Glia-neuronal transitions in development: significance in medical research and treatment of pathologies

D Kamenev¹, E Kotsyuba¹, A Kalachev¹, V Milichko², V Dyachuk¹,²*¹

¹ National Scientific Center of Marine Biology, Far Eastern Branch, Russian Academy of Sciences, Vladivostok 690041, Russia
² ITMO University, St. Petersburg 197101, Russia

Abstract. The questions of how autonomic neurons and their fibers select the target organs and whether parasympathetic innervation affects the development and growth of diverse organs are still open. We hypothesize that glia-neuronal transitions in development is crucial for correct development and homeostasis of innervated tissues in mice. The result of this preliminary experiment using genetic tracing showed that the mice mutants with lack autonomic ganglia indeed have a problem with development of target organs and support idea that autonomic nervous system directly involved in innervated organs morphogenesis.

Although the autonomic nervous systems regulate the functions of numerous internal organs in adult mammals, the role of innervations in the development of target organs such as glands, the heart, and blood vessels remains to be explored. The submandibular gland (SMG) of the mouse is the most widely used ex vivo model for investigation of the role of peripheral nerves in epithelial morphogenesis and the parasympathetic nerve innervating this gland develops in parallel with the salivary parenchyma [1] before sympathetic stimulation is even present [2]. Moreover, removal of the parasympathetic ganglion from mice was recently found to reduce the number of their epithelial progenitor cells, thereby perturbing epithelial morphogenesis [3, 4]. Indeed, the same effect was achieved with chemical inhibition of acetylcholine (ACh) release, antagonists of muscarinic receptors and gene knockdown of these same receptors in the epithelium [5]. Our previous data changes current views concerning the development of the parasympathetic nervous system is formed in development. We have shown that parasympathetic ganglia arise from Schwann cells that migrate along nerve fibers to peripheral targets and give rise not only to non-neuronal cells but also and to differentiate into parasympathetic neurons within a short period during embryonic development. The nerve tracks involved include the very same fibers that ultimately innervate the parasympathetic neurons once they reach their destination and mature [6]. Moreover, a significant population of the mesenchymal stem cells that play a role in the development, self-renewal, and repair of a tooth is derived from glia associated with peripheral nerves [7].

Apparently, the parasympathetic innervation maintains a reservoir of undifferentiated progenitor cells in the SMG through ACh signaling and the receptor for epidermal growth factor [8]. Recently, parasympathetic innervation was found to coordinate tubulogenesis in the developing salivary gland via signaling by vasoactive intestinal peptide (VIP-) activated cyclic adenosine 3’,5’-monophosphate (cAMP) and protein kinase A (VIP/cAMP/PKA),...
rather than ACh [9]. However, Bowel and colleagues (2014) showed that the airway branching of *Drosophila* and mouse embryo persists even when cholinergic neurotransmission is blocked [10]. Thus, the neurotransmitters or/and neurotrophic factors released by nerves that support epithelial stem cells and promote their differentiation in the SMG remain unidentified.

Another important recent observation is that in *ex vivo* culture induction of apoptosis in parasympathetic neurons of the submandibular ganglia by irradiation eliminates the capacity of both the murine and human gland to regenerate. Moreover, the neurotrophic factor neurturin improves regeneration and restores parasympathetic function after damage, possibly by maintaining a pool of undifferentiated epithelial progenitor cells [8]. In fact, neurotrophic factors released by parasympathetic neurons are vital both for neuronal survival and recovery of the target tissues [4, 11, 12], but the underlying mechanisms remain somewhat unclear.

Obviously, that glia-neuronal transitions discovered in mice development has medical significance and improve our understanding of innervation-dependent pathological mechanisms in various human tissues. The more than twenty different forms of autonomic dysfunction presently known give rise to symptoms such as heartburn and intestinal gas, flatulence, diarrhea, constipation, colitis, dry mouth, heart failure, difficulties with urination, and, last but not the least, sexual dysfunction. The exact mechanisms underlying these problems, which have not yet been elucidated, may involve stem cell niches and physiological tuning. In addition, autonomic neurons may play a negative role in the development of cancer in its target cells.

References:

[1] Coughlin M D 1975 *Dev Biol* 43 140-158.
[2] Bottaro B and Cutler L S 1984 *Arch Oral Biol.* 29 237-242.
[3] Knox S M, Lombaert I M, Reed X, Vitale-Cross L, Gutkind J S and Hoffman M P 2010 *Science* 329 1645-1647.
[4] Ferreira J N and Hoffman M P 2013 *Organogenesis* 9 199-205.
[5] Holmberg K V and Hoffman M P 2014 *Monogr Oral Sci.* 24 1-13.
[6] Dyachuk V, Furlan A, Shahidi M K, Giovenco M, Kaukua N, Konstantinidou C, Pachnis V, Memic F, Marklund U, Müller T, Birchmeier C, Fried K, Ernfors P and Adameyko I 2014 *Science* 345 82-87.
[7] Kaukua N, Shahidi M K, Konstantinidou C, Dyachuk V, Kaucka M, Furlan A, An Z, Wang L, Hultman I, Ahrlund-Richter L, Blom H, Brismar H, Lopes N A, Pachnis V, Suter U, Clevers H, Thesleff I, Sharpe P, Ernfors P, Fried K and Adameyko I 2014 *Nature* 513 551-554.
[8] Knox S M, Lombaert I M, Haddock C L, Abrams S R, Cotrim A, Wilson A J and Hoffman M P 2013 *Nat Commun.* 4 1494.
[9] Nedvetsky P I, Emmerson E, Finley J K, Ettinger A, Cruz-Pacheco N, Prochazka J, Haddock C L, Northrup E, Hodges C, Mostov K E, Hoffman M P and Knox S M 2014 *Dev Cell.* 30 449-462.
[10] Bower D V, Lee H K, Lansford R, Zinn K, Warburton D, Fraser S E and Jesudason E C 2014 *BMC Biol.* 12 92.
[11] Enomoto H, Heuckeroth R O, Golden J P, Johnson E M and Milbrandt J 2000 *Development* 127 4877-4889.
[12] Airaksinen M S and Saarma M 2002 *Nat Rev Neurosci.* 3 383-394.

Acknowledgments

The work was financially supported by the Russian Science Foundation, grants №18-75-10005 and 17-19-01637.