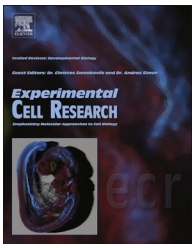
EXPERIMENTAL CELL RESEARCH 321 (2014) 17–24

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/yexcr



Review Article

Non-canonical functions of the peripheral nerve

*Markéta Kaucká**, *Igor Adameyko**

Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden

ARTICLE INFORMATION

Article Chronology:
Received 29 July 2013
Received in revised form
1 October 2013
Accepted 5 October 2013
Available online 15 October 2013

Keywords:
Peripheral nerve
Schwann cells
Multipotency
Regeneration
Melanocyte

ABSTRACT

The peripheral nervous system (PNS) is complex and omnipresent. The PNS targets all parts of the body starting from early stages of embryonic development, and in large part, is derived from multipotent migratory neural crest stem cells. Current opinion mostly perceives the PNS as a means of communication and information exchange between the central nervous system, the rest of the body and the environment. Additionally, the PNS is largely associated with autonomic control. Being an "alternative brain" it provides local regulation of processes in organs. However, it has become evident in recent years that in addition to these main canonical functions the PNS possesses a number of other important roles in development and homeostasis of targeted tissues, for instance, in nerve-dependent regeneration. The PNS represents a niche that hosts neural crest-derived peripheral glial cells, or, in other words, neural crest-like multipotent cells throughout the entire body. These multipotent nerve-adjacent cells can be reprogrammed in vivo and play a number of roles from creating pigmentation to controlling regeneration of a limb in amphibians or skin in rodents. In the current review we outline newly emerged, non-canonical functions of the PNS and briefly describe cellular and molecular aspects of these alternative functions.

Contents

Introduction to the PNS

The peripheral nervous system (PNS) is one of the largest and most complex structures in the body. Multiple components of the PNS are produced at various stages of embryonic development. In fact, PNS is a collective name for a number of heterogeneous entities including nerves, sensory receptors and ganglia outside of the central nervous system (CNS) that is represented by brain and

*Corresponding authors.
E-mail addresses: marketa.kaucka@ki.se (M. Kaucká), igor.adameyko@ki.se (I. Adameyko).

0014-4827/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.yexcr.2013.10.004

spinal cord. The main functions of the PNS are mainly perceived to be a connection between CNS and peripheral structures, and last but not least, autonomous regulation of local physiology in the tissue.

The PNS is commonly divided into three branches according to the function they are fulfilling: the autonomic nervous system (ANS), somatic nervous system (SNS) and enteric nervous system (ENS). The ANS is a key player in maintaining homeostasis and acts mainly at a subconscious level. Neurons of the ANS innervate smooth muscles, cardiac muscles and various glands and thereby control processes such as heart and respiratory rate, levels of O_2, CO_2 and blood glucose, digestion, perspiration, etc. The ANS is composed of both sensory, inter- and motor neurons. Autonomic sensory neurons mediate informational flow from the autonomic sensory receptors in the visceral organs to the CNS. The opposite direction of information transfer is mediated by autonomic motor neurons, which results e.g. in smooth and cardiac muscle contraction and secretion from the glands. Furthermore, the ANS is divided into the sympathetic nervous system arranging the fast, emergency actions, and the parasympathetic branch mediating a slower, dampening response. The SNS is linked to the voluntary control of the body, with its neurons innervating the skeletal muscles and driving the movement. The SNS also participates in the reflex arc, which creates an automatic connection between sensory information entry and specific motor activity reaction. The ENS is comprised of a surprisingly high number of neurons that innervate the whole gastrointestinal (GI) tract. The ENS possesses both sensory and motor neurons, and thus, can operate independently of the CNS. The main role of the ENS is to control secretion of acids and enzymes, contraction of the smooth muscles and monitoring the chemical environment of the GI tract. Similar to the ANS, the ENS drives visceral processes [15]. In summary, the different parts of the PNS innervate all destinations in the body including internal organs and peripheral tissues.

Importantly, the peripheral innervation of the body develops very early in the embryo (Fig. 1). Already at embryonic days 10.5–11.5 in the mouse and around days 4–5 in chick, the peripheral nerves enter the limb buds [28,31]. During early embryonic development the PNS originates from three main sources: neurogenic placodes, CNS (for instance, motor nerves) and multipotent and migratory neural crest cells (NCCs) [29], a population that gives rise to more than 100 cell types, including a wide array of mesenchymal components. NCCs originate from the dorsal lips of the folding neural plate and after delamination they migrate along specific pathways, giving rise to a broad range of cell types (Fig. 1B). The NCCs can differentiate into sensory, sympathetic and parasympathetic neurons and glia of the PNS, neurosecretory cells of the adrenal gland and melanocytes [30]. In addition to neuro-glial fates, neural crest cells produce a variety of mesenchymal types including fibroblasts, adipocytes, smooth muscle cells, bone marrow stromal cells, chondrocytes and osteocytes.

Under certain circumstances, NCC-derived cells can dedifferentiate, proliferate and replace other cell types. One of the important cell types produced by the neural crest are the peripheral glial cells that can be defined by their dependence on contact with nerve fibers [19]. Peripheral glial cells protect and support neurons and facilitate fast propagation of action potentials. Within the mature PNS, glial cells are represented by myelinating and non-myelinating Schwann cells, terminal Schwann cells and also by satellite glial cells that are located in the ganglia. As we review below, peripheral glial cells are multipotent in vitro and in vivo similar to NCCs, which renders them as perfect candidates for a number of non-canonical functions related to innervation.

It is becoming evident that many processes in the developing embryo and in the adult organism are nerve-dependent. Since the PNS targets every area of the body, beginning from early developmental stages, multipotent cells associated with the PNS, including glia, might have important developmental and regenerative functions. It seems that the PNS not only transduces and processes information, but also hosts cells retaining at least some of the plasticity of the original neural crest lineage.

Nerve as a local provider of multipotent neural crest-like cells

Even before the onset of gliogenesis in the CNS, the neural crest already gives rise to early glial cells, which are found along the axons of nascent peripheral nerves. These early glia are called Schwann cell precursors (SCPs) and they eventually reach all parts of the body together with the outgrowing nerves. SCPs largely differentiate into mature myelinating and non-myelinating glial cells, which account for protection and trophic support of the perinatal nerves. Recently, a novel function of SCPs was discovered: SCPs were found to serve as a developmental source of non-glial cell types.

The lineage relationship between functionally distant cell types originating from the neural crest was not clear for many years. It was thought that melanoblasts, the precursors of the pigment cells, are derived directly from neural crest cells that migrate from the dorsal neural tube under the epidermis, and that the melanocyte fate is established early after the delamination. Multipotent potential of SCPs was suggested earlier by several groups that showed the ability of SCPs to give rise or to melanocytes, neurons, Schwann cells and smooth muscle cells in vitro [11,38]. The use of lineage tracing, gene ablation and microsurgery in mouse and chick embryos revealed an alternative origin of melanocytes and uncovered the unique plasticity of Schwann cell precursors both in vivo and in vitro [2,34] (Fig. 1C). Genetic tracing of adult myelinating Schwann cells upon nerve injury revealed that these cells retain the ability to dedifferentiate, re-enter the cell cycle and give rise to adult pigmentation. The Schwann cell versus melanocyte fate decision seems to be dependent on Foxd3, Sox2 and is strongly influenced by contact with peripheral nerve [1–3,34]. The maintenance of SCP fate is strictly dependent on Nrg1 ligand provided by the nerve. Nrg1 signals through the Erbb2/Erbb3 heterodimer tyrosine kinase receptors on the cell surface of SCP cell and supports survival and a glial phenotype [6]. Fgf2 and Notch signaling is further supporting the maturation of SCP into the immature Schwann cell. However, the transition from an immature Schwann cell into both myelinating and non-myelinating Schwann cell fate is still considered to be reversible.

For a long time researchers were speculating where the melanocyte stem cells reside in fish. Zebrafish serves as a good model for exploring the origin of these stem cells especially given the fact that adult pigmentation requires pigment pattern metamorphosis. Melanophores are fish homologs of mammalian