Semi-adaptive response and noise attenuation in BMP signaling

Tian Hong[1,2], Ernest S. Fung[2,3], Lei Zhang[4], Grace Huynh[3], Edwin S. Monuki[2,3], Qing Nie[1,2]

***Short Abstract* - Temporal dynamics of morphogen-driven signaling events are critical for proper embryonic development. During development, cells translate extracellular bone morphogenetic protein (BMP) gradients, often subject to noise, into graded intracellular tail-phosphorylated SMAD (TP-SMAD) levels. Using modeling and experimental approaches, we found that BMPs induce TP-SMAD responses in neural precursor cells (NPCs) in a concentration-dependent manner, which are semi-adaptive within a specific intermediate range of BMP concentration. These semi-adaptive TP-SMAD responses involve an intrinsically-slow deactivation of BMP receptors, which attenuates noise by prolonging SMAD deactivation time after BMP withdrawal, but increases response time. Interestingly, negative feedback on BMP receptors is also required for semi-adaptation, which benefits both noise attenuation and response time, and therefore balances the tradeoff seen with slow BMP receptor deactivation. These results highlight the rich dynamics of SMAD regulation in response to graded BMP concentration, and elucidate general design principles for balancing noise attenuation and activation speed in signaling systems.**

***Keywords* — Activation time / adaptive response / noise attenuation / signaling speed / deactivation**

I. Background

Bone morphogenetic proteins (BMPs) play critical roles in embryogenesis and tissue patterning. As morphogens, BMPs regulate patterning by forming concentration gradients within developing tissues [1] and specify multiple cell fates in a concentration-dependent manner. Central to BMP-induced intracellular signaling is phosphorylation of SMAD transcription factors [2]. Tail-phosphorylated SMADs (TP-SMADs) are imported into the nucleus to regulate transcription.

In neural precursor cells (NPCs) of the developing cerebral cortex, steady-state TP-SMAD levels form a dorsoventral gradient *in vivo* [3] and approximate extracellular BMP concentrations *in vitro* [4], suggesting that TP-SMAD is a direct and proportional readout of extracellular BMP concentration. In addition to steady-state responses, pulse-like responses to morphogens can be critical for tissue development [5]. While BMPs can generate this type of response at the level of SMAD1 [6], the temporal dynamics of SMAD1 activation to graded BMP signals is poorly understood.

[1]Department of Mathematics, [2]Center for Complex Biological Systems, [3]Department of Pathology and Laboratory Medicine, University of California, Irvine, CA, USA E-mail: hong.tian@uci.edu

[4]Beijing International Center for Mathematical Research, Peking University, Beijing, China

II. Results

We combined experimental and modeling approaches to investigate the dynamics of SMAD1 activation in NPCs responding to graded BMP signals. We showed that an intermediate range of BMP concentration triggers semi-adaptive SMAD1 responses, which differ from the non-adaptive responses stimulated by higher or lower BMP levels and accelerate cell responses.

Using sensitivity analysis, we found that BMP receptor deactivation rate has pronounced effect in attenuating fluctuations of BMP signals. In particular, slow receptor deactivation rate benefits noise attenuation, but exhibits the tradeoff of increasing response time. Interestingly, BMP receptor inhibition through negative feedback, which is required for the semi-adaptation, exhibits no such tradeoff.

III. Conclusion

Our experimental observations and computational analysis demonstrate unique dynamic features of cellular responses to graded BMP signals. Our findings suggest a general cell-intrinsic control mechanism for creating fast adaptive responses with attenuated noise within a morphogen gradient. Combination of slow morphogen receptor deactivation rate with negative feedback can optimize both activation speed and noise attenuation property.

References

[1] E. L. Ferguson and K. V. Anderson, "Decapentaplegic acts as a morphogen to organize dorsal-ventral pattern in the Drosophila embryo," *Cell*, vol. 71, pp. 451-61, 1992.

[2] J. Massague, J. Seoane, and D. Wotton, "Smad transcription factors," *Genes & development*, vol. 19, pp. 2783-810, 2005.

[3] X. Cheng, C.-m. Hsu, D. S. Currle, J. S. Hu, a. J. Barkovich, and E. S. Monuki, "Central roles of the roof plate in telencephalic development and holoprosencephaly," *The Journal of neuroscience*, vol. 26, pp. 7640-9, 2006.

[4] J. S. Hu, L. T. Doan, D. S. Currle, M. Paff, J. Y. Rheem, R. Schreyer, *et al.*, "Border formation in a Bmp gradient reduced to single dissociated cells," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, pp. 3398-403, 2008.

[5] N. Balaskas, A. Ribeiro, J. Panovska, E. Dessaud, N. Sasai, K. M. Page, *et al.*, "Gene regulatory logic for reading the Sonic Hedgehog signaling gradient in the vertebrate neural tube," *Cell*, vol. 148, pp. 273-84, 2012.

[6] M. Knockaert, G. Sapkota, C. Alarcon, J. Massague, and A. H. Brivanlou, "Unique players in the BMP pathway: small C-terminal domain phosphatases dephosphorylate Smad1 to attenuate BMP signaling," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 103, pp. 11940-5, 2006.