学位の種類	博士（医学）
報告番号	甲第１６７５号
学位記番号	第１１９２号
氏名	藤掛　数馬
授与年月日	平成 31 年 3 月 25 日
学位論文の題名	Detachment of chain-forming neuroblasts by Fyn-mediated control of cell-cell adhesion in the postnatal brain （出生後の脳における Fyn を介した細胞間接着制御による新生ニューロンの鎖状塊からの離脱） The Journal of Neuroscience. Vol. 38 : P.4598-4609, 2018
論文審査担当者	主査：　飛田 秀樹 副査：　浅井 清文，祖父江 和哉

Detachment of chain-forming neuroblasts by Fyn-mediated control of cell-cell adhesion in the postnatal brain

藤掛数馬

Abstract (modified)

The dynamic control of cell-cell adhesion is an important process in brain development and function. Migrating neurons continuously change their cell-cell adhesion state by destroying and reconstructing adhesion structures in various aspects of brain development, such as exit from the neurogenic niche (Famulski et al., 2010; Itoh et al., 2013) and the maintenance and termination of neuronal migration (Kawauchi et al., 2010; Luccardini et al., 2013; Sekine et al., 2012). Thus, elucidating the mechanisms controlling the cell adhesion of neural cells could provide new insight for understanding brain morphogenesis and novel strategies for brain pathologies. The chain migration of neuroblasts in the postnatal rodent brain involved in olfaction is a powerful model for examining the dynamics of cell adhesion during neuronal migration (Ghashghaei et al., 2007; Kaneko et al., 2017; Sawada et al., 2011).

In the rodent olfactory system, neuroblasts produced in the ventricular-subventricular zone of the postnatal brain migrate tangentially in chain-like cell aggregates toward the olfactory bulb (OB) through the rostral migratory stream (RMS). (Doetsch et al., 1999;, (Lois et al., 1996; Sawamoto et al., 2006; Wichterle et al., 1997).After reaching the OB, the chains are dissociated and the neuroblasts migrate individually and radially toward their final destination. (Garcia-Gonzalez et al., 2017; Lois and Alvarez-Buylla, 1994; Luskin, 1993; Petri et al., 2017; Sawada et al., 2018) Previous studies suggest that extracellular matrix molecules such as Reelin, Tenascin-R, and Prokineticin 2 (PK2) have important roles in the detachment of neuroblasts from chains (Hack et al., 2002; Ng et al., 2005; Saghatelyan et al., 2004). In addition, downregulation of the sphingosine 1-phosphate receptor (S1P1) promotes neuroblast detachment in the postnatal OB (Alfonso et al., 2015). However, The cellular and molecular mechanisms controlling cell-cell adhesion during this detachment remain unclear. Here we report that Fyn, a non-receptor tyrosine kinase, regulates the detachment of neuroblasts from chains in the male and female mouse OB. By performing chemical screening and in vivo loss- and gain-of-function experiments, we found that Fyn promotes somal disengagement from the chains, and is involved in neuronal migration from the RMS into the granule cell layer of the OB. Fyn knockdown or Dab1 deficiency caused p120-catenin to accumulate and adherens junction-like structures to be sustained at the contact sites between neuroblasts. Moreover, a Fyn and N-cadherin double-knockdown experiment indicated that Fyn regulates the N-cadherin-mediated cell adhesion between neuroblasts. These results

suggest that the Fyn-mediated control of cell-cell adhesion is critical for the detachment of chain-forming neuroblasts in the postnatal OB.