Beta-arrestin -assisted signal amplification during cell chemotaxis

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***Short Abstract* — We use microfluidic devices to study the cell morphology and beta-arrestin signaling during the cell chemotaxis in a gradient environment. By correlating the readout from Angiotensin receptor, beta-arrestin scaffold, phosphorylated ERK, actin and the receptor-arrestin complex, we infer that the arrestin-mediated signal amplification plays an important role in the gradient sensing, which can be well fit into an ODE model.**

***Keywords* — Chemotaxis, Microfluidic, beta-arrestin, MAPK,FRET**

I. Purpose

How cells sense gradients of chemoattractants with frequently exquisite precision still remains an intriguing question [1]. One possibility is that internal scaffold proteins might supply an important needed local signaling control. Here we focus on an example scaffold protein to investigate this possibility.

Classically, arrestins act as a receptor internalization partners, serving to desensitize the cell response to environment. More recently, however, beta-arrestins, an arrestin sub-family, have been found to play a more complicated role in regulation of cell signaling pathways [2]. Specifically, they physically scaffold diverse signaling transduction complexes to mediate a variety of cell responses, including cytoskeleton organization [3], apoptosis or survival [4], protein synthesis [5], vesicle trafficking [6], receptor transactivation [7],and chemotaxis [8]. We now address the role of the beta-arrestin scaffold-mediated signal transduction through the ERK MAPK signaling pathway [9] in regulation of chemotaxis in response to Angiotensin II. Using microfluidic device [10] and a library of single cell fluorescence based probes [11, 12], we can investigate the signaling events in cells both in spatially homogeneous and graded Angiotensin II concentrations at the single-cell scale and sub-minute resolution. By exploring signaling from upstream angiotensin receptor distribution, through beta-arrestin2-receptor complex and beta-arrestin2 distribution, to downstream -ERK phosphorylation and actin translocation, we illustrate how cells can amplify the shallow gradient cues to generate strong and directed migration force. Finally, we use mathematical model to confirm that the beta-arrestin scaffold can serve a critical role in gradients sensing and directed cell locomotion.

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II. Conclusion

Optimized arrestin concentration is regulated by the balance of receptor recruit and ubquitin [13]. Also, it has been suggested that scaffold has a biphasic behavior [14]. Our model and experiment show that at its optimized value, the arrestins may amplify upstream signals, assemble downstream ERK and actin to help the filopodia formation.

References

[1] Kay RR, et al. (2009) Title of paper with long list of authors. *Nature Reviews of Mol. Cell Biol.* **9**, 455.

[2] Lefkowtiz RJ, Shenoy SK (2005) Transduction of receptor signals by beta-arrestin, *Science* **308**, 512.

[3] Barnes WG, et al. (2005) beta-Arrestin 1 and Galphaq/11 coordinately activate RhoA and stress fiber formation following receptor stimulation, *J. Biol. Chem.* **280**, 8041.

[4] Ahn S, et al. (2009) {beta}-Arrestin-2 Mediates Anti-apoptotic Signaling through Regulation of BAD Phosphorylation, *J. Biol. Chem.* **284**, 8855.

[5] DeWire SM, et al. (2008) Beta-arrestin-mediated signaling regulates protein synthesis, *J. Biol. Chem.* **283**, 10611.

[6] Ozawa K, et al. (2008) S-nitrosylation of beta-arrestin regulates beta-adrenergic receptor trafficking, *Mol. Cell* **8**, 395.

[7] Kim J, et al. (2009) Independent beta-arrestin2 and Gq/protein kinase Czeta pathways for ERK stimulated by angiotensin type 1A receptors in vascular smooth muscle cells converge on transactivation of the epidermal growth factor receptor, *J. Biol. Chem.* **284**, 11509.

[8] Hinton DL, et al. (2005) Beta-arrestin 2-dependent angiotensin II type 1A receptor-mediated pathway of chemotaxis, *Mol Pharmacol.* **67**, 1229.

[9] Shenoy SK, et al. (2006) beta-arrestin-dependent, G protein-independent ERK1/2 activation by the beta2 adrenergic receptor, *J. Biol. Chem* **281**, 1261.

[10] Paliwas S, et al. (2008) MAPK-mediated bimodal gene expression and adaptive gradient sensing in yeast, *Nature* **446**, 46.

[11] Violin JD , et al. (2006) G-protein-coupled receptor kinase specificity for beta-arrestin recruitment to the beta2-adrenergic receptor revealed by fluorescence resonance energy transfer, *J. Biol. Chem.* **281**, 20577.

[12] Harvey CD, et al. (2008) A genetically encoded fluorescent sensor of ERK activity, *Proc. Natl. Acad. Sci.* **108**, 19264.

[13] DeWire SM, et al. (2007) Beta-arrestins and cell signaling, *Annu Rev Physiol* **69**, 483.

[14] Levchenko A, et al. (2000) Scaffold proteins may biphasically affect the levels of mitogen-activated protein kinase signaling and reduce its threshold properties, *Proc. Natl. Acad. Sci.* **108**, 19264