



Tues 15 Oct 19  
12pm – 1pm



NUS, CeLS Seminar  
Room 1, Level 1 @ 28  
Medical Drive,  
S117456



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## Talin1 Regulates TLR Complex Assembly And Signaling Via Direct Interactions With Myd88 And PIP5K To Control Dendritic Cell Activation



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#### Abstract

Talin critically controls integrin-dependent cell migration, but its regulatory role in skin dendritic cells (DCs) during inflammatory responses has not been investigated. Here, we show that talin1 regulates not only integrin-dependent Langerhans cell (LC) migration, but also MyD88-dependent toll-like receptor (TLR)-stimulated DC activation. Talin1-deficient LCs failed to exit the epidermis, resulting in reduced LC migration to skin-draining lymph nodes (sdLNs) and defective skin tolerance induction, while talin1-deficient dermal DCs unexpectedly accumulated in the dermis despite their actomyosin-dependent migratory capabilities. Furthermore, talin1-deficient DCs exhibited compromised chemotaxis, NF $\kappa$ B activation, and pro-inflammatory cytokine production. Mechanistically, talin1 was required for the formation of pre-assembled TLR complexes in DCs at steady state via direct interaction with MyD88 and PIP5K. Local production of PIP2 by PIP5K then recruited TIRAP to the pre-assembled complexes, which were required for TLR signalosome assembly during DC activation. Thus, talin1 regulates MyD88-dependent TLR signaling pathways in DCs through a novel mechanism with implications for antimicrobial and inflammatory immune responses

#### RECOMMENDED READING

Lim, T.J.F. & Su, I.H\*. Talin1 Methylation Is Required for Neutrophil Infiltration and Lipopolysaccharide-Induced Lethality. *J Immunol* 201, 3651-3661 (2018).

Gunawan, M. Venkatesan, N., Loh, J. T., Wong, J. F., Berger, H., Neo, W. H., Li, L. Y. J., La Win, M. K., Yau, Y. H., Guo, T., See, P. C. E., Yamazaki, S., Chin, K. C., Gingras, A. R., Shochat, S. G., Ng, L. G., Sze, S. K., Ginhoux, F., and Su, I.H.\* The methyltransferase Ezh2 controls cell adhesion and migration through direct methylation of the extranuclear regulatory protein talin. *Nature Immunology* 16, 505-516 (2015).

Su, I.H.\* Dobenecker, M. W., Dickinson, E., Oser, M., Basavaraj, A., Marqueron, R., Viale, A., Reinberg, D., Wulfig, C., and Tarakhovsky, A.\* Polycomb group protein Ezh2 controls actin polymerization and cell signaling. *Cell* 121, 425-436 (2005).

Su, I.H., Basavaraj, A., Krutchinsky, A. N., Hobert, O., Ullrich, A., Chait, B. T., and Tarakhovsky, A. Ezh2 controls B cell development through histone H3 methylation and Igh rearrangement. *Nature Immunology* 4, 124-131 (2003).