kines produce their effects in a synergistic manner. It also appears that the combinations and concentrations optimal for neurogenesis and oligodendrogenesis are different.

Discussion

In the postnatal mammalian brain, neural stem cells (NSCs) are mainly localized in two areas: the forebrain SVZ (Doetsch and Scharff, 2001) and the subgranular zone of the dentate gyrus (Zerlin et al., 2004) of the hippocampus (Gould et al., 1999; Lie et al., 2004). The microenvironments that are permissive for neurogenesis and gliogenesis are composed of a variety of cell types, such as stem cells, progenitor cells, astrocyte cells, and microglial cells. Increasing evidence indicates the importance of the surrounding glial cells in neurogenesis (Doetsch et al., 1999; Temple, 2001). Goings et al. (2006) have shown that microglia in the adult SVZ are semiactivated, but microglial contribution to neurogenesis is complex. So far, the role of microglia in neurogenesis has been examined mainly in pathological conditions (Ekdahl et al., 2003; Monje et al., 2003). Activated microglia in inflammatory settings, such as intraperitoneal administration of LPS, inhibited neurogenesis (Ekdahl et al., 2003; Monje et al., 2003; Cacci et al., 2008). However, a growing number of studies have suggested that activated microglia are beneficial for neurogenesis (Aarum et al., 2003; Butovsky et al., 2005, 2006a; Walton et al., 2006; Ziv et al., 2006; Hanisch and Kettenmann, 2007; Ekdahl et al., 2009; Bachstetter et al., 2011; Ekdahl, 2012; Vukovic et al., 2012), even in pathological conditions, such as an animal model of multiple sclerosis (Butovsky et al., 2006b), ischemia (Thored et al., 2009; Deierborg et al., 2010), and epilepsy (Bonde et al., 2006). Such variability concerning the effects of microglia on neurogenesis may reflect the different polarization of microglia and/or the precise status of NSCs/neuronal progenitor cells (NPCs) (Cacci et al., 2008; Li et al., 2010; Ekdahl, 2012; Ortega et al., 2013), and crosstalk between them (Mosher et al., 2012).

Concerning the origin of microglia, various data have been reported. *In vivo* lineage tracing studies have established that microglia differentiate from primitive myeloid progenitors that arise before embryonic day 8 and are identified in the CNS parenchyma even before definitive hematopoiesis (Ginhoux et al., 2010), although it has been shown that microglia migrate from lateral ventricle into brain via SVZ in the postnatal brain (Mohri et al., 2003). Microglia in the embryonic SVZ limit the production of cortical neurons by phagocytosing neural precursor cells (Cunningham et al., 2013). Even in the adult brain, microglia appear densely populated in neurogenic niches, such as the SVZ (Mosher et al., 2012), and appear more activated in the adult SVZ than in non-neurogenic zones (Goings et al., 2006). Although these data strongly suggest that microglia play important roles in CNS development and an increasing number of studies have elucidated various roles of microglia during developmental periods (Wu et al., 1993; Pont-Lezica et al., 2011; Tremblay et al., 2011), the detailed dynamics of microglia in the SVZ from early postnatal stages to a young adult stage remain to be elucidated. Furthermore, few studies have examined the role of microglia in normal developmental processes during this period. In this study, we found that activated microglia first accumulated in the SVZ and then dispersed to white matter, where they became more ramified. In addition, the number of activated microglia was largest in the medial SVZ throughout the studied period (P30). We here elucidated that activated microglia in the early postnatal SVZ enhance neurogenesis and oligodendrogenesis through the mechanisms described below. Our present data and the previous reports concerning developmental changes in the distribution suggest that the developmental roles of microglia in the SVZ are not transient but more general throughout life.

Using a combination of *in vivo* and *in vitro* approaches, we demonstrated that these activated microglia in the early postnatal SVZ enhanced neurogenesis and oligodendrogenesis through releasing cytokines. Butovsky et al. (2006a) reported that the beneficial effects of microglia on adult neurogenesis/oligodendrogenesis was achieved by IGF-1 after IL-4 and IFN-γ release from activated microglia. In our study, although the activated microglia in the early postnatal SVZ did produce IGF-1, the effects of activated microglia on neurogenesis and oligodendrogenesis observed here were independent of IGF-1. We clarified that the SVZ microglia facilitate neurogenesis and oligodendrogenesis via production of cytokines. Interestingly, in *in vitro* coculture experiments, the enhancement of neurogenesis and oligodendrogenesis was suppressed by a mixture of function-blocking antibodies (anti-IL-1β, anti-IL-6, anti-TNF-α, anti-IFN-γ), but not by a single function-blocking antibody. These results suggest that microglial cytokines enhance neurogenesis and oligodendrogenesis in combinations. In support of this, among the cytokines we examined, only IL-1β and IFN-γ enhanced neurogenesis, whereas only IL-1β and IL-6 showed potentials of enhancing oligodendrogenesis. Previous reports have shown that NPCs express IL-1β, IL-1RI and IL-1RII, and IL-1β regulates the proliferation and differentiation of NPCs (Wang et al., 2007). It has been shown that IL-1β promotes proliferation and differentiation of oligodendrocyte progenitor cells (Vela et al., 2002). Furthermore, IL-6 and IL-6R are reported to promote neurogenesis and gliogenesis (Islam et al., 2009; Oh et al., 2010). Li et al. (2010) showed that IFN-γ stimulated neurosphere formation from embryonic brain, but the effects of IFN-γ are modified in the presence of microglia, supporting the complementary interactions between cytokines.

These proinflammatory cytokines had been thought to cause suppression of neurogenesis in pathological conditions, such as chronic LPS stimulation (Monje et al., 2003), allergic encephalomyelitis (Ben-Hur et al., 2003), and status epilepticus (Iosif et al., 2006; Koo and Duman, 2008). However, recent reports have shown that that the different polarizations of microglia are induced by different application protocols of LPS (Cacci et al., 2008), suggesting that the combination and the concentration of cytokines released by microglia change depending on the ambient conditions. Indeed, some previous reports suggest that each cytokine reveals different effects at different concentrations (Bernardino et al., 2008; Cacci et al., 2008; Das and Basu, 2008; Russo et al., 2011). Bernardino et al. (2008) have shown that TNF-α results in proliferation of neural stem cells at 1 ng/ml but caused apoptosis at 10–100 ng/ml. Microglia in the developmental brains may sense the change of environment and release a certain combination of cytokines at suitable concentrations for neurogenesis and oligodendrogenesis, whereas overactivation of microglia in pathological inflammation or nerve injury induces massive proinflammatory cytokine production, resulting in the suppression of neurogenesis. Nakanishi et al. (2007) showed that IL-6 promoted astrocytogenesis from the SVZ neurospheres. In our study, however, although activated microglia release IL-6, the effects on astrocytogenesis were not observed either *in vivo* or *in vitro*. This might be because of different medium compositions (i.e., growth factors) used for differentiation of neurosphere. Compared with the other cytokines, only IFN-γ suppressed oligodendrogenesis, suggesting that a proper concentration range of IFN-γ to enhance oligodendrogenesis might be narrower than the other cytokines.

Of interest, our results suggest that activated microglia significantly increased $O4^+$ cells while decreasing $PDGFR\alpha^+$ cells. These results suggest that activated microglia enhance oligodendrogenesis at later stages of oligodendrocyte differentiation. Recently, Miron et al. (2013) showed that a switch from M1 to M2 occurred in microglia during remyelination, and oligodendrocyte differentiation was enhanced by M2 cell releasing factors. A comprehensive analysis about the released factors from microglia, including cytokines, and the precise identification of the cell population (NSCs and/or NPCs) that are responsive to these factors will be necessary to understand fully the mechanisms underlying the effects of microglia on neurogenesis and gliogenesis.

In conclusion, we have found a population of activated microglia accumulating in the early postnatal SVZ that facilitate neurogenesis and oligodendrogenesis. A synergism among cytokines was important for the effects. To our knowledge, this is the first report to show that microglia regulate cell differentiation via releasing cytokines in early postnatal brain development.

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平成 26 年度厚生労働科学研究委託費

医薬品等規制調和・評価研究事業

V. 班会議プログラム

平成 26 年度 厚生労働科学研究委託費(医薬品等規制調和・評価 研究事業)

「ヒト iPS 細胞由来神経細胞等を用いた新規 *in vitro* 医薬品安全性評価法の開発」
第 1 回 班会議

日時:平成 26 年 8 月 27 日

場所:国立医薬品食品衛生研究所(東京都世田谷区上用賀 1-18-1)
講堂(11 号館 3 階)

出席者: 白尾、関野、植村、佐藤、宮本、池谷、小山(敬称略)

司会: 佐藤 薫(国立医薬品食品衛生研究所 薬理部)

プログラム

13:00 – 17:00 班会議
「平成 26 年度 準備状況、研究計画、ゴール設定」

13:00-13:10 ごあいさつ 佐藤 薫(国立医薬品食品衛生研究所 薬理部)

13:10-13:40 「脳神経機能を再現したヒト iPS 細胞由来神経細胞等およびそれを用いた薬理評価系の開発」 佐藤 薫(国立医薬品食品衛生研究所 薬理部)

13:40-14:10 「グリア細胞を利用した神経回路形成及び多点平面電極システムによる安全性評価試験法の確立」 宮本憲優(エーザイ株式会社筑波研究所・安全性評価)

14:10-14:25 Coffee Break

14:25-14:55 「ヒト iPS 細胞由来神経細胞等のシナプス機能の定量的評価法の開発と医薬品安全性評価への応用」 白尾智明(群馬大学大学院医学系研究科)

14:55-15:25 「脳疾患を再現した *in vitro* 実験系におけるヒト iPS 細胞由来神経細胞等の構造・機能の解析」 池谷裕二(東京大学・大学院薬学系研究科)

15:25-15:40 Coffee Break

15:40-16:45 総合討論

16:45-17:00 おわりに

平成 26 年度　厚生労働科学研究委託費（　医薬品等規制調和・評価　研究事業）

「ヒト iPS 細胞由来神経細胞等を用いた新規 *in vitro* 医薬品安全性評価法の開発」
第 2 回 iNCENS 班会議

日時：平成 27 年 2 月 25 日（水）14:10-17:30

場所：国立医薬品食品衛生研究所（東京都世田谷区上用賀 1-18-1）
第一会議室　（28 号館 3 階）

出席者：　白尾、関野、宮本、池谷、小山、佐藤、高橋、最上、片山、干川、中條（敬称略）

司会：　佐藤　薫（国立医薬品食品衛生研究所　薬理部）

プログラム

14:10 – 17:30　班会議
「平成 26 年度　成果報告　と　来年度計画」

14:10-14:15　ごあいさつ　　佐藤　薫（国立医薬品食品衛生研究所　薬理部）

14:15-14:45　「脳神経機能を再現したヒト iPS 細胞由来神経細胞等およびそれを用いた薬理評価系の開発」　　佐藤　薫（国立医薬品食品衛生研究所　薬理部）

14:45-15:15　「グリア細胞を利用した神経回路形成及び多点平面電極システムによる安全性評価試験法の確立」　　宮本憲優（エーザイ株式会社筑波研究所・安全性評価）

15:15-15:25　Coffee Break

15:25-15:55　「ヒト iPS 細胞由来神経細胞等のシナプス機能の定量的評価法の開発と医薬品安全性評価への応用」　　白尾智明（群馬大学大学院医学系研究科）

15:55-16:25　「脳疾患を再現した *in vitro* 実験系におけるヒト iPS 細胞由来神経細胞等の構造・機能の解析」　　池谷裕二（東京大学・大学院薬学系研究科）

16:25-17:25　総合討論・事務連絡

17:25-17:30　おわりに