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Regulation of thalamic development by Sonic hedgehog

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The thalamus is strategically positioned within the caudal diencephalic area of the forebrain, between the mesencephalon and telencephalon. This location is important for unique aspects of thalamic function, to process and relay sensory and motor information to and from the cerebral cortex. How the thalamus comes to reside within this region of the central nervous system has been the subject of much investigation. Extracellular signals secreted from key locations both extrinsic and intrinsic to the thalamic primordium have recently been identified and shown to play important roles in the growth, regionalization, and specification of thalamic progenitors. One factor in particular, the secreted morphogen Sonic hedgehog (Shh), has been implicated in spatiotemporal and threshold models of thalamic development that differ from other areas of the CNS due, in large part, to its expression within two signaling centers, the basal plate and the zona limitans intrathalamica, a dorsally projecting spike that separates the thalamus from the subthalamic region. Shh signaling from these dual sources exhibit unique and overlapping functions in the control of thalamic progenitor identity and nuclei specification. This review will highlight recent advances in our understanding of Shh function during thalamic development, revealing similarities, and differences that exist between species.

Keywords: thalamus, diencephalon, forebrain, zli, Shh, morphogen

THE PROSOMERE MODEL OF FOREBRAIN DEVELOPMENT

Almost 20 years ago, Puelles and Rubenstein (1993) described a model to help explain how the complex architecture of the mouse forebrain is generated from discrete developmental territories termed prosomeres. The purpose of the prosomere model was to relate the bent longitudinal axis of the forebrain to that of more posterior regions of the neural tube and to define its primary subdivisions along the anteroposterior (a/p) and dorsoventral axes. Initially, the spatial patterns of 45 genes were mapped onto the prosomeric model with many respecting the hypothesized transverse and longitudinal boundaries of the forebrain (Puelles and Rubenstein, 1993). Over the years, hundreds of new genes have been added to the list and further testing of the model has led to its reinterpretation (Puelles and Rubenstein, 2003). As it stands, the prosomere model stipulates that the caudal forebrain is organized into three prosomeres (p1–p3) corresponding to the pretectum, thalamus, and prethalamus, respectively, whereas the rostral forebrain (telencephalon and hypothalamus) represents a complex protosegment not divided into prosomeres (**Figure 1**).

Functional genetic experiments performed over the past decade in several model organisms have further validated the prosomere model and have greatly enhanced our understanding of the molecular mechanisms underlying forebrain formation and evolution (Hébert and Fishell, 2008; Scholpp and Lumsden, 2010). A common theme that has emerged from these and other studies of nervous system development is that compartmentalization of the neuroepithelium into functional units is facilitated by its exposure to extrinsic factors secreted from localized signaling centers (Jessell, 2000; Hébert and Fishell, 2008; Scholpp and Lumsden, 2010). In the case of the caudal forebrain, the secreted morphogen Sonic hedgehog (Shh), has been shown to play a multifaceted role in regulating the growth and identity of distinct neuronal progenitor subtypes within the thalamic complex, as well as the formation of the zona limitans intrathalamica (zli), a dorsally projecting boundary between p2 and p3 that also serves as a critical signaling center for thalamic and prethalamic development (**Figure 1**). This review will highlight the diverse functions of Shh at different stages of thalamic development, including a feature unique to the caudal forebrain whereby Shh secreted from two orthogonal sources (basal plate and zli) contributes to a morphogenic signaling gradient that patterns an alar structure, the thalamic primordium.

Shh SIGNALING IN THE SPINAL CORD: LESSONS LEARNED FROM 20 YEARS OF STUDY

Much of what we know about Shh signaling has come from studies of its role in spinal cord development. A summary of the principal concepts learned from this work is described below and will serve as a framework for comparison with the roles of Shh signaling during thalamic development. For more comprehensive reviews on this subject the reader is encouraged to consult the following references (Dessaud et al., 2008; Matise and Wang, 2011).

Sonic hedgehog is a secreted protein that provides positional information to a wide variety of developing tissues, including the CNS (Dessaud et al., 2008; Ingham et al., 2011; Matise and Wang, 2011). *Shh* is expressed in the axial mesoderm (prechordal plate and notochord) and ventral midline (floor plate) of the overlying neural tube throughout most of the a/p neuraxis (Echelard et al., 1993; Roelink et al., 1994). It is from these sources that a ventral to dorsal concentration gradient of Shh is established in the ventral neural tube. Over the past several years a compelling body of evidence has been generated to explain how the Shh signaling gradient

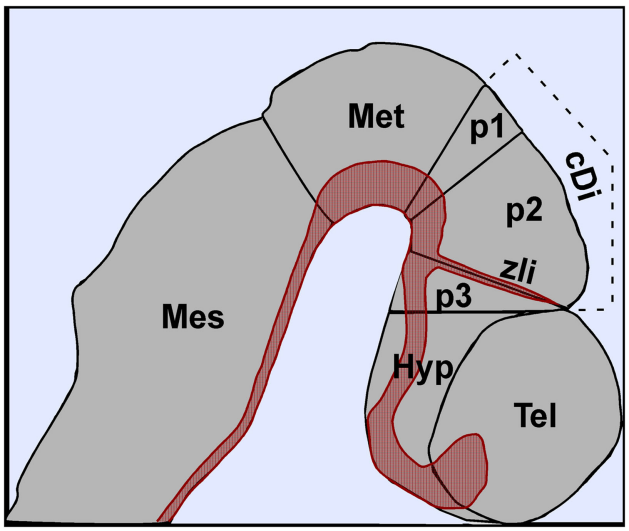

FIGURE 1 | Regionalization of the central nervous system along the anteroposterior axis of the mouse at embryonic day 10.5. The caudal diencephalon is divided into three prosomeres (p1, p2, p3) corresponding to the pretectum, thalamaus, and prethalamus, respectively. The zona limitans intrathalamica (zli) is located at the p2–p3 boundary. The expression of *Shh* in the ventral midline and zli is depicted in red. Abbreviations: cDi, caudal diencephalon; Hyp, hypothalamus; Mes, mesencephalon; Met, metencephalon; Tel, telencephalon.

is interpreted by neuronal and glial progenitors to account for the diverse array of cell types present in the ventral spinal cord. The prevailing model stipulates that the fate of a given progenitor is determined by the level and duration of Shh signaling to which it is exposed (Ericson et al., 1996, 1997; Dessaud et al., 2007, 2010). For instance, the identity of the ventral-most neuronal progenitors in the spinal cord (p3 domain) is determined by the highest concentration of Shh for the longest period of time, whereas, the identities of progenitors occupying progressively more dorsal positions in the spinal cord (pMN, p2–p0) are dependent on correspondingly lower levels of Shh signaling for shorter periods of time (Dessaud et al., 2007, 2010).

To fully appreciate the intricacies of the molecular mechanism by which ventral neuronal progenitors interpret the level and duration of Shh signaling, a brief overview of the Shh signal transduction cascade is necessary. In the absence of Shh ligand, the pathway is kept in an off state by Patched (Ptch1), a 12-pass transmembrane protein that also functions as an integral component of the Shh receptor complex (Marigo et al., 1996; Stone et al., 1996; Allen et al., 2011). Ptch1 suppresses Shh signaling by antagonizing the function of Smoothened (Smo), a 7-pass transmembrane protein with an essential role in Hedgehog signal transduction (Chen and Struhl, 1996; Zhang et al., 2001; Taipale et al., 2002). Blockage of Smo activity results in the phosphorylation and proteolytic processing of the zinc finger containing transcriptional regulators, Gli3, and to a lesser extent Gli2, into transcriptional repressors (Wilson and Chuang, 2010). When Shh binds to the Ptch1 receptor complex, the repression on Smo is relieved, thus permitting the production and nuclear entry of full-length Gli proteins and their transcriptional activation of target genes, including Gli1 and Ptch1.

In response to its position along the Shh morphogen gradient, a progenitor cell elicits distinct temporal profiles of Gli activity (Stamataki et al., 2005; Dessaud et al., 2007, 2010). This is a dynamic process given that progenitors become desensitized to Shh over time, as a result of the negative feedback loop with Ptch1. Therefore, to keep its position along the dorsoventral axis, the progenitor cell must maintain a certain threshold of Shh signaling over time (Dessaud et al., 2010).

Each progenitor domain can be identified by the expression of a distinct set of homeodomain and bHLH transcription factors (Briscoe and Ericson, 2001; Lupo et al., 2006). Boundaries between progenitor domains are generated over time by the mutual repression of complementary pairs of transcription factors (Muhr et al., 2001). Once the boundaries are fixed, the unique combination of transcription factors assigned to a given progenitor domain further directs the fate of differentiating neurons.

THE MULTIPLE ROLES OF Shh DURING THALAMIC DEVELOPMENT

While significant advances have been made in elucidating the requirements of Shh signaling in posterior regions of the CNS, it is only recently that similar progress has been described for the diencephalon (Scholpp and Lumsden, 2010). The thalamic primordium develops from the alar plate of p2. *Shh* expression is localized to the basal plate of p1–p3 by the 12-somite stage of development and over a day later (25-somites) is initiated in the zli, where it becomes fully activated by E10.5 (**Figure 1**).

The exposure of the thalamus to two *Shh* signaling centers has made it somewhat of a challenge to reconcile the specific roles of either one in regulating the growth, patterning and neuronal identity of thalamic progenitors. However, recent studies using a combination of genetic and tissue perturbation approaches in mouse, chicken, and zebrafish embryos have developed a clearer picture of the multifaceted roles of Shh signaling during thalamic development (Hashimoto-Torii et al., 2003; Kiecker and Lumsden, 2004; Vieira et al., 2005; Scholpp et al., 2006; Szabó et al., 2009; Vue et al., 2009; Jeong et al., 2011).

EARLY ROLES FOR Shh AS A MITOGEN

The dependency of thalamic development on Shh is temporally regulated. As early as the 15-somite stage of mouse development, $Shh^{-/-}$ embryos show reduced proliferation and survival of diencephalic precursors (Ishibashi and McMahon, 2002). This mitogenic role for Shh occurs well before zli formation and is therefore attributed to Shh signaling from the prechordal plate and/or ventral midline of the diencephalon. Since the cell proliferation defects in $Shh^{-/-}$ embryos were also observed in alar regions of the diencephalon, well out of range of Shh secreted from ventral sources, a Shh-dependent relay signal was proposed to regulate the growth of thalamic progenitors. Fgf15 appeared to be an ideal candidate to fulfill this function as its dorsal growth promoting properties were dependent on Shh, at least when overexpressed in cultured mouse brain explants (Ishibashi and McMahon, 2002). However, recent loss of function studies do not support this conclusion, as $Fgf15^{-/-}$ mutants show increased proliferation of dorsal neural progenitors

and decreased neurogenesis in the developing midbrain and neocortex, consistent with Fgf15 functioning as a growth suppressor (Borello et al., 2008; Fischer et al., 2011). The identity of the Shh-dependent regulator of thalamic growth and survival remains to be identified. Wnt ligands are good candidates based on the finding that several are expressed in the thalamic primordium, as well as the fact that the expression of *Tcf4*, a transcriptional mediator of Wnt signaling, is downregulated in the diencephalon of $Shh^{-/-}$ embryos (Ishibashi and McMahon, 2002). While Wnt signaling may, in some instances, act antagonistically to Shh in the specification of some neural cell fates (Robertson et al., 2004), this is likely to be context dependent, as Wnt signaling is also dependent on Shh for the proliferation of neural progenitors in the spinal cord (Alvarez-Medina et al., 2009).

Zli FORMATION

The epichordal/prechordal interface marks the territory from where the zli will emerge (Vieira et al., 2005). The expression of the homeodomain transcription factor Otx2 on the posterior (epichordal) side of the zli and the zinc finger proteins Fezf1 and Fezf2 on the anterior (prechordal) side of the p2/p3 border are required for zli formation (Hirata et al., 2006; Jeong et al., 2007; Scholpp et al., 2007). Whether these transcription factors play a direct role in regulating *Shh* expression in the zli, or provide a permissive environment for *Shh* to be transcribed, remains unresolved. Interestingly, mouse mutants lacking the bHLH trancription factors Hes1 and Hes5 also show a loss of *Shh* expression in the zli (Baek et al., 2006). It is intriguing to speculate that Hes1/5 might be functioning downstream of a cross repressive interaction between Otx2 and Fezf2 to regulate Shh expression in the zli. Of course, other regulatory relationships are equally possible.

The zli is a key partition between the thalamic and prethalamic territories and also serves as an important signaling center for the regionalization of the a/p axis of the caudal diencephalon (Scholpp and Lumsden, 2010). The zli extends dorsally from the ventral midline at the p2/p3 boundary, coinciding with the anterior limit of the notochord (**Figure 1**; Vieira et al., 2005). *Shh* expression is first detected in the zli at the 25 somite stage of chick and mouse embryos and expands dorsally at a rate of $\sim$20 μm/h until it reaches a length of 600 μm (Zeltser, 2005). The dorsal progression of *Shh* transcription was inhibited in chick embryos upon insertion of a microbarrier between the basal plate and the zli, or when Shh signaling was blocked with a constitutively active form of Ptch1 (Kiecker and Lumsden, 2004; Zeltser, 2005; Vieira and Martinez, 2006). These results suggested that *Shh* expression in the zli is regulated by a ligand-dependent feed-forward signaling mechanism.

A Shh-dependent vertical signaling model to explain the spread of Shh transcription along the zli is not entirely consistent with the finding that *Shh* continues to be expressed in the zli of mutant mouse embryos lacking principle components of the Shh transduction cascade, including Gli2, Gli3, and Smo (Hashimoto-Torii et al., 2003; Vue et al., 2009). Since it is likely that the inactivation of Smo function in *Nestin-cre*; $Smo^{loxp/loxp}$ embryos occurred after *Shh* expression was already initiated in the zli, these results might suggest that the maintenance, but not the initiation, of *Shh* expression in the zli is independent of Shh signaling. A more substantial challenge to the vertical signaling model comes from the observation that *Shh* expression was initiated in the zli of $Gli2^{-/-}$; $Gli3^{-/-}$ mouse mutants, as well as zebrafish oep mutants (which lack the nodal co-receptor tdgf1/cripto), despite the lack of *Shh* expression in the basal plate of the caudal diencephalon, which was thought to be the initiating source of the vertical signal (Hashimoto-Torii et al., 2003; Scholpp et al., 2006). Clearly, more work will be needed to sort out the molecular details of zli formation. A more thorough analysis of the critical cis and trans determinants of *Shh* expression in the zli may help explain the direct regulatory mechanisms underlying the formation of this structure (Epstein et al., 1999; Jeong et al., 2006).

The thalamus and prethalamus express different sets of genes in response to Shh signaling from the zli (Kiecker and Lumsden, 2004; Scholpp et al., 2006; Vieira and Martinez, 2006). To explain how this differential response to Shh is orchestrated, Kiecker and Lumsden (2004) proposed that the thalamus and prethalamus are prepatterned. In support of their hypothesis, they showed that the homeobox gene Irx3 acts as a thalamic competence factor. When misexpressed in the prethalamus of chick embryos, Irx3 ectopically activated genes typically expressed posterior to the zli in a Shh-dependent manner. While loss of function studies with Irx3 are likely confounded by functional redundancy with other family members, it is nonetheless intriguing that in zebrafish Irx1b morphants, the zli is posteriorly expanded at the expense of the thalamus, suggesting that Irx1b is necessary to restrict zli formation on the epichordal side of the zli (Scholpp et al., 2007).

Shh PATTERNS THE THALAMUS ALONG A MORPHOGENIC GRADIENT

The spatial arrangement of thalamic nuclei is important for generating the precise topographical relationship needed to fulfill its role as a relay center. Despite the many advances in our knowledge of the early events regulating thalamic growth, and regionalization, we still know relatively little concerning the mechanisms by which heterogeneous clusters of thalamic neurons become specified and aggregate into discrete thalamic nuclei. One particular challenge has been to correlate the patterns of gene expression initiated by Shh and other signaling pathways at early stages of thalamic development with discrete nuclei and/or neuronal subtypes that form at later postnatal stages (Nakagawa and O'Leary, 2001; Jones and Rubenstein, 2004; Vue et al., 2007, 2009; Szabó et al., 2009; Suzuki-Hirano et al., 2011; Yuge et al., 2011).

The neurons contributing to thalamic nuclei are derived from at least two distinct progenitor domains. The caudal population of thalamic progenitors, pTH-C, is the larger of the two groups, and gives rise to all thalamic nuclei that relay sensory information from the periphery to primary sensory regions of the neocortex via thalamocortical axons (**Figure 2**; Vue et al., 2007). The rostral population of thalamic progenitors, pTH-R, comprises a narrow band of cells sandwiched between pTH-C and the zli (**Figure 2**). Thalamic neurons derived from pTH-R progenitors are thought to contribute to two dorsolaterally positioned thalamic nuclei, the ventrolateral geniculate nucleus (vLG), and the

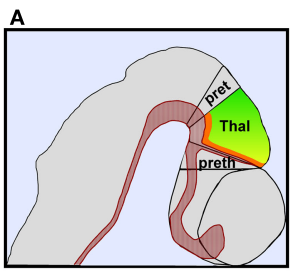

FIGURE 2 | A morphogenetic gradient of Shh signaling establishes distinct thalamic progenitor domains. (A) Schematic representation of a lateral view of the caudal diencephalon color-coded as follows: *Shh* expressing cells (red); pTH-C_2 domain (yellow); pTH-C_1 domain (green); pTH-R domain (orange). **(B)** Comparison of a representative set of genes expressed in thalamic and ventral spinal cord progenitor domains.

intergeniculate leaflet (IGL), neither of which project axons to the cortex (Horowitz et al., 2004; Morin and Blanchard, 2005; Jones, 2007; Vue et al., 2007, 2009).

In addition to its role in early patterning events, Shh signaling is also required to specify neuronal subtypes that contribute to a broad array of thalamic nuclei. The current model proposes that graded Shh signaling is necessary and sufficient to promote distinct classes of thalamic progenitors (Hashimoto-Torii et al., 2003; Scholpp et al., 2009; Szabó et al., 2009; Vue et al., 2009). The pTH-R domain, which develops closest to the zli, is dependent on the highest concentration of Shh, whereas, the rostroventral (pTH-C_2) and caudodorsal (pTH-C_1) populations of pTH-C progenitors, developing several cell diameters away from the zli, are dependent on progressively lower concentrations of Shh (**Figure 2**; Hashimoto-Torii et al., 2003; Szabó et al., 2009; Vue et al., 2009).

The conditional inactivation of either Shh or Smo in the diencephalon results in the loss of pTH-R progenitors and their post-mitotic derivatives in the vLG and IGL, as well as a sizeable reduction in the population of pTH-C progenitors and the Gbx2 expressing, cortex-projecting, thalamic neurons that differentiate from these cells (Szabó et al., 2009; Vue et al., 2009; Jeong et al., 2011). Although Szabó et al. (2009) and Vue et al. (2009) both described varying degrees of thalamic deficits in the absence of Shh, the phenotypes described by Szabó et al. (2009) were more severe and correlated with a greater loss of Gbx2 expression, which was likely attributed to the use of an earlier acting and more robust Cre line (*Foxb1-Cre* versus *Netrin-Cre*) to delete *Shh* from the thalamic primordium.

How does Shh signaling determine the different classes of thalamic progenitors? At first glance, a model similar to that described for neuronal subtype identity in the ventral spinal cord could be envisioned, whereby distinct thalamic progenitors are specified by their exposure to different thresholds of Shh signaling activity. However, another possibility is that the two classes of Shh-dependent thalamic progenitors, pTH-R and pTH-C, are specified by two spatially distinct sources of Shh, the basal plate, and zli, respectively. For the latter model to be valid, different phenotypes should arise from the inactivation of Shh from discrete signaling territories.

To help resolve this question, Jeong et al. (2011) examined mutant mice containing a targeted deletion of a *Shh* regulatory element required for *Shh* expression in the basal plate of the caudal diencephalon, but not the zli. This analysis showed that the expression of high threshold target genes in pTH-R (*Nkx2.2*, *Ascl1*, *Tal1*) was reduced, concomitant with an expanded expression domain of lower threshold, pTH-C target genes (*Ngn2*). While this result may, in part, reflect temporal differences in the dependency of pTH-R on Shh, it might also be the case that prolonged Shh signaling activity from both diencephalic sources is required to promote pTH-R identity. Given that the blockade of Shh signaling from the zli in chick embryos also results in a loss of *Nkx2.2* expression in the pTH-R domain, the most parsimonious explanation of the data is that both sources of Shh surrounding the thalamus are necessary for pTH-R identity (Kiecker and Lumsden, 2004; Jeong et al., 2011). Therefore, Shh secreted from two signaling sources, the basal plate and zli, supplies the Shh signaling gradient that shapes thalamic progenitor identity over time.

The similarity in signaling mechanisms by which Shh regulates neuronal progenitor subtype identity in the thalamus and ventral spinal cord also extends to the use of some of the same transcriptional regulators mediating these cell fate decisions (**Figure 2**). For instance, pTH-R and p3 neuronal progenitors form closest to their respective sources of Shh in the thalamus and spinal cord, respectively, and both populations express Nkx2.2. The rostroventral pTH-C (classified as pTH-C_2) and pMN domains reside at slightly greater distances from their respective sources of Shh and both express the bHLH transcription factors Olig2, Ngn1, and Ngn2. Finally, the caudodorsal region of pTH-C in the thalamus (classified as pTH-C_1) and p0 domain of the spinal cord both express Dbx1 and are at the tail end of the Shh responsive territories.

FUTURE DIRECTIONS

The specificity of thalamic progenitors are not solely determined by Shh. Clearly, additional signaling pathways (Fgf, Wnt, and others) must play significant roles in generating the diversity of progenitor subtypes that have been, and remain to be, discovered in the thalamus (Braun et al., 2003; Zhou et al., 2004; Miyake et al., 2005; Vieira and Martinez, 2005; Kataoka and Shimogori, 2008; Bluske et al., 2009; Martinez-Ferre and Martinez, 2009; Peukert et al., 2011). Future research will undoubtedly uncover how these signaling pathways integrate to generate the transcriptional network that programs each of the thalamic progenitor domains and gives rise to the full complement of thalamic nuclei. Hopefully, in the not too distant future, our understanding of thalamic development will match that of the intricately detailed patterning events that occur in the spinal cord (Alaynick et al., 2011).

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