Molecular Cell
Article

LGN/mInsc and LGN/NuMA Complex Structures Suggest Distinct Functions in Asymmetric Cell Division for the Par3/mInsc/LGN and Gαi/LGN/NuMA Pathways

Jinwei Zhu,[1,2,3,6] Wenyu Wen,[1,2,6] Zhen Zheng,[4,5] Yuan Shang,[3] Zhiyi Wei,[3] Zhuoni Xiao,[4,5] Zhu Pan,[1,2] Quansheng Du,[4,5,*] Wenning Wang,[1,2,*] and Mingjie Zhang[2,3,*]
[1]Department of Chemistry, Shanghai Key Laboratory of Molecular Catalysis and Innovative Materials
[2]Institutes of Biomedical Sciences
Fudan University, Shanghai, P.R. China
[3]Division of Life Science, State Key Laboratory of Molecular Neuroscience, Molecular Neuroscience Center, Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong, P.R. China
[4]Institute of Molecular Medicine and Genetics
[5]Department of Neurology
Georgia Health Sciences University, Augusta, GA 30912, USA
[6]These authors contributed equally to this work
*Correspondence: qdu@georgiahealth.edu (Q.D.), wnwang@fudan.edu.cn (W.W.), mzhang@ust.hk (M.Z.)
DOI 10.1016/j.molcel.2011.07.011

SUMMARY

Asymmetric cell division requires the establishment of cortical cell polarity and the orientation of the mitotic spindle along the axis of cell polarity. Evidence from invertebrates demonstrates that the Par3/Par6/aPKC and NuMA/LGN/Gαi complexes, which are thought to be physically linked by the adaptor protein mInscuteable (mInsc), play indispensable roles in this process. However, the molecular basis for the binding of LGN to NuMA and mInsc is poorly understood. The high-resolution structures of the LGN/NuMA and LGN/mInsc complexes presented here provide mechanistic insights into the distinct and highly specific interactions of the LGN TPRs with mInsc and NuMA. Structural comparisons, together with biochemical and cell biology studies, demonstrate that the interactions of NuMA and mInsc with LGN are mutually exclusive, with mInsc binding preferentially. Our results suggest that the Par3/mInsc/LGN and NuMA/LGN/Gαi complexes play sequential and partially overlapping roles in asymmetric cell division.

INTRODUCTION

Asymmetric cell division (ACD), the process by which a mother cell gives rise to two distinct daughter cells, is a fundamental process widely used to regulate stem cell function and generate cellular diversity during development in metazoa (Cowan and Hyman, 2004; Morrison and Kimble, 2006; Neumüller and Knoblich, 2009; Siller and Doe, 2009). This process is governed by two mechanisms (Horvitz and Herskowitz, 1992). External cues such as niche-derived signals or external polarity surrounding mother cells can lead to ACD (Lin, 2002; Morrison and Spradling, 2008; Zigman et al., 2005). Alternatively, asymmetric partitioning of cell fate determinants within mother cells (i.e., via the "intrinsic" mechanism that is independent of surrounding cells) can also cause cells to divide asymmetrically (Gönczy, 2008; Knoblich, 2008; Neumüller and Knoblich, 2009).

Drosophila neuroblasts (NBs) provide an excellent model system for studying ACD. ACD generally involves three steps: the establishment of mother cell polarity, the orientation of mitotic spindles, and the segregation of cell fate determinants. NBs inherit apical-basal polarity cues from the neuroepithelium, which contains the Par complex, an evolutionarily conserved tripartite complex composed of atypical protein kinase C (aPKC) (Wodarz et al., 2000), Par6 (Petronczki and Knoblich, 2001), and Bazooka (Baz, a *Drosophila* homolog of Par3) (Kuchinke et al., 1998). The Par complex is localized in a crescent at the apical cell cortex right below the overlaying epithelium (Kuchinke et al., 1998; Petronczki and Knoblich, 2001; Wodarz et al., 2000). Temporally, the Par proteins are the first molecules to localize to the apical cortices of cells. During late interphase and early prophase, Baz recruits the adaptor protein Inscuteable (Insc) (Kraut and Campos-Ortega, 1996; Kraut et al., 1996), which in turn recruits Partner of Inscuteable (Pins; its mammalian counterpart is LGN) to the apical cortex, as Insc can simultaneously bind to Baz (Schober et al., 1999; Wodarz et al., 1999) and Pins (Parmentier et al., 2000; Yu et al., 2000). The apical Pins then serves as a molecular linker to build up another evolutionarily conserved tripartite complex, Mud/Pins/Gαi (NuMA/LGN/Gαi in mammals), which functions in a receptor-independent G protein pathway to orient mitotic spindles along the apical-basal axes of cells (Bowman et al., 2006; Izumi et al., 2006; Schaefer et al., 2001; Siller et al., 2006), likely via dynein-mediated pulling forces on astral microtubules (Siller and Doe, 2009), ensuring that the mitotic cleavage plane is perpendicular to the apical-basal axis.

Pins associates with GDP-bound Gαi via the three GoLoco motifs at its C terminus (Parmentier et al., 2000; Schaefer