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Autonomic Neuroscience: Basic and Clinical 126–127 (2006) 225–231

AUTONOMIC NEUROSCIENCE: Basic & Clinical

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Review

Perspectives on integration of cell extrinsic and cell intrinsic pathways of signaling required for differentiation of noradrenergic sympathetic ganglion neurons

Anjali A. Sarkar, Marthe J. Howard *

Department of Neurosciences, Program in Cellular and Molecular Neurobiology, Medical University of Ohio, 3000 Arlington Avenue, Toledo, OH 43614, USA

Received 8 January 2006; received in revised form 21 February 2006; accepted 27 February 2006

Abstract

This review presents an analysis of current research aimed at deciphering the interplay of cell extrinsic and intrinsic signals required for specification and differentiation of noradrenergic sympathetic ganglion neurons. The development of noradrenergic sympathetic ganglion neurons depends upon expression of a core set of DNA regulatory molecules, including the Phox2 homeodomain proteins and the basic helix–loop–helix proteins, HAND2 and MASH1 whose expression is dependent upon cell extrinsic cues. Both bone morphogenetic protein(s) and cAMP have an integral role in the specification/differentiation of noradrenergic sympathetic ganglion neurons but how signaling downstream of these molecules is integrated and identification of their particular functions is just beginning to be elucidated. Data currently available suggests a model with BMP providing both instructive and permissive cues in a pathway integrated by cAMP and MAPK by activation of both canonical and non-canonical intracellular signaling cascades.
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Keywords: HAND2; Phox2a; PKA; BMP; Intracellular signaling; Noradrenergic sympathetic ganglion neurons; cAMP

Contents

1. Introduction

Neurons share many features in common but are distinguished by expression of phenotypic characteristics that define their specific function, location or connectivity. One aspect of neuronal diversity, neurotransmitter phenotype, is a hallmark of neuron function that has proven extremely useful as a tool for defining mechanisms of neural development. During development, generation of neuronal diversity involves integration of extrinsic and intrinsic instructive cues resulting in expression of core sets of regulatory molecules. For neural crest-derived peripheral

* Corresponding author. Tel.: +1 419 383 5439; fax: +1 419 383 3008.
E-mail address: mhoward@meduohio.edu (M.J. Howard).

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doi:10.1016/j.autneu.2006.02.029

autonomic neurons, a core of DNA binding proteins required for the development of sympathetic, parasympathetic and enteric neurons has been identified. This transcription factor network includes the homeodomain (HD) factor(s) Phox2b and Phox2a and the basic helix–loop–helix (bHLH) factor MASH1 (CASH). The specificity of response to expression of these transcriptional regulators is modified/modulated by the recruitment of additional transcription factors in a subtype-specific manner. For autonomic neurons, we and others have shown that expression of the basic helix–loop–helix (bHLH) DNA binding protein HAND2 likely specifies neuronal precursors as noradrenergic sympathetic ganglion neurons (Howard et al., 2000; Muller and Rohrer, 2002; Liu et al., 2005; reviewed in Howard, 2005).

The HAND2 gene is a novel member of the TWIST family of bHLH transcription factors (Cross et al., 1995;Hollenberg et al., 1995), whose neuronal expression is confined to neurons in sympathetic and enteric ganglia (Cserjesi et al., 1995; Howard et al., 1999; Wu and Howard, 2002). Loss-of-function studies demonstrate a developmental requirement for HAND2 in various aspects of cell specification, differentiation or patterning in the heart, limb bud, cranio-facial bone and noradrenergic sympathetic ganglion neurons; all structures with neural crest cell contributions. Interestingly, for many of these structures, expression of HAND2 is regulated in response to signaling initiated by bone morphogenetic protein(s) (BMP) (Reissmann et al., 1996; Schneider et al., 1999; Fernandez et al., 2000; Howard et al., 2000; te Welcher et al., 2002; Lien et al., 2002). It is thus a challenge to identify additional instructive and/or permissive cues imparting specificity of response to HAND2 in the various cell types requiring its function for acquisition of cell type-specific attributes.

A large body of data suggest that determination of neurotransmitter identity is closely linked to other phenotypic characteristics specified during neurogenesis (Liu et al., 2005; reviewed in Bertrand et al., 2002). Investigations into how neurotransmitter choice is determined have revealed a molecular mechanism suggesting coordinate expression of pan-neuronal genes with cell type-specific genes. An integral part of the specification/differentiation of noradrenergic sympathetic ganglion neurons is the apparent dual function of HAND2 to link aspects of neuron specification and phenotypic choice. Our current model suggests that HAND2 and Phox2 proteins together link aspects of neurogenesis with neurotransmitter identity and function (Liu et al., 2005). The molecular features of this linkage have begun to be elucidated but remain an intense area of investigation. This mini-review will thus focus on the intersection of cell extrinsic and intrinsic instructive factors shown to be sufficient and/or necessary for the development of noradrenergic sympathetic ganglion neurons linking specification, cell type-specific gene expression and function of biosynthetic enzymes regulating norepinephrine synthesis.

2. Extrinsic cell signaling in development of noradrenergic sympathetic ganglion neurons

Two groups of factors, bone morphogenetic proteins (BMPs) and Wnts, have been established as extrinsic signals imparting instructive information necessary for fate determination of neural crest-derived neural progenitors (Howard and Gershon, 1993; Shah et al., 1996; Reissmann et al., 1996; Schneider et al., 1999; Howard et al., 2000; Hagedorn et al., 2000; Morrison et al., 1999; Hari et al., 2002; Paratore et al., 2002; Lee et al., 2004; Kléber and Sommer, 2004; Kléber et al., 2005). Wnts are instructive for precursors of neural crest-derived sensory neurons (Hari et al., 2002; Lee et al., 2004; Ille and Sommer, 2005) and BMPs are instructive for autonomic neuron precursors (Reissmann et al., 1996; Shah et al., 1996; Schneider et al., 1999; Howard et al., 2000; Liu et al., 2005). Interestingly, together Wnt and BMP support maintenance of neural crest-derived cells in a pluripotent but non-differentiated state (Kléber et al., 2005). These factors each independently antagonize the activity of the other providing a possible explanation for the paradox that all trunk level neural crest-derived cells differentiate as neither sensory nor autonomic neurons (cf. Howard, 2005; Kléber et al., 2005). The instructive information imparted by Wnts and BMPs may not be simply reflected in expression of downstream genes. In the autonomic neuron lineage, BMP signaling appears to impart both instructive and permissive cues (Liu et al., 2005). The recent description of non-canonical BMP-mediated intracellular signaling via PKA activity suggests that linear models describing intersection of cell extrinsic and cell intrinsic patterns of response may not fully account for specification and differentiation.

3. Intracellular pathways relaying extrinsic pro-differentiation signals

One aspect of signaling mediated downstream of BMPs is expression of the aforementioned core DNA regulatory network (Fig. 1). Although all members of this network may not as yet have been identified, the network is comprised of two parallel pathways: Phox2b is the “initiator” in one path and MASH1(CASH) in the other. Recent data suggest that Phox2b is the master regulator for generation of autonomic neurons and the major noradrenergic centers in the CNS (Coppola et al., 2005). It is thus very interesting to try to parse out the mechanisms underlying generation of neuronal diversity in the autonomic nervous system. Attention has focused on identifying the intracellular signaling molecules that link expression of the core DNA binding factor network and the resulting effects of their expression on either neurogenesis or expression of noradrenergic marker genes.

In the developing sympathetic chain ganglia, trunk neural crest-derived cells generate noradrenergic and a limited number of cholinergic neurons while mesencephalic neural

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