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Review

The molecular mechanisms controlling morphogenesis and wiring of the habenula

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ABSTRACT

The habenula is an evolutionarily conserved brain region comprising bilaterally paired nuclei that plays a key role in processing reward information and mediating aversive responses to negative stimuli. An important aspect underlying habenula function is relaying information between forebrain and mid- and hindbrain areas. This is mediated by its complex organization into multiple subdomains and corresponding complexity in circuit organization. Additionally, in many species habenular nuclei display left-right differences at the anatomical and functional level. In order to ensure proper functional organization of habenular circuitry, sophisticated molecular programs control the morphogenesis and wiring of the habenula during development. Knowledge of how these mechanisms shape the habenula is crucial for obtaining a complete understanding of this brain region and can provide invaluable tools to study habenula evolution and function. In this review we will discuss how these molecular mechanisms pattern the early embryonic nervous system and control the formation of the habenula, how they shape its asymmetric organization, and how these mechanisms ensure proper wiring of the habenular circuit. Finally, we will address unexplored aspects of habenula development and how these may direct future research.

1. Introduction

The habenula is an evolutionarily conserved brain region comprising bilaterally paired nuclei that play a key role in connecting forebrain with mid- and hindbrain areas. As part of the epithalamus, it receives input from limbic areas and the basal ganglia through the stria medullaris, while its efferents form the fasciculus retroflexus (FR), which projects to areas in the mid- and hindbrain. The habenula is comprised of two distinct subdomains: the medial habenula (mHb) and lateral habenula (lHb) (Bianco and Wilson, 2009). Homologs for both these subdomains, including their connectivity patterns, have been identified in mammalian and non-mammalian species. The evolutionary conservation of this circuitry, from phylogenetically old animals such as the lamprey to modern humans, suggests a crucial role for the habenula in controlling brain function and behavior (Aizawa et al., 2011; Concha and Wilson, 2001). Indeed, the habenula regulates monoaminergic systems, i.e. dopaminergic, serotonergic, and noradrenergic systems (Lecourtier and Kelly, 2007). As a result, it plays a crucial role in behaviors such as value-based decision making and avoidance of negative stimuli. Moreover, the dopaminergic and serotonergic systems have been implicated in multiple neurological diseases and psychiatric disorders. Recent studies have suggested a potential role for the habenula in these diseases, including major depressive disorder (MDD) and schizophrenia (Hikosaka, 2010; Lawson et al., 2016; Proulx et al., 2014).

Over the course of evolution, the habenular circuit continued to be critically embedded in brains of increasing complexity. Molecular programs that control development and wiring of this brain region act to ensure proper functional organization and integration. Insights into the molecular mechanisms that dictate the development of the habenula are therefore invaluable for obtaining a complete understanding of the role of this brain region in both the healthy and diseased brain. In addition, studying such an evolutionarily conserved brain region allows for unique insight into common molecular principles that govern brain development, and simultaneously furthers our understanding of how these mechanisms have evolved to govern the development of the astonishing complex human brain. Finally, knowledge of the genetic, molecular and cellular mechanisms that control formation, wiring and function of the habenula will provide invaluable tools to manipulate and probe its role in regulating brain function and behavior.

Here, we will review the currently available data on the molecular mechanisms that underlie development and function of the habenula.

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We will discuss how these mechanisms ensure proper organization and function of habenular circuitry and address unexplored avenues that may provide directions for future research.

2. Ontogeny and asymmetrical development of the habenula

During early embryonic development, the neural tube consists of distinct segments, known as neuromeres, that form along the rostrocaudal axis (Rubenstein et al., 1994). These neuromeres function as developmental compartments that allow for regional expression of extracellular signals and transcription factors. Together, these molecular signals control the cell fate of progenitors and direct patterning of the brain into distinct regions. Habenular nuclei form from the alar plate of prosomere 2 (p2), a neuromere located within the developing caudal forebrain. Interestingly, the habenula develops asymmetrically with distinct anatomical differences between the left and right nuclei. This asymmetry has been shown to play an important functional role in various types of behavior. In the next section, we will discuss the molecular mechanisms that control the morphogenesis of the habenula and explain how these mechanisms lead to the asymmetrical organization of the habenular nuclei.

2.1. Early patterning of the nervous system is crucial for the formation of the habenula

An important patterning event in p2 is the emergence of an epithalamic subdomain that is distinct from the nearby thalamic domain. While epithalamic and thalamic progenitors in p2 share expression of many of the known molecules that control cell fate specification, recent studies have shown how extracellular signals and regional expression of transcription factors selectively steer progenitors towards an epithalamic or thalamic cell fate (Chatterjee et al., 2014; Mallika et al., 2015; Martinez-Ferre and Martinez, 2009). An important regulator for establishing the epithalamic domain within p2 is fibroblast growth factor 8 (Fgf8) (Martinez-Ferre and Martinez, 2009). Hypomorphic mice in which Fgf8 levels are severely reduced show a decrease in the size of the developing epithalamus, which was found to be caused by a decrease in cell proliferation. Interestingly, in zebrafish, Fgf8a was found to directly regulate expression of developing brain homeobox 1b (Dbx1b) (Dean et al., 2014). Dbx1 is highly enriched in the developing habenular nuclei of both mouse and zebrafish (Dean et al., 2014; Vue et al., 2007), and was previously shown to be an important regulator of neuronal cell fate specification in various brain regions (Bouvier et al., 2010; Gray et al., 2010; Inamata and Shirasaki, 2014; Pierani et al., 2001; Sokolowski et al., 2015). Although the function of Dbx1 in the development of the habenula remains unknown, these results hint at a role for Dbx1 in acting downstream of Fgf8 to control differentiation and proliferation of habenular progenitors. In addition to an effect on Dbx1, reduction of Fgf8 levels in developing mouse embryos also caused an expansion of Wnt1 expression into the dorsal roof of p2 and a reduction in Wnt3 expression (Martinez-Ferre and Martinez, 2009). Several studies have found evidence for the requirement of the Wnt pathway in the development of the habenula (Beretta et al., 2013; Kuan et al., 2015). Zebrafish lacking the Wnt signaling component transcription factor 7 like 2 (tcf7l2) no longer form the ventral subdomain of the habenula. Wntless zebrafish mutants, in which Wnt signaling is reduced, have smaller dorsal subdomains, which likely results from a reduced formation and/or migration of habenular progenitors. However, the precise role of different members of the Wnt pathway, and whether they act as positive or negative regulators of habenula development, remains unclear. Together these studies suggest that Fgf8 may act as a master regulator to control patterning in the early developing nervous system crucial for proper habenular morphogenesis.

The molecular identity of the thalamus is acquired by selective expression of the transcription factor gastrulation brain homeobox 2 (Gbx2) (Mallika et al., 2015). Interestingly, knocking out Gbx2 in mouse partially changes the molecular profile from thalamic to epithalamic, and thalamic neurons lacking Gbx2 aberrantly extend their axons through the FR, the major output bundle of the habenula (Chatterjee et al., 2012; Mallika et al., 2015). Similarly, Sonic hedgehog (Shh) expression at the mid-diencephalic organizer (MDO), located at the border between p2 and p3, suppresses an epithalamic cell fate and promotes a thalamic identity. Interestingly, knocking out the transcription factor Pax6, a member of the paired box (Pax) protein family, increases the size of the MDO/Shh region in both mice and zebrafish, and results in expansion of the thalamus and prethalamus at the expense of the developing epithalamus. In contrast, when Shh signaling was reduced, the epithalamic region, including the habenula, was increased and multiple FR bundles could be observed (Chatterjee et al., 2014). Using a combination of C-X-C chemokine receptor type 4b (Cxcr4b) and brain-specific homeobox/POU domain protein 3A (Brn3a) as markers for habenular progenitors and post-mitotic habenular neurons, respectively, a recent study confirmed the importance of Pax6a and Shh for development of the habenula in zebrafish (Halluin et al., 2016). In mutants for the receptor required for Hedgehog signaling (*smoothened*; *smo*^{hi229}) or sonic hedgehog (shha^{tbx392}), a reduction or loss of habenular neurogenesis was observed. In addition, treatment with cyclopamine to disrupt the Hedgehog pathway resulted in impaired habenula neurogenesis. Surprisingly, cyclopamine treatment also reduced Pax6a levels, suggesting that Shh acts upstream of Pax6a. Morpholinos targeted against Pax6a furthermore revealed that Pax6a expression is required for expression of neurogenin 1 (Neurog1) and neuronal differentiation 4 (Neurod4), two transcription factors that together are crucial for habenula neurogenesis. These data suggest that Shh-Pax6a-Neurog1/NeuroD4 signaling critically regulates habenula neurogenesis. However, with Shh acting upstream of Pax6a, these results are in apparent conflict with an earlier study by Chatterjee et al., 2014. Similar results have been reported previously and together these studies suggest a complex, mutual antagonistic effect of Shh and Pax6 during early embryonic nervous system patterning (Caballero et al., 2014; Ericson et al., 1997; Pratt et al., 2000; Robertshaw et al., 2013). Shh/Pax6 signaling may be highly dependent on the anatomical and cellular context in which these molecules function and, depending on this context, influence various developmental processes, such as patterning and neurogenesis (Chatterjee et al., 2014; Halluin et al., 2016).

Interestingly, some of the pathways described in this section also play an important role in defining the asymmetric organization of the habenula. As we will discuss in the next section, these studies confirm that the habenula is an excellent model for studying the molecular pathways underlying lateralization of the brain.

2.2. Asymmetry in the development and organization of the habenula

In many species the habenular nuclei exhibit left-right asymmetry in size, neuroanatomical organization, and connectivity (Aizawa et al., 2005; Bianco et al., 2008; Bianco and Wilson, 2009; Concha and Wilson, 2001; Hong et al., 2013; Ichijo et al., 2017; Turner et al., 2016). While this is most apparent in fish, amphibians, and reptiles, asymmetries have also been reported for mammalian species, including mice and humans (Fig. 1; (Ahumada-Galleguillos et al., 2016; Hétu et al., 2016; Ichijo et al., 2015; Villalón et al., 2012)). Asymmetry of the brain, including that of the habenula, plays an important role in the lateralized function of neuronal circuits and in some species leads to lateralized behavior (Concha et al., 2012; Dreosti et al., 2014; Ichijo et al., 2017). Lateralization of the human brain plays a role in functions such as speech, and disruptions in brain lateralization may be associated with several neurological disorders (Brandler et al., 2013; Duboc et al., 2015; Francks et al., 2007; Herbert et al., 2005; Sommer et al., 2001). However, studying brain lateralization has been notoriously difficult. Prominent asymmetry and lateralization of the habenula in genetically tractable species such as zebrafish is therefore invaluable for studying the mechanisms that dictate brain lateralization and for understanding

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