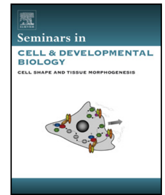
Seminars in Cell & Developmental Biology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

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



Review

Transcriptional regulation of graded Hedgehog signaling

Kristin N. Falkenstein, Steven A. Vokes*

Department of Molecular Biosciences, Institute for Cellular and Molecular Biology, University of Texas at Austin, 2500 Speedway Stop A4800, Austin, TX 78712, USA

ARTICLE INFO

Article history:
Available online xxx

Keywords:
Gli
Hedgehog
Morphogen
Development

ABSTRACT

The Hedgehog (Hh) pathway plays conserved roles in regulating a diverse spectrum of developmental processes. In some developmental contexts, a gradient of Hh protein specifies multiple cell types in a dose-dependent fashion, thereby acting as a morphogen. Hh signaling ultimately acts on the transcriptional level through GLI proteins. In the presence of Hh signaling full length GLI proteins act as transcriptional activators of target genes. Conversely, in the absence of Hh, GLI proteins act as transcriptional repressors. This review will highlight mechanisms contributing to how graded Hh signaling might translate to differential GLI activity and be interpreted into distinct transcriptional responses.

© 2014 Elsevier Ltd. All rights reserved.

Contents

1. The Hedgehog signaling pathway overview 00
2. Processing of GLI proteins into transcriptional repressors 00
3. Regulated activity of full length GLI proteins 00
4. Phosphorylation state can influence full length GLI activity 00
5. Hh driven patterning requires transcriptional activation and de-repression 00
6. The role of de-repression in patterning 00
7. The importance of transcriptional activation by GLI activator 00
8. Relative levels of GLI proteins along the Hh gradient 00
9. Deciphering the GLI activation gradient 00
10. Duration of Hh signaling contributes to tissue patterning 00
11. How prolonged Hh signaling translates to GLI activity during neural tube patterning 00
12. How graded GLI activation drives differential transcriptional responses 00
13. Defining the tissue specific response to a generic GLI activation gradient 00
14. GLI binding motif quality and distinct transcriptional responses 00
15. Additive inputs of multiple GLI binding motifs 00
16. GLI binding regions are context dependent 00
17. Concluding remarks 00
Acknowledgements 00
References 00

1. The Hedgehog signaling pathway overview

The Hedgehog (Hh) signaling pathway regulates a large number of tissue patterning events during development, acting as a growth factor, survival agent, and inductive signal in a context-dependent fashion. Although aspects of the nature, timing and response to Hh ligands are all areas of active research, Hh ultimately acts through GLI transcription factors to elicit tissue-specific responses. Because the Hh ligand is secreted, it has the ability to evoke concentration-specific responses in some contexts, fitting the functional criteria for a morphogen [1–4].

The role of graded Hh signaling as a morphogen has been most intensively studied in the context of Drosophila wing imaginal disc patterning, as well as in the vertebrate limb bud and neural tube (Fig. 1). In all three systems, distinct transcriptional responses are associated with different doses of the Hh ligand. The underlying principles of Hh signaling and response are well conserved with the

* Corresponding author. Tel.: +1 512 232 8359; fax: +1 512 471 2149.
E-mail address: svokes@austin.utexas.edu (S.A. Vokes).

http://dx.doi.org/10.1016/j.semcdb.2014.05.010
1084-9521/© 2014 Elsevier Ltd. All rights reserved.

Please cite this article in press as: Falkenstein KN, Vokes SA. Transcriptional regulation of graded Hedgehog signaling. Semin Cell Dev Biol (2014), http://dx.doi.org/10.1016/j.semcdb.2014.05.010

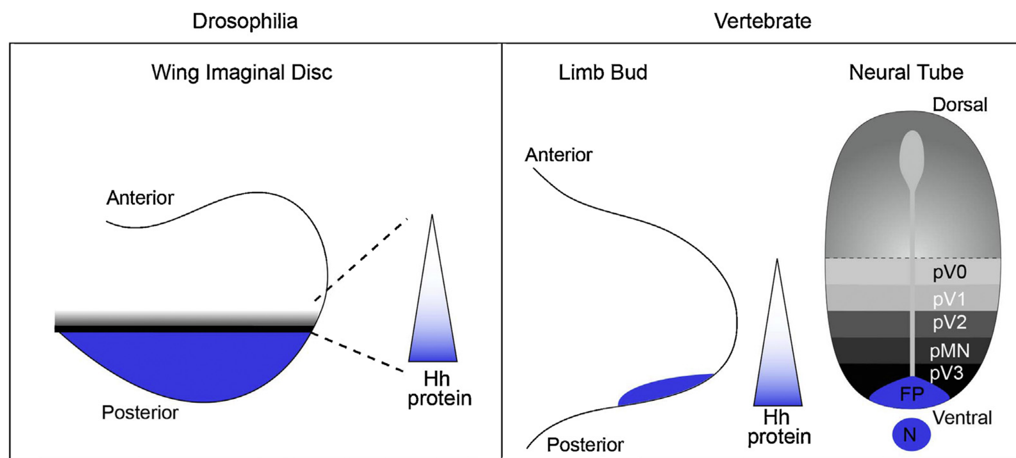


Fig. 1. Model systems for Hedgehog morphogens. (L-R) Drosophila wing imaginal disc, vertebrate limb bud, vertebrate neural tube. The Hh secreting populations are shown in blue with the resulting protein gradient schematized in the triangle. The ventral progenitor domains are highlighted on the right side of the neural tube. Abbreviations: N, notochord; FP, floorplate.

notable exception that the cilia functions as a processing center for Hh signal transduction and GLI processing in vertebrates [5]. Hh is secreted by a population of signaling cells into the surrounding tissue where it binds to the transmembrane receptor protein Patched (Ptch) on signal receiving cells. In the absence of Hh, Ptch inhibits the activity of another transmembrane protein, Smoothened (Smo). Upon Hh binding to Ptch, Smo is activated and subsequently results in the activation of GLI transcription factors which include GLI1-3 in vertebrates, and the homologous Cubitus interruptus (Ci) transcription factor in Drosophila [6–8]. All GLI family proteins recognize and bind to the same binding motif (Gli binding motif or GBM) [9–12]. Transcriptional activation of *Ptch* by GLI transcription factors in response to Hh signaling provides negative feedback to restrict Hh signaling both spatially and temporally [13–15]. This negative feedback is integral to Hh signaling, as in the absence of Ptch, responsive tissues have constitutively high levels of Hh pathway activation [16,17]. The transcriptional response to Hh signaling occurs solely through the activity of GLI family proteins [18,19]. This review will highlight efforts toward understanding how GLI family proteins resolve graded Hh signaling and translate it into a discrete transcriptional output.

2. Processing of GLI proteins into transcriptional repressors

In the absence of Hh signaling, GLI3 as well as the Drosophila Ci are subject to processing by the proteasome into their truncated, transcriptional repressor forms (GLI-R/Ci-R) (Fig. 1) [20–22,51]. GLI2 has the potential to be processed in a similar fashion but is primarily degraded in the absence of Hh signal [22]. The processing of GLIs is driven by a protein complex containing Suppressor of fused (Sufu) that results in Protein Kinase A (PKA) mediated phosphorylation [23–25]. Both GLI2 and GLI3 have a cluster of six conserved serine residues on the carboxy terminal side of their DNA binding domain (ser1-6). Phosphorylation of the first four serines (ser1-4) by PKA provokes a subsequent cascade of further phosphorylation by GSK3 and Casein Kinase 1 family proteins. The combined activity of these kinases on GLI2/3 and Ci ultimately leads to binding of E3 SCF ubiquitin ligase and processing of GLI2, GLI3 and Ci to their truncated repressor forms [8,22,26–32,51]. The mechanisms by which GLI proteins repress target genes is poorly understood, but includes histone deacetylation [33].

3. Regulated activity of full length GLI proteins

Hh activation prevents processing of GLI2, GLI3, and Ci [19–21,34,35]. The resultant full length proteins then undergo additional processing steps that enable them to activate transcription (GLI-A/Ci-A) (Fig. 1). However, multiple mechanisms for modulating full length GLI activity have been described. These mechanisms include binding of proteins that either promote or antagonize the stability of full length GLI proteins [25,36,37], cytosolic sequestration [38–40], and differential post-translational modification events [28,41–44].

4. Phosphorylation state can influence full length GLI activity

Phosphorylation events are implicated in tuning the activation state of full length GLI. For example, PKA phosphorylation on ser6 of the previously mentioned ser1-6 cluster propagates the binding of the 14-3-3 protein to GLI proteins. This interaction decreases the transcriptional activating potential of GLI proteins [45]. The phosphorylation of ser6 by PKA is sensitive to the state of Hh signaling, and therefore has the potential to serve as a method to tune GLI activity according to graded Hh exposure. A second mechanism for how phosphorylation influences the transition of GLI proteins into a fully activated state arose from the identification of a second conserved cluster of 5 phosphorylation sites (c-g) whose phosphorylation state correlates with GLI activity. Although sites c-g were identified as partial consensus sites for PKA, they are not subject to phosphorylation by PKA, and the kinase that phosphorylates these sites has not been identified (Fig. 2) [42]. In contrast to phosphorylation of ser1-6, the phosphorylation of sites c-g is countered by PKA activation and increases in a graded manner in response to graded activation of the Hh pathway [42]. The apparent graded responsiveness of GLI phosphorylation state to graded Hh input provides an attractive model for how incremental changes in Hh have the potential to directly translate into incremental increases in transcriptional activation. Although technically challenging, it will be very interesting to see how differential phosphorylation of GLI activators occurs in response to endogenous Hh gradients and how this phosphorylation changes over time. It is presently not known if analogous mechanisms govern the repressive potency of GLI-R.

Please cite this article in press as: Falkenstein KN, Vokes SA. Transcriptional regulation of graded Hedgehog signaling. Semin Cell Dev Biol (2014), http://dx.doi.org/10.1016/j.semcdb.2014.05.010

Download English Version:

https://daneshyari.com/en/article/8480644

Download Persian Version:

https://daneshyari.com/article/8480644

Daneshyari.com