Ran-1), A5E3,

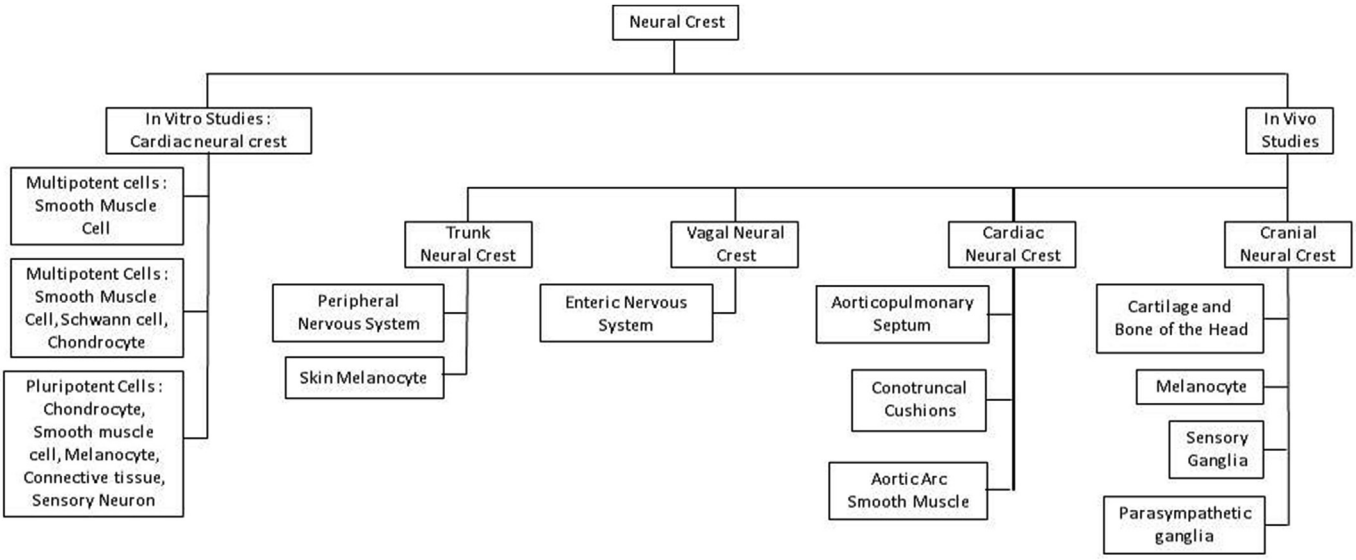

Fig. 2. Neural crest pluripotency patterns as investigated by *in vitro* and *in vivo* analysis.

GFAP and neural cell adhesion molecule (NCAM); however gaining myelin sheet causes down regulation of these proteins. Myelinated Schwann cells express P0, myelin-associated glycoprotein (MAG), myelin basic protein (MBP) as (Jessen et al., 1990) whilst the paired box protein Pax-6 (AN2) protein is expressed by immature non-myelinated Schwann cell at the embryo stage. Although AN2 expression is needed at the initiation of myelination, recent investigations revealed that AN2 expression is down regulated at the late stages of myelination when the cells upregulate myelin genes (Schneider et al., 2001). AN2 expression is very low in chemically defined cultures, which suggest that AN2 expression needs axonal interaction as well as neural growth factors. After nerve damage, AN2 expression does not show any change due to non-specific expression in the fibroblasts (Schneider et al., 2001). Conversely, S100, neurotrophin receptor 75 ($p75^{NTR}$) and E3 SUMO-protein ligase EGR2 (Krox20) are not expressed in the early stages but expressed in mature non-myelinated and myelinated Schwann cells. It is interesting to note that the expression levels of Sox2 and Sox10 are the same at every cell stage limiting their use neural stage protein markers. Other suitable markers for Schwann cells include POU domain, class 3, transcription factor 1 (Oct6), which is expressed in more than 80% of Schwann cells, and NCAM that is highly expressed by Schwann cells. In contrast, the GAP43 protein is not expressed in mature myelin-forming Schwann cells but shows basal expression in immature and non-myelinated Schwann cells suggesting its potential as a protein marker. MPZ and BMP are expressed in all developmental phases of Schwann cells but the expression levels increase during differentiation (Z. Liu et al., 2015b).

Sensory and motor Schwann cells have rather different expression characteristics. In the sensory Schwann cells MBP, NLGN1, brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factors (GDNF) are significantly expressed, whilst in the motor Schwann cells protein kinase C iota type (PRKCi), negative elongation factor E (NELF), vascular endothelial growth factor (VEGF) and pleiotrophin (PTN) are highly expressed and are considered as reliable protein markers (Jesuraj et al., 2013). Among the above-mentioned proteins, PRKCi and NEFL are involved in motor Schwann cells signaling and myelination whilst NEFL participates in the microtubule assembly and axon support. Specifically, PRKCi provides axonal support, intercellular signaling, microtubule dynamics and cell survival (Jesuraj et al., 2013). PTN also plays key roles in neural differentiation, migration, and proliferation where PTN expression is down-regulated due to lack of axonal signaling. Indeed these factors should be considered in the context of defining protein markers in cell culture as important environmental cues may be absent in cell culture (Jesuraj et al., 2013).

2.2. Dorsal root ganglion

The dorsal root ganglion (DRG) refers to the collection of cell bodies of pseudounipolar sensory neurons, which send signals from the periphery to the CNS. Ran-1 and S100 are expressed by Schwann cells of the dorsal root ganglion. Similarly, fibroblasts are detected by Thy-1 membrane glycoprotein (Thy-1) and fibronectin-1 (LETS) and Neurons of DRG are double positive for Tetanus binding protein and Thy-1. It is worth mentioning that Tetanus binding protein is an essential component of Tetanus toxicity (driven from *Clostridium tetani*) aiding the binding to neurons (Fields et al., 1978).

2.3. Enteric nervous system

The gastrointestinal tract contains its own nervous system, which is called the ENS and is often considered “the second brain”. Although it works in harmony with the CNS, it can also operate independently. It consists of two major plexuses which supply the entire gastrointestinal tract: the myenteric plexuses settled between the inner and outer layer of the muscular external and submucosal plexuses placed at submucosa (Nezami and Srinivasan, 2010).

The myenteric plexuses form a linear cluster of neurons whose stimulation leads to increased tone, velocity, and intensity of interactions in the gut. The submucosal plexuses provide local secretion, absorption, and muscle movement. Different sets of protein markers describe the type of neurons and glial cells of the ENS. The neuromodulin (GAP43) and embryonic lethal, abnormal vision, Drosophila-like protein2/4 (Elavl2/4) protein markers define early differentiation of neurons whereas the same stage is determined by fatty acid-binding protein (Fabp7) for glial cells (Heanue and Pachnis, 2006). Furthermore, early migration and axon extension are illustrated by the high expression levels of collapsin response mediator protein 1 (Crmp1), dihydropyrimidinase-related protein 3 (Dpysl3) and neuropilin-1 (Nrp1). When neurons approach the end of differentiation, they can be detected by VIP and cocaine- and amphetamine-regulated transcript protein (CART). In the postnatal ENS ganglia, the specific expression of fibroblast growth factor receptor 2 (FGFR2) has been clearly documented and it is noteworthy that stathmin2/3 (Stmn2/3) and neuronal migration protein doublecortin (Dcx) are markers of axonal outgrowth and S100b as a glial cell marker (Heanue and Pachnis, 2006)Similar to other parts of the neural system, Sox2 is known as a neural progenitor marker for the ENS. Other markers for ENS include Sty11 and synaptosomal-associated protein 25 (Snap25) (markers of synaptogenesis) Hu and Gap43 (Pan-neuronal markers). Moreover, the expression of proto-oncogene tyrosine-protein kinase receptor Ret (Ret), mitogen-activated protein kinase10 (MAPK10) and Stmn2 are correlated with axonal rearrangement and neuronal outgrowth (Heanue and Pachnis, 2006). More recently novel protein markers, such as ensconsin (ENS), distal-less homeobox protein (Dlx1), ETS variant 1 (Etv1) and T-box transcription factor (TBX1) Tbx3 have been investigated and suggested to represent new protein markers for ENS development (Heanue and Pachnis, 2006).

2.4. Adrenal medulla lineage

The adrenal medulla represents the central part of adrenal glands covered by the adrenal cortex. It contains shapeless cells surrounded by blood vessels and links to the sympathetic part of the autonomic nervous system, generally called the sympathoadrenal (SA) system. It includes three types of cells: Chromaffin cells, neurons, and small intense fluorescence cells (SIF cells); each characterized by specific markers. Being stimulated by preganglionic nerves through secretion of acetylcholine, Chromaffin cells secret norepinephrine and mostly epinephrine to blood vessels to induce fight or flight response in the body (McCorry, 2007). Neurofilament (NF) and tetrasialogangliosid A2B5 are expressed in SA progenitors. Down-regulation of these markers are observed at later stages in non-neural cells (like chromaffin cells) and they maintain its expression in neurons. Peripherin is also highly expressed in the neurons of SA. Tetanus binding protein is also detected in chromaffin cells (Huber, 2006). Nitric oxide synthase (NOS) is significantly expressed in SIF cells. The tyrosine hydroxylase (TH), dopamine beta-hydroxylase (DBH), nucleotide sugar epimerase (NSE), PGP9.5, NCAM and chromogranin-A (CGA) proteins are major markers of SIF cells. These markers, as well as phenylethanolamine N-methyltransferase (PNMT), SNAP -25 and GC receptors, verified as chromaffin cell markers (Huber, 2006). SA1-5 antibodies are specifically marking chromaffin cells.

Although these antibodies detect antigens of SA progenitors, the expression pattern of these antigens maintains in the chromaffin cells. These antigens firstly appear in the cytoplasm and gradually move to the cell membrane during the developing process. It is also noteworthy that Catecholamines are non-specific markers of SA progenitors (Patterson, 1991). Similarly, TH, DBH, NF, NSE, PGP9.5, B2, GAP-43, NCAM, neural cell adhesion molecule L1 (L1), CGA, neuropeptide Y (NPY) and acetylcholinesterase (Ach) are key markers of SA neurons (Huber, 2006).

2.5. Carotid bodies

Carotid bodies are a set of chemosensitive cells in the fork of carotid arteries. Carotid body cells are divided into three types of cells namely glomus cells (type1 and 2), sustentacular cells and nerve endings. Glomus cells have special chemoreceptors which are sensitive to oxygen and carbon dioxide pressure in the arterial blood flow and also to the pH and temperature (Kumar and Prabhakar, 2012). Glomus cells and sympathetic neurons are detectable by Tuj1, PGP9.5, TH, and NPY. Furthermore, no glomus cells are dependent on achaete-scute homolog 1 (Mash1) because superior cervical ganglion requires Mash1 function to stimulate the neural progenitors to differentiate into glomus cell subtype (Kameda, 2005). In contrast, retinal cells develop glial cells which do not require Mash1. In mutant cells, GFAP and S100 reactive cells appear which represent sustentacular cells, formed from ectomesenchymal cells and, like sensory neurons, are generated independently of Mash1expression (Kameda, 2005).

2.6. Melanocyte

Melanocytes are pigmented, neural crest-derived cells in the skin, hair follicles, mucosa, cochlea (ear), iris (eye) and mesencephalon (brain). Melanogenesis establishes strong protection against ultraviolet radiation (Yamaguchi and Hearing, 2014). The L-dopachrome tautomerase (TRP2/DT) protein is the initiatory marker that determines neural crest offspring to form the melanoblast cell lineage (10dpc) in mouse (Steel et al., 1992). Dopa-premelanin reactive melanoblast is detected from 14.5 dpc (Steel et al., 1992). Melanocyte antigens M2 and M3 are primary markers of melanocyte differentiation while no pigmentation has yet occurred and epithelial morphology is observable. In humans, these markers are also detectable in some subsets of melanomas. The M4, M5, and M6 antigens are intermediate markers of melanocyte differentiation (Houghton, Alan N. Eisinger, Magdalena. Albino, Anthony P. Cairncross, J Gregory. Old, 1982). Spindle morphology and light pigmentation are detected, occurring in fetal and newborn melanocytes. Furthermore, the M9 and M10 proteins are late markers of melanocyte differentiation which correspond to dendritic morphology and full pigmentation and these types of melanocytes are characterized as adult melanocytes. Albeit low levels of tyrosinase expression in early and intermediate levels of differentiation, late level of development is characterized by the high expression of tyrosinase (Houghton, Alan N. Eisinger, Magdalena. Albino, Anthony P. Cairncross, J Gregory. Old, 1982).

2.7. Meninges

Meninges are the three membranes that envelope the brain and spinal cord protecting the CNS. The membranes include the pia mater, the arachnoid mater and the dura mater (Decimo et al., 2012). The Pia mater is a thin, fibrous layer perforated by blood vessels that feed the brain. The Pia mater is firmly attached to the brain and spinal cord. The nomenclature of the arachnoid mater is due to its net-like structure formed from fibrous tissue. Cerebrospinal fluid is localized under the arachnoid mater and covers the pia mater. The dura mater is the outmost layer of meninges with a dense structure without extracellular spaces. It covers dural sinuses which collect and drive the blood from brain to heart. Interestingly, the meninges membranes are not limited to the space surrounded by the CNS and covering bones but it also penetrates into neuronal tissue suggesting that the meninges have additional physiological roles beside protection (Decimo et al., 2012). Meninges contain three joints including the blood-CSF barrier through arachnoid mater, the blood-CSF barrier in pial microvessels, and the utmost the CSF-brain barrier that includes the glial end feet layer (Brøchner et al., 2015). One main protein marker for the meninges is the Dcx protein that is highly expressed throughout this structure. There is also considerable evidence that excitatory amino acid transporter 1 (EAAT1), IL-13Rα2, brain-lipid binding protein (BLBP) can be used as markers of the glial end-feet layer. Leptomeningeal cells and the end feet glial cell layer are also marked with stage-specific embryonic antigen-4 (SSEA-4) and chitinase 3 like 1 (YKL-40) (Brøchner et al., 2015). Indeed, the YKL-40 protein is strongly expressed at the pia-arachnoid tissue whilst the collagen-1 protein is expressed specifically in the pia mater and moreover, the claudin-11 and connexin 43 (Cx43) are specifically located in the arachnoid mater (Bifari et al., 2015). Moreover, it is noteworthy that the leptomeningeal cells contain a subset of cells with neural progenitor markers including Sox2, nestin, and vimentin. This knowledge suggests that meninges are the host of neural progenitor cells during both embryonic development and adulthood. Similarly, high expression of growth factors like epidermal growth factor receptor (EGFR), fibroblast growth factor receptor1 (FGFR1) and homing chemotactic agents such as SDF-1 in the leptomeninges section indicates the cellular dynamic state of the CNS (Bifari et al., 2015).

2.8. Dental pulp

The pulp is a connective tissue consisting of odontoblasts which contain blood vessels and nerve fibers. A large proportion of pulp is placed within pulp chambers (central cavity of the tooth) and trauma and infection represent major drives for the dental pulp stem cells (DPSCs) to regenerate pulp tissue, e.g. odontoblasts. Recent studies have shown the presence of differentiation protein markers including bone gamma-carboxyglutamate protein (OCN), dentin sialophosphoprotein (DSPP), alkaline phosphatase (ALP) and matrix extracellular phosphoglycoprotein (MEPE) in DPSCs(Wei et al., 2007). Stromal cell surface marker-1 (STRO-1) and CD146 also represent dental pulp cell markers (Wei et al., 2007) and interestingly CD51/CD140α acts as a specific marker for dental stem cells which can generate both odontoblasts and chondroblasts (Alvarez et al., 2015). Another protein marker, CD271, probably represents the most suitable markers to isolate dental mesenchymal stem cells (Alvarez et al., 2015). Due to the beneficial characteristics of DPSCs and the promising findings on the use of these cells in cell therapy, the identification of protein markers for these cells is gaining traction. One interesting finding is that the *in vitro* enrichment of TNF-α boosts the stem cell-like features of dental pulp cells and increases the expression of stem cell markers such as SSEA-4, CD146, STRO-1, OCT-4, and NANOG (Ueda et al., 2014).

2.9. Parathyroid glands

Four small parathyroid glands are located behind the thyroid gland in the neck. In spite of their anatomical connection, parathyroid glands have no physiological connection to the thyroid gland. The primary lateral components are developed from the

neural crest and are therefore of ectodermal origin. However, the median part originates from the third and fourth pharyngeal pouches of the endoderm (Molina, 2010). Parathyroid glands produce the parathyroid hormone (PTH) that helps regulate calcium levels in the blood (within the range of 8.5–10.5 mg/dl). Calcium is a crucial element of muscle contractions and signal conduction in neurons and an imbalance of calcium levels may lead to neuronal or muscular damage. PTH ensures calcium and phosphate hemostasis in the body within blood and bones. When the circulating calcium level is a too low large amount of PTH is released to blood vessels targeting bones, gastrointestinal tract, and kidneys to respectively release and preserve calcium. The opposite effect of PTH on phosphate levels is mediated through the targeting of the proximal tubule of kidney nephrons to finally decrease phosphate levels in the blood when calcium levels are going to increase. Parathyroid glands contain two types of cells: Chief cells and Oxyphil cells. Chief cells are the major cells found in large number with round nuclei and they are responsible for the synthesis of PTH whereas Oxyphil cells are lesser in number and have a smaller nucleus with eosinophilic cytoplasm. They appear at the commencement of puberty and no function has yet been declared for these cells (Molina, 2010). Collectively, the above data suggest that PTH is a robust marker for chief cells. Additionally, the calcium-sensing receptor (CaSR), which detects calcium blood levels, represents yet another protein marker of Chief cells. Glial cells missing 2 (GCM2) protein is a transcription factor responsible for the development of the parathyroid gland from pharyngeal pouches (Gonzalez Campos, 2014). GCM2 loss-of-function mutations cause hyperthyroidism with the absolute absence of PTH. Both PTH and GCM2 are present in the Oxyphil cells making them suitable protein markers for these cells (Gonzalez Campos, 2014). The CGA is a secretory protein from the Granin family which is involved in parathyroid hormone secretion. This protein can bind to calcium and form bulks of calcium supply and also regulate PTH release (Gonzalez Campos, 2014). The CGA protein is the main granin expressed in Chief cells and thus is considered as a good protein marker for these cells. Moreover, various studies have shown that the C-C motif chemokine 21(CCL21) protein is a specific marker of parathyroid development (Bingham et al., 2009). Similarly, studies on adenoma primary cultures have revealed the expression of steroid-related markers, such as mineralocorticoid Receptor (MR), Glucocorticoid receptor (GR), and corticosteroid 11-beta-dehydrogenase isozyme 2 (11βHSD2) in these cells suggesting a possible presumptive effect of hyperparathyroidism to induce hyperaldosteronism (Gonzalez Campos, 2014).

3. Neural tube

The neural tube is the embryonic structure which develops the CNS. Formation of the neural tube occurs through two processes: primary neurulation and secondary neurulation. Primary neurulation starts when the cells in the border of the neural plate migrate toward the midline and fusing in the center of the neural fold. Secondary neurulation cast a hollow neural tube in the center of the neural plate. The neural tube ultimately forms the brain (Prosencephalon, Mesencephalon, and Rhombencephalon) and the spinal cord.

3.1. Central nervous system

The central nervous system comprises the brain and spinal cord. The brain is protected by the osseous skull and the spinal cord by the spinal canal. The brain is divided into three major parts including the forebrain, midbrain, and hindbrain. The forebrain controls speech, thoughts, perception, and processes sensory inputs and provides motor functions. The midbrain, in concert with the hindbrain, constructs the brain stem. In effect, the midbrain represents the part that connects the forebrain to the hindbrain. Lastly, the hindbrain extends from the spinal cord and includes pons and cerebellum which ensures movement harmony, balance, and guidance of sensory signals (Matter et al., 1991).

The spinal cord is a long cord that stretches out from the neck to the lower back. It is a bundle of nerve fibers that launch sensory signals (ascending or afferent inputs) from the periphery to the brain and transmits motor instructions (descending or efferent inputs) from the brain to the periphery. The spinal cord solely coordinates muscle responses in response to exterior impulses.

The CNS comprises neurons and different subtypes of glial cells. Glial cells provide neuronal protection, regulates signal transduction, synapse conduction and repair processes after injury (Purves D, Augustine GJ, Fitzpatrick D, 2001). Classified by size, they are divided into two groups: the microglia and the macroglia. The microglia consists of macrophages that act as the immune system agents in the CNS. They are mobile and they monitor brain infections and injuries. However, the macroglia is subdivided into astrocytes, oligodendrocytes, ependymal cells, and radial glial cells.

Astrocytes act as mediator cells between neurons and blood vessels. They mediate delicate connections to blood vessels in order to nourish neuronal cells and to establish the blood-brain barrier. They control the ECM in relation to ion and neurotransmitter concentrations. Astrocytes react to any slight CNS inflammation which produces a pathological state called astrogliosis. Astrogliosis mediates many clinical complications of CNS disorders (Purves D, Augustine GJ, Fitzpatrick D, 2001) and they are reactive to GFAP and GS (Anlauf and Derouiche, 2013).

Oligodendrocytes are the Schwann cells counterparts in the CNS. They produce myelin sheath around surrounding axons. One interesting difference is that oligodendrocytes support myelination of several axons whilst Schwann cells surround only one axon. At the onset of oligodendrocyte differentiation, the gut tumor suppressor gene adenomatous polyposis coli (Apc) is the first marker observed and reticulon-4 (Nogo-A) and MBP are observed as mature oligodendrocyte protein markers (Fancy et al., 2014). In addition, MAG, MOG, oligodendrocyte-myelin glycoprotein (OMgp), and 2′,3′-cyclic nucleotide 3′ phosphodiesterase (CNPase) act as appropriate markers for mature oligodendrocytes (Miron et al., 2011).

Ependymal cells are epithelial shaped cells that cover the ventricles of the brain, the central canal of the spinal cord and the choroid plexus. They possess specific structures called cilia which regulate CSF flow to produce a homogeneous matrix that supplies neurons with nutrients and remove unwanted metabolites. The ependymal cells are characterized by the expression of activating transcription factor 3 (ATF3) which is initially detectable in the cytoplasm of ependymal spinal stem cells although at a later time point located in the nucleus of activated cells (Mladinic et al., 2014).

Radial glial cells are bipolar shaped multifunctional cells which develop from neuroepithelium of the CNS during fetal development (Rakic, 2009). Some populations of radial glial cells remain functioning in the adult brain in the neurogenic niches. They lodge in the cerebral cortex in the ventricle zone. Apart from playing as a constructive element for neuronal routing, they are also known as precursors that develop neurons, astrocytes, and oligodendrocytes (Barry et al., 2014). During the migration, BLBP, neuregulin, and astrotactin have potential functions in neuronal guidance (Parnavelas and Nadarajah, 2001). Moreover, radial glial cells are reactive to granulocyte colony-stimulating factor receptor (G-CSFR) in prenatal murine brain development (Kirsch et al., 2008). Through radial glial cell differentiation to astrocyte cells, they gradually abolish the expression of nestin (RC2, RAT401), and

vimentin while gaining GFAP expression (Parnavelas and Nadarajah, 2001). Various studies indicate that astrocyte-specific glutamate transporter (GLAST), BLBP, and vimentin are radial glial cell protein markers. A recent investigation demonstrated that BLBP may trigger neuronal fate of radial glial cells and GLAST drives radial glial cells toward gliogenesis (Howard et al., 2008). This information suggests the multipotent capacity of radial glial cells and their importance in regenerative medicine studies.

Beside specific marker proteins that define cell type in the CNS, different regions of the CNS have specific expression patterns aligned to their function. For example, the substantia nigra is located in the midbrain and is a basal ganglia structure consisting of dopaminergic neurons (DA) (Jami et al., 2015; M. Jami et al., 2014b). It is known that Folate receptor alpha (FolR1) is a marker of dopaminergic neuronal progenitors in the midbrain and CD166 antigen (Alcam), SUN domain-containing ossification factor (Ch1), immunoglobulin superfamily member 8 (Igsf8), and GDNF family receptor alpha (GFra) represent markers for DA. Similarly, the bonafide midbrain dopaminergic lineage marker LIM homeobox transcription factor 1-alpha (Lmx1a) is expressed during prenatal murine development (Gennet et al., 2016). Other examples include fer3-like protein (Nato3) and Hes family bHLH transcription factor 1 (Hes1) (in floor plate), orthodenticle homeobox 2 (Otx2) (in forebrain and midbrain), gastrulation brain homeobox 2 (Gbx2) (in posterior and anterior rhombencephalon), nuclear receptor subfamily 4 group A member 2 (Nurr1) and pituitary homeobox 3 (Pitx3) (in ventral midbrain with a suggested role in ventral midbrain (VM) dopaminergic neuronal survival) and engrailed homeobox 1/2 (En1/2) (in the border of midbrain-hindbrain). One protein markers of the development of the telencephalon are EphrinA5 (Hegarty et al., 2013). Furthermore, high expression of paired box protein Pax-6 (Pax6) has been demonstrated in the dorsal parts of the telencephalon whereas GS homeobox 2 (Gsh2) is a protein marker of the middle part of the telencephalon and the central region of the telencephalon is specified by the high expression of NK2 homeobox (Nkx2) and oligodendrocyte transcription factor 2 (Olig2) (Rallu et al., 2002).

4. Surface ectoderm

The surface ectoderm generally develops skin, cornea, and tooth enamel. The major signaling pathways regulating lineage commitment of surface ectoderm are BMP, Wnt/β-catenin, Hedgehog, and Fgf (Qu et al., 2016). Here we discuss the biomarkers of the largest derivative of surface ectoderm, skin. Skin is composed of four different cell types including Keratinocytes, Merkel cells, Melanocytes, and Langerhans cells.

Keratinocytes are the dominant cells type in the epidermis. P63 is the transcription factor that preserves keratinocytes precursors and involucrin is essential in the terminal differentiation of keratinocytes (Green et al., 2003). One of the well-studied epidermal proteins is Keratin 19 which has been suggested as a good protein marker of human epidermal stem cells in the hair follicle bulge and the outer root sheath of hair. High expression of β1 integrin and its rapid attachment to collagen IV and fibronectin leads to a population of epidermal stem cells. A recent investigation revealed a method for isolating a population of cells containing both epidermal stem cells and transient amplifying cells (Watt, 1998). Despite low expression of β1 integrin and the slow attachment to the extracellular matrix (ECM), the use of antibodies reactive to β1 integrin, E-cadherin, β-catenin, and plakoglobin have proven to be successful in isolating relatively pure populations of epidermal stem cells (Watt, 1998). However, more recent findings have demonstrated that α6 integrin is more suitable for detecting epidermal stem cells and by using a combination of β1integrin and α6 integrin it may be possible to increase the purity of epidermal stem cells (Lavker and Sun, 2000). It is also noteworthy that other studies have introduced lectin as a suitable marker for mature keratinocytes (Reano et al., 1982). Expression of involucrin and the keratins genes are regulated by keratinocyte differentiation and multiple external stimuli such as calcium and vitamin A (Eckert and Rorket, 1989).

Merkel cells are post-mitotic neuroendocrine cutaneous cells primarily localized within the compact epidermal sensory network in the epidermal bulge. There is a great site variation in the density of Merkel cells. Merkel cells are distinguished with different putative markers of cutaneous cell type of which Cytokeratin 20 is known for the highest rate of selectivity (Polakovicova, 2011).

5. Ear

The ear anatomy is made of three distinctive structures known as the external ear (pinna and ear canal), the middle ear (tympanic membrane and ossicles), and the inner ear (semicircular canals, vestibule, and cochlea). The pinna directs sound to tympanic membrane and vibration of the tympanic membrane is transmitted to the cochlea via ossicles. In cochlea movements of fluids is converted to neural signals by specialized cells known as hair cells. Hair cells are capped with stereocilia in which the dynamics of the stereocilia is exchanged to neural signals and transmitted to the auditory cortex in the temporal lobe (Anbuhl et al., 2016; Graven and Browne, 2008).

5.1. Inner ear

The inner ear emerges from a non-neural ectoderm region named as otic placode adjacent to the caudal part of the hindbrain. The otic placode is one of the ectodermal thickenings arisen around the edge of the anterior neural plate (Whitfield, 2015). It is further developed to Cochlea (allocated to hearing) and Vestibular System (specialized for balance) (Torres and Giraldez, 1998).

The otic placode is indeed the origin of most of the inner ear cell types, including sensory neurons, sensory hair cells, supporting cells and secretory cells (Whitfield, 2015). Pax2-8, Eyes absent homolog 1- homeobox protein six (Eya1-Six1), and Sox2 transcription factors increase expression of Neurogenin1 (Neurog1) in otic progenitor cells leading toward a primary auditory nerve lineage (Gunewardene et al., 2014). Neurog1-expressed cells exfoliate from the otic vesicle to centrally create auditory nerve cells and the vestibular ganglion neurons laterally which is significantly distinguished by Insulin gene enhancer protein ISL-1 (ISLET1) (Gunewardene et al., 2014; Li et al., 2004). The exfoliated neurons down regulate the expression of Neurog1. In this stage, they could be discovered by expression of the neurogenin differentiation factor1 (Neuro D1), Brn3a, and transcription factor GATA3 during their differentiation into sensory neurons. Thereafter, the mature auditory neurons express the characteristics of pan-neuronal cytoskeletal markers NF, βIII tubulin, the vesicular glutamate transporter (VGLUT1), the tyrosine receptor kinase B (Trk B), and C (Trk C), BDNF, neurotrophin 3 (NT3), Calretinin, Tau, Neurog1, glutamate receptor 4 (GluR4), and NeuroD (Gunewardene et al., 2014; Peng et al., 2015).

Both cochlea and vestibular system consist of an intricate apparatus (hair cells) to maintain hearing ability and balance. The differentiation of hair cells begins from 10 to 12 weeks and primarily starts with inner hair cells and lastly with outer hair cells (Graven and Browne, 2008).

The inner hair cells recognized the auditory signal while outer hair cells intensify the signals. The neural signal is then carried by vestibulocochlear (VIII) cranial nerve to the brainstem (Bonito and

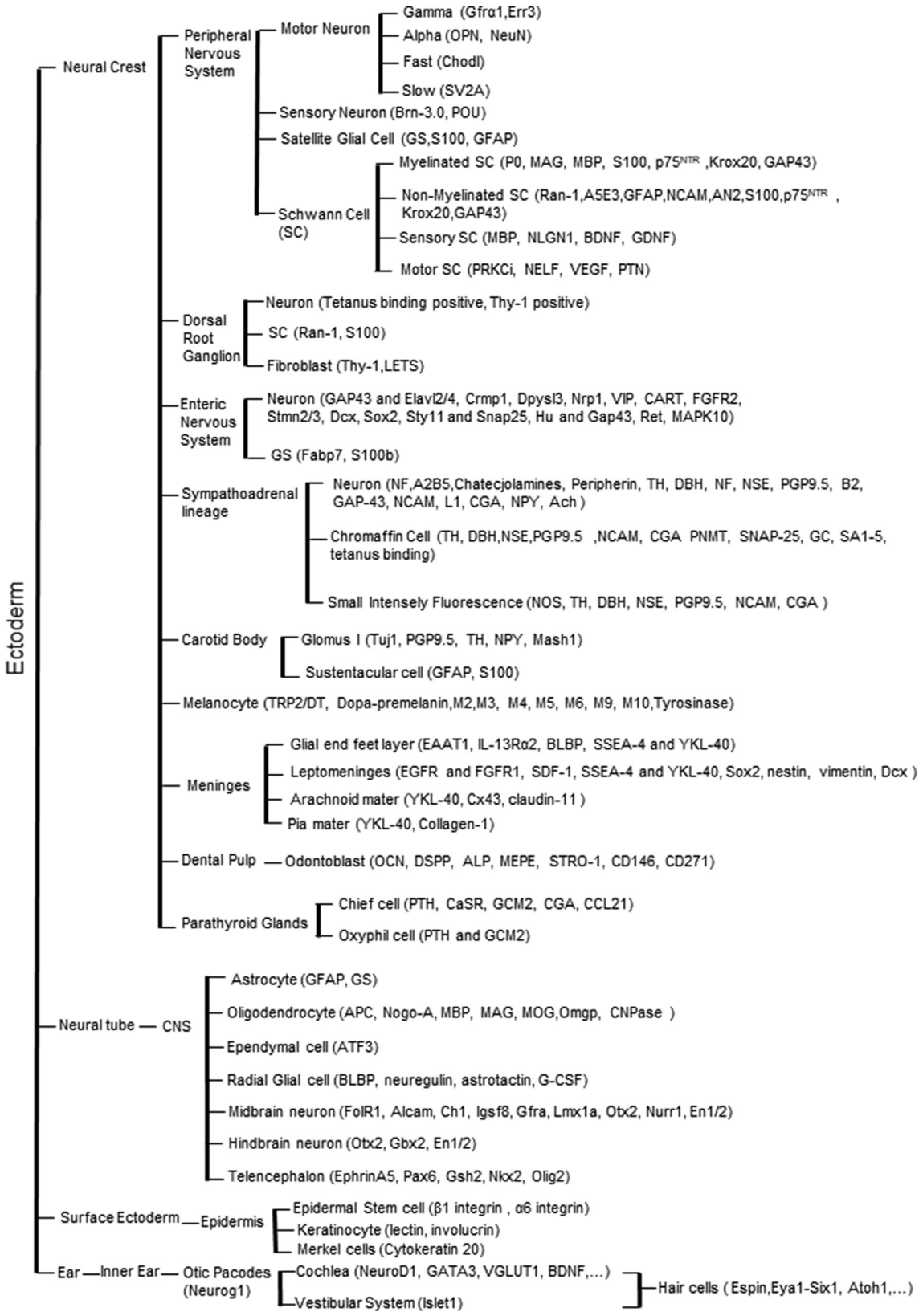

Fig. 3. Compartmentation of ectoderm derived tissues. Representative biomarkers for each tissue are included in parenthesis.

Studer, 2017).

The internal ear stem cells differentiate into pro-neural cells, non-sensory cells, and pro-sensory cells. To develop pro-neural cells from stem cells Sox2 and Neurog1 are necessary. Jagged1, Notch1, SOX2, BMP-4, FGF, and IGF-1 are essential to creating pro-sensory cells. Brn3c, Espin Barhl1, Myosin VI, VIIA, and XV are required in the terminal differentiation, maintenance and survival of hair cells (Liu et al., 2014). Brn3c is required for maturation and survival of inner ear hair cells (Xiang et al., 1998). Prestin is the prominent candidate of cochlear outer hair cells biomarkers. It is a member of anion transporters that is expressed in the lateral membrane of cochlear outer hair cells. It is responsible for electromotility of outer hair cells (Liberman et al., 2002). Lack of functional Prestin in the knock out mice leads to sever hearing loss. *In vivo* studies of lack of outer hair cells presented an upregulation of Prestin in the remaining outer hair cells to retaliate the loss of outer hair cells in the cochlea and reduced force production (Xia et al., 2013). Beside upregulation in the cellular level, the amount of Prestin release in the serum is also increased by cochlear damage. Thus it is considered as an early indicator of cochlear trauma (Dogan et al., 2018).

Myosin VII-A along with Espin, parvalbumin alpha 3, and AchRα9 are characterized as differentiated protein biomarkers of Hair cells (Li et al., 2003). Moreover, as recent studies of stem cell differentiation into hair cells have reported parvalbumin alpha3, Pou4f3 (Brn3c), unconventional myosin-XV (MyoXV), Espin (Q. Liu et al., 2015a), Eya1-Six1, protein atonal homolog 1 (Atoh1), Sox2, and MyoVIIA are of the most recognized markers of hair cells (Ahmed et al., 2012; Mahmoudian-Sani et al., 2018). Atoh1, Jagged2, and Delta1 direct the differentiation process toward hair cells (Liu et al., 2014).

Other putative hair cells biomarkers are discovered by RNA-seq data on in-vitro studies which are beyond the capacity of this article to discuss (Taylor et al., 2018).

Inner and outer hair cells are separated from each other by supporting cells. Supporting cells have the same origin as the hair cells' with physiological and morphological differences. These differences are also observed between inner and outer hair cells. For instance, inner hair cells are round and small but outer hair cells are long and thin. Inner hair cells are arrayed in a single row and outer hair cells are arrayed in three parallel rows. Furthermore, damage to the inner hair cells causes sensory neural hearing loss (SNHL) but any trauma to the outer hair cells will affect qualities of cochlear signals to the brain (Devarajan et al., 2011). Surveys such as that conducted by Li et al. have shown that inner and outer hair cells transcriptome profiles are distinctively dissimilar. For example Calb2, Calm1, Nhih1, Otof, are significantly expressed in inner hair cells by a much higher rate than outer hair cells. While Lmod3, Ptgir and Ptprq are exclusively expressed in outer hair cells more than inner hair cells (Li et al., 2018).

The mammalian auditory system has two main types of supporting cells: the Deiter's cells support the outer hair cells at the base, and the Pillar cells facilitate the formation of the reticular lamina, which isolates the stereocilia from their cell bodies. A few other supporting cells types include inner Phalangeal cells, Hensen's cells, Claudius cells and Boettcher cells that are specialized cells and are not associated with hair cells (White et al., 2006). Supporting cells of the vestibular system have not yet fully understood (Matsui et al., 2005; Matsui and Ryals, 2005).

BETA2/Neurod1, Jagged2 are key regulators of supporting cell fate (Wang et al., 2010; Zine et al., 2000). Cyclin-dependent kinase (cdk) inhibitors (p27kip1, p19Ink4d, and Rb) and Notch Signaling also interfere with hair cell differentiation and establishes supporting cell fate in the differentiation process (Devarajan et al., 2011; Liu et al., 2014). Both hair and supporting cells are derived from pro-sensory progenitors. (Liu et al., 2014). Transcription factors Hes1-5 contributes to the development of supporting cells by generation of supporting cells by ceasing Atoh1 expression. However, TGF-α promotes trans-differentiation of supporting cells into hair cells (Liu et al., 2014).

Ectoderm layer is composed of different tissue with diversely specialized biomarkers imprinting their territories. Not all tissues are embedded in this review. An outline of tissue related biomarkers is drawn in Fig. 3.

6. Conclusion

In this review we provided a detailed picture of biomarkers in the normal form of neural tissues and some other ectodermal derivatives to exclusively put the protein biomarkers on the map of research and clinic. Biomarkers are in fact very good indicators of biological and pathogenic processes and can be used to evaluate ongoing molecular phenomena within the cells. In this regard, a brighter overview on the protein biomarker expression profile in different neural tissues would definitely benefit other studies dealing with the pathogenic processes and/or pharmacological responses to therapeutic interventions for clinical or diagnostic purposes.

The formation of the neural crest, neural tube and surface ectoderm provides early specific expression pattern of protein markers in different parts of fetal tissues. As an example, protein markers that characterize the PNS neuronal lineage include OPN, SV2A, Chodl, just to mention a few. Furthermore, the ENS neuronal cells become distinct by expression of Elavl2/4, Crmp1, Nrp1, and Stmn2/3. Some non-neuronal lineages, such as melanocytes, are distinguished by TRP2/DT, Dopa-pre-melanin, and tyrosine in different developmental stages. Even different zones of the brain are distinguishable by a series of distinct protein markers. For example, the midbrain is identified by Alcam, Igsf8, Gfra expression. Moreover, the telencephalon is characterized by the expression of Gsh2, Nkx2, and Olig2. In order to gain a thorough understanding of cell development (differentiation, regeneration, and dedifferentiation) from zygote to specialized tissues there is a need to further identify and characterize protein markers at each stage of neural cell development and from this create a comprehensive protein network blueprint.

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Availability of data and materials

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Conflict of interests

The authors declare that they have no conflict of interests.

Appendix A. Supplementary data

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