Mutations in the Reelin pathway are associated with abnormal expression of microglial IgG FC receptors in the cerebellar cortex

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Abstract
Microglia are the immune cells of the central nervous system involved in a variety of developmental processes, such as regulation of cell death and survival, spatial patterning, and contribute to the development of Purkinje cells (PCs) during migration. Microglia express immunoglobulin G Fc receptors (FcgRs). In this report, we describe microglial FcgR expression and its relation to abnormal PC migration in the cerebellum during development. To detect microglial FcgR, the direct anti-IgG (secondary antisera) and high concentrations of Triton X-100 were applied as a method for labeling microglial cells without the use of any specific primary antiserum. By using Acp2−/− mice, which show an excessive PC migration into the molecular layer (ml), and 3 different types of mice with a null to alter the Reelin pathway (Reeler, Dab1 (SCM)-, and Apoer mutant mice), we studied the location of PCs and the expression of FcgRs. Wild type littermates were used as controls in all studies. We show that the expression of microglial FcgRs was absent and PCs were ectopically located in the white matter in the cerebella of all mutant mice, except for the Acp2−/− mice (PCs were located in the ml). These results suggest a role for FcgRs in the Reelin signaling pathway, not in regulating PC migration, but rather in the adaptation to an environment with a relatively large number of ectopically located PCs. However, the exact correlation between the ectopic location of PCs and lack of FcgRs in Reeler, SCM, and Apoer−/− mice and the presence of FcgRs and directed PC location in the ml in Acp2−/− mice are yet to be determined.

Keywords Reelin · Purkinje cells · Cerebellum · Microglia · IgG FC receptors · Mice

Introduction

Purkinje cells (PCs) constitute the main output of the cerebellar cortex and contribute to a variety of cerebellar functions, including coordination and motor learning [1]. Following mitotic division at embryonic day (E) 10.5–12.5, PCs start the migration and form the PC plate, which is a multilayer structure consisting of PCs in the mantle zone [2]. The migration of PCs during cerebellar development is tightly controlled and the Reelin pathway plays an important role during this process [3]. Reelin is a large protein secreted by the granule cell precursors and cerebellar nuclei neurons in the external germinal zone and cerebellar nuclei, respectively [4]. Reelin binds to VLDLR (very low-density lipoprotein receptor) and ApoER2 (apolipoprotein-E receptor 2), and activates a protein known as Dab1 (Disabled 1). Dab1 is an adaptor protein essential for the intracellular transduction of Reelin signaling and regulates the migration and differentiation of post-mitotic neurons during brain development.

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Previous studies have shown that mutations in Reelin, Dab1, Apoer2, and Vldlr genes resulted in a lack of dispersal of PCs from the cluster and hindered migration of PCs during cerebellar development [5–7]. On the other hand, a spontaneous mutation in the lysosomal acid phosphatase 2 (Acp2) (nax-naked-ataxia) in mice is associated with excessive migration of PCs to the molecular layer (ml) and a lack of PCs monolayer formation [8, 9].

Microglia are myeloid-derived cells in the central nervous system (CNS) involved in a variety of developmental processes, such as regulation of cell death and survival, spatial patterning, formation and refinement of neural circuits, and synaptic wiring in the CNS [10, 11]. There is evidence to suggest that microglia contribute to the development of PCs during migration by controlling the survival and synaptogenesis of these cells [12, 13]. Microglia express immunoglobulin G Fc receptors (FcγR), which are involved in phagocytic activity, oxidative burst, and inflammatory responses of microglia [14]. Although recent studies shed some light on the role of certain specific mechanisms in PC migration, it is not clear whether abnormal migration is associated with microglial FcγR during cerebellar development.

In this study, we used three different knockout mouse models in which the Reelin pathway is affected and PC migration is decreased (Reeler-, Dab1 (SCM)-, and Apoer2 mutant mice), and nax mice (Acp2<sup>−/−</sup>) in which PC migration is increased, to investigate the potential association between expression of microglial FcγRs in the cerebellar cortex and PC migration.

Materials and methods

Animal maintenance and tissue processing

All animal procedures were performed in accordance with institutional regulations and the Guide to the Care and Use of Experimental Animals from the Canadian Council for Animal Care and has been approved by local authorities “the Bannatyne Campus Animal Care Committee”, University of Manitoba Animal Care Committee (ACC), and University of Calgary Animal Care Committee (ACC). Animals were housed at room temperature and relative humidity (50–60%) with a 12-h light dark cycle. All efforts were made to minimize the number of mice used; animals were treated in a humane manner. In this study, we used nax (Acp2<sup>−/−</sup>), Reeler (Reelin mutant), SCM (Dab1 mutant), and Apoer (apoE receptor mutant) mice. An Acp2<sup>−/−</sup> colony was established in the Genetic Modeling Center at the Faculty of Health Sciences, University of Manitoba, by breeding mice (C57BL/6) heterozygous for the Acp2<sup>−/−</sup> mutation [15, 16]. Mice null for Reelin ([B6C3Fe a/a-Reln/J; [17, 18]], Dab1 (CBY.129S4-Dab1tm1Cpr/J; [19–21]), and Apoer [B6;129S6-Lrp8tm1Her/J; [4, 7]) were a generous gift from Dr. Richard Hawkes (University of Calgary), and were originally purchased from The Jackson Laboratory. Wild type littermates were used as controls in all studies. The animals were perfused and post-fixed with 4% paraformaldehyde and then cryosectioned at 20 μm and processed for immunohistochemistry according to methods described in Bailey et al. [16].

Antisera

We used rabbit polyclonal Anti-Iba1 antibody (Millipore #MABN92). Iba1 is a 17-kDa EF hand protein that is specifically expressed in macrophages/microglia [22]. Biotinylated anti-FcγRs (α-IgGs; secondary antibodies or antisera) can be detected with the ABC method and avidin-bound fluorochromes (Vectastain, Vector Laboratories Inc., Burlingame CA., USA), as we used this method to detect microglia [23]. Rabbit anti-GFAP (1:2000 dilution, Chemicon Inc. Temecula U.S.A.) specifically recognizes astrocytes. We also used rabbit polyclonal anti-MBP (Santa Cruz #sc-13914) and mouse monoclonal anti-Calb1 [24].

Immunohistochemistry

 Peroxidase immunohistochemistry was carried out on cerebellar sections as described previously [15, 25]. Briefly, tissue sections were washed thoroughly, blocked with 10% normal goat serum (Jackson Immunoresearch Laboratories, West Grove, PA), and incubated in 0.1 M PBS buffer containing 0.1% Triton-X and the primary antibody for 16–18 h at 4 °C. Secondary incubation in horseradish peroxidase (HRP) conjugated goat anti-rabbit or HRP-conjugated goat anti-mouse antibody (diluted 1:200 in PBS; Jackson Immunoresearch Laboratories, West Grove, PA) lasted 2 h at room temperature. Diaminobenzidine (DAB, 0.5 mg/ml) was used to visualize the reaction product. Cerebellar sections for double-label fluorescent immunohistochemistry were processed as described previously [25]. To detect microglial immunoglobulin G Fc receptors (FcγR), the direct anti-IgG (secondary antisera) and high concentrations of Triton X-100 (1%) were applied as a method for labeling microglial cells without the use of any specific primary antisera [23]. Biotinylated anti-FcγRs (α-IgGs; secondary antibodies or antisera) can be detected with the avidin–biotin–immunoperoxidase (ABC) method and with avidin-bound fluorochromes. To reveal the secondary antisera binding, the ABC method was used. Biotinylated secondary antisera were diluted at 1:200 in PBS and used for incubation for 2 h. The Vectastain Elite ABC kit (Vector, Burlingame, CA; #PK-61000) was diluted at 1:200 as well and used for a 3 h incubation. Tissue-bound peroxidase was revealed by incubating the sections in a solution containing 0.002% (w/v)
3,3'-diaminobenzidine (DAB; Sigma, St Louis, MO) and 0.003% (v/v) H$_2$O$_2$ in 0.05 M Tris–HCl buffer, pH 7.6. The sections were mounted, dehydrated, and cover-slipped with Entellan (Merck; Darmstadt, Germany).

**Figure preparation**

For bright field microscopy, an Olympus BH-2 microscope was used and images were captured using Image-Pro Express software. For fluorescence microscopy, a Zeiss Lumar V12 stereomicroscope was used to capture images of entire cerebellar sections using AxioVision 4 software. For high magnification fluorescence microscopy a Zeiss Z1. Imager with AxioVision 4 software and a Zeiss LSM 700 confocal microscope with Zen software were used to obtain images. Images were cropped, corrected for brightness and contrast, and assembled into montages using Adobe Photoshop CS5 Version 12.

**Results**

To visualize the microglia, we utilized biotinylated anti-mouse FcgR secondary antibody by addition of high concentrations of Triton X-100 (1%) and revealed secondary antibody binding by the avidin–biotin-immunoperoxidase (ABC) method [23, 26]. Application of this method revealed the non-neuronal cells with branches similar to the microglia in the cerebellar cortex and raised the speculation that FcgRs are localized on microglia under normal, healthy conditions (Fig. 1a, d). To further confirm this observation, the ionized calcium binding adaptor molecule 1 (Iba1) marker was used to demonstrate the morphological features of microglial cells [27, 28]. A transverse section of the cerebellum immunostained with Iba1 showed that microglia are the only immuno-reactive cells for this marker and the morphology closely resembled that of the FcgRs$^+$ cells. (Fig. 1b, c). Double immunostaining confirmed that FcgRs$^+$ cells are indeed co-labeled with Iba1 (Fig. 1f); the detail of co-localization of FcgR and Iba1 is demonstrated by higher magnification (Fig. 1d–f).

To determine whether FcgR is expressed in other non-neuronal cells, the wt cerebellar sections were stained by double-fluorescence immunohistochemistry. FcgR immunoreactivity was not observed in GFAP-positive astrocytes (Fig. 2a–c) or MBP-positive oligodendrocytes (Fig. 2d–f).

To study the expression of FcgRs during the development of microglia, cerebellar sections obtained during perinatal development were used. FcgR immunoreactivity was distinguishable at the prenatal stages of development, and by E17, FcgR immunoreactivity was weak at the core of the cerebellar sections in the developing white matter (Suppl. Figure 1A, B). The FcgR immunoreactivity was strong in microglial precursor cells, which are located in developing white matter at around P1 (Suppl. Figure 1C) and P3 (Suppl. Figure 1D). At P10, developing microglial cells with their

![Fig. 1](image_url) The expression of FcgR in the normal, healthy adult mouse cerebellum. a–c Double immunofluorescence staining for FcgRs (a—red) and Iba1 (b—green; c—merged) of a transverse section of an adult mouse cerebellum showing the microglia (arrows) that scattered in a non-overlapping manner in the molecular layer (ml), Purkinje cell layer (Pcl), and granular layer (gl). d–f A high magnification view of the microglia double immunofluorescence staining for FcgR (d—red) and Iba1 (e—green; f—merged) showing detail of FcgR distribution on a typical microglial cell body (asterisks) and its branches (arrowheads). Scale bars: 100 μm (c applies to a, b); 25 μm (f applies to d, e). (Color figure online)
extended process were clearly detectable by FcgR expression, which was highly abundant in the white matter and indicated a stream migratory pathway to the cerebellar cortex (Suppl. Figure 1E, F).

To determine whether the FcgR expression profile is altered in the cerebellum when PC migration is abnormal, we compared the cerebella of nax mutant mice, which show an excessive PC migration, with those of Reelin mutant mice, characterized by prominent ectopic PCs in the white matter and a lack of PC cluster dispersal. The cerebellar cortex of nax mice is abnormal and the three layers of the cortex are indistinguishable, with PCs invading the ml [16]. In a P17 wt mouse cerebellum, PC bodies form a monolayer-like structure while their dendrite extensions are apparent in the developing ml and are specifically directed toward the pial surface (Fig. 3a). In the nax cerebellum, PC bodies exhibit less dendritic arborization and form a multi- rather than a monolayer of cells in the cortex (Fig. 3d). In addition, these multilayered PCs occupy all of the ml and their dendrites are branched in a multidirectional pattern (Fig. 3d) in comparison to the wt (Fig. 3a). Recently, we have shown a difference in the distribution of both ramified and activated microglial cells between nax and wt cerebella [29]. Despite the excessive PC migration in nax cerebella with activated microglia, FcgR and Iba1 expression are colocalized in nax at P17, in a similar fashion as in the wt cerebellum (Fig. 3b, e; higher magnification in Fig. 3c, f). To determine the FcgR expression profile in cerebellar with ectopic localization of PCs in the white matter, FcgR and Iba1 immunoperoxidase staining was performed in sections obtained from the SCM cerebellum (Fig. 4). Unexpectedly, no FcgR immunoreactivity was observed in these sections (Fig. 4d, e). Iba1 immunostaining was utilized to determine if the lack of FcgR expression was associated with an absence of microglia in the cerebellum. Results revealed the existence of ramified microglia which are not activated in response to an ectopic neuronal environment (Fig. 4f, g). To test the hypothesis that FcgR expression is absent due to disruption of the Reelin pathway, we further pursued our experiments in Reeler and Apoer−/− mutants. Double immunofluorescent staining using FcgR and Iba1 antibodies (Fig. 5) in wt mice confirmed the colocalization of the FcgR and Iba1 under normal conditions (Fig. 5a–c). In contrast, double immunofluorescent staining in Reeler (Fig. 5d–f), Apoer−/− (Fig. 5g–i), and Scm (Fig. 5j–l) mutants revealed a lack of FcgR expression in the microglia, despite a well-organized and similar to wt (Fig. 5a–c) microglial Iba1 expression profile in these mutant mice.

**Discussion**

In the current work, we found that cerebellar microglia express FcgRs during development starting at E17 until postnatal stage P10. We also observed an increase in the
expression of microglial FcgRs at the postnatal as compared to the prenatal stage in the cerebellum. Previous studies have shown that FcgRs are expressed in a variety of cell types in the adult brain [14], but there are only a few studies on the role and expression of FcgRs during the gestational period and early development [30]. We showed that cerebellar astrocytes do not express FcgRs, which is consistent with a previous study in human cerebellar tissue [31]. Although some evidence exists on the expression of FcgRs on cerebellar microglia during the gestational period [30, 32], our data more definitively confirmed the presence of microglial FcgRs, suggesting their involvement in early cerebellar development. It has been shown that the numbers of microglia increase progressively during cerebellar development (E11.5) until the postnatal period [33]. In addition, evidence indicates that programmed cell death plays an important role in brain development [34, 35], and microglia are responsible for the phagocytosis of neurons following apoptosis in order to clear pathways for developing cortical afferents and efferents during cerebellar development [13, 33, 36]. It is important to note that FcgRs are essential for the phagocytic activity of microglia, and increased expression of FcgRs on cerebellar microglia in our study is associated with the increased number of microglia during development [37, 38].

Further, we demonstrated that manipulation of the Reelin pathway was associated with the lack of dispersal of PCs from the cluster and hindered migration of PCs during cerebellar development. In this context, previous studies have shown that Reeler mice (mutation in the Reln gene), scrambler mice (mutation in the Dab1 gene), and Apoer2−/− mice exhibit ectopic PCs and impairments in PC migration [5–7]. On the other hand, nax mice (mutation in the Acp2 gene) show excessive migration of PCs to the ml and a lack of PC monolayer formation. In this study, our observations in the cerebella from both ‘Reelin pathway manipulated’ mice and nax mice suggest that microglia are present in the cerebella of all animals and that neither a decreased or increased PC migration affects Iba1 expression. Interestingly, unlike in nax mice, microglia in the cerebella of Reeler, SCM, and Apoe2−/− mice did not express FcgRs. Our results unequivocally revealed that manipulations in the Reelin pathway affected the...
expression of microglial FcgRs in the cerebellum. Previous studies demonstrated that manipulation of Reelin signaling directly changes radial glia morphology and biochemical maturation [39–41]. Radial glial cells play a crucial role in the radial migration of neurons and are characterized by their astroglial properties and long radial processes [42]. To date, the impact of Reelin signaling on cerebellar microglia during development is not clear. Microglia express the Reelin target receptors VLDL and ApoE2 [43–45], and it has been indicated that activation of these receptors is associated with an improved microglial ability to phagocytize and clear apoptotic bodies [45–47]. Our results showed that microglia of Reeler, SCM, and Apoe2-/- mice do not express FcgRs. Research by Bigler and colleagues showed that lipoproteins (namely low density lipoproteins) are important regulators of FcgR-mediated phagocytosis [48]. In addition, Dab1 is associated with phagocytic activity of macrophages/microglia [49]. In our study, lack of LDL receptor family members (such as Apoe2) and their associated downstream signaling (Dab1) resulted in the absence of microglial FcgR expression. Since phagocytic activity of microglia is important during cerebellar development, it is possible that manipulations of Reelin signaling affect microglial activity through ablation of FcgRs in case of developmental disorders. In conclusion, the results of our study indicate a modulatory role for FcgRs in the reelin signaling pathway, not in regulating PC migration, but rather in the adaptation to an environment with a relatively large number of ectopically located PCs. However, the exact correlations between the ectopic location of PCs and lack of FcgR expression on microglial cells in Reeler, SCM, and Apoe2-/- mice and the presence of FcgRs and directed PC location in the ml in Acp2-/- mice are yet to be elucidated.
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**Data availability** Data will be provided upon request.

**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest/competing interests.

**Research involving human participants and/or animals** Animal study was performed under certificate number 15-066/1/2. This research is not involved any human subjects.

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**Fig. 5** Transverse sections of wild type, SCM (Dab1−/−), Reeler (rl−/−), and Apoer−− cerebella immunostained with anti-FcgRs and anti-Iba1. a–c Transverse sections of wild type cerebellum immunostained with anti-FcgRs (a—red) and anti-Iba1 (b—green; c—merged) showing FcgR and Iba1 co-localization in microglia. d–f Transverse sections of SCM (Dab1−/−) cerebellum double immunostained with anti-FcgRs (d—red) and anti-Iba1 (e—green; f—merged) showing that FcgR is not expressed in microglia, which are present and express Iba1. g–i Transverse sections of Reeler (rl−/−) cerebellum double immunostained with anti-FcgRs (g—red) and anti-Iba1 (h—green; i—merged) showing that FcgR is not expressed in microglia, which are present and express Iba1. j–l Transverse sections of Apoer−− cerebellum double immunostained with anti-FcgRs (j—red) and anti-Iba1 (k—green; l—merged) showing that FcgR is not expressed in microglia, which are present and express Iba1. Scale bars: 40 μm (c applies to a, b and l applies to j, k); 25 μm (f applies to d, e); 20 μm (i apply to g, h). (Color figure online)
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