Int J Clin Exp Pathol 2013;6(7):1261-1271
www.ijcep.com /ISSN:1936-2625/IJCEP1303056

Original Article

Delayed but not loss of gliogenesis in *Rbpj*-deficient trigeminal ganglion

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Received March 28, 2013; Accepted May 22, 2013; Epub June 15, 2013; Published July 1, 2013

Abstract: Somatosensory ganglia including dorsal root ganglion (DRG) and trigeminal ganglion (TG) are derived from a common pool of neural crest stem cells (NCCs), and are good systems to study the mechanisms of neurogenesis and gliogenesis. Previous studies have reported that deletion of Rbpj, a critical integrator of activation signals from all Notch receptors, in NCCs and their derived cells resulted in the delayed gliogenesis at early stage and a loss of glial cells at later stage in the DRG. But the phenotypes in the TG have not been described. Here we reported although the gliogenesis was also delayed initially in *Rbpj*-deficient TG, it was recovered as the development progressed, as shown by the presence of large number of glial cells in the TG at later stages. However, neuronal reduction was observed in *Rbpj*-deficient TG, which is similar to what observed in *Rbpj*-deficient DRG. Taken together, our data indicate the function of Rbpj is diversified and context dependent in the gliogenesis of somatosensory ganglia.

Keywords: Dorsal root ganglion, trigeminal ganglion, *Rbpj*, gliogenesis

Introduction

The dorsal root ganglion (DRG) and trigeminal ganglion (TG) containing the first order afferent neurons in the somatosensory pathway relay somatosensory stimuli including touch, pain and temperature from the body and the orofacial region, respectively [1]. Both of them composed of well-characterized populations of peripheral sensory neurons and glial cells that are derived from a common pool of neural crest stem cells (NCCs), and are good systems to study the mechanisms of neurogenesis and gliogenesis [2, 3].

So far most of our knowledge about the development and differentiation of peripheral sensory neurons and glial cells have come from the study of DRG [3]. Although some genes that play important roles in the development of DRG are also expressed in the TG, their functions in TG are seldom reported. Because of the high similarities in the cellular origin, components and functions between DRG and TG, the genes expressed both in DRG and TG are always thought to play similar roles in these two different sensory ganglia. However, previous studies have shown that the molecular mechanisms that underlie the specification and differentiation of sensory neurons in TG were not identical to those in DRG. For example, in the mice lacking the POU domain-containing transcription factor Brn-3a, about 70% sensory neurons in TG were gradually lost, whereas the number of sensory neurons in DRG was not changed [4]. In addition, Brn-3a was necessary for the expression of TrkC in TG but not in DRG [4]. Since TG has its own structural modality and functional features, it's crucial to reveal the specific molecular mechanisms underlying its development [5].

Recombination signal binding protein for immunoglobulin kappa J region (Rbpj) is the transcription factor that can interact with the intracellular domains of all four Notch receptors and is required to mediate their transcriptional effects [6]. Therefore, deletion of Rbpj would be

expected to completely abolish canonical Notch signaling, which plays the two fundamental roles in the development of the nervous system: maintaining undifferentiated progenitors by inhibiting neuronal differentiation, and promoting glial determination [7]. Consistently, the deletion of Rbpj expression in NCCs and NCC-derived cells caused the reduction of sensory neurons and a complete loss of glial cells in DRG [8, 9]. Recently Mead TJ et al reported that over-expression of Notch receptor in NCCs resulted in decreased neurogenesis and defective axonal projections in TG, and inactivation of *Rbpj* in the NCCs led to normal formation of TG but delayed peripheral axonal growth of TG neurons [10]. However, the morphogenesis of TG was examined only at E10.5 and it is unclear if there are any developmental defects in *Rbpj*-deficient TG at later embryonic stages.

In the present study, we found the initiation of BFABP expression in glial progenitors was delayed and the separation of P75 and Sox10 expression in NCCs did not occur in the TG of *Wnt1-Cre; Rbpj*$^{flox/flox}$ conditional knock out (CKO) mice suggesting that the multipotency of NCCs was abnormally maintained. The number of neurons in *Rbpj*-deficient TG became dramatically decreased compared with the wild-type, which is consistent with what had happened in the *Rbpj*-deficient DRG. Surprisingly the gliogenesis was largely recovered in *Rbpj*-deficient TG at later stages indicating a divergent function of Rbpj in the control of TG gliogenesis.

Material and methods

Mouse breeding and genotyping

Wnt1-Cre and *Rbpj*$^{flox/flox}$ mice were generated and genotyped as described previously [11, 12]. To inactivate *Rbpj* expression in the neural crest, we crossed Wnt1-Cre mice with *Rbpj*$^{flox/flox}$ mice to obtain *Wnt1-Cre; Rbpj*$^{flox/+}$ progeny. Then *Wnt1-Cre; Rbpj*$^{flox/+}$ mice were crossed with each other to obtain *Wnt1-Cre; Rbp*$^{flox/flox}$ progeny. The morning of the day on which the vaginal plug appeared was designated as E0.5. In each set of experiments, at least three CKO embryos and an equal number of littermate control mice (e.g., wild-type, *Rbpj*$^{flox/+}$ or *Wnt1-Cre; Rbpj*$^{flox/+}$) were used. Animal care procedures were reviewed and approved by the Animal Studies Committee at the East China University of Science and Technology, School of Pharmacy, Shanghai, China.

In situ hybridization and immunofluorescence

In situ hybridization and immunofluorescence on brain sections were performed as previously described [13]. The SCG10 mouse antisense RNA probes were used [14]. For immunofluorescence, the following primary antibodies were used: rabbit anti-P75 (1:500; Promega, Fitchburg, Wisconsin, USA), goat anti-Sox10 (1:500; Santa Cruz, California, USA), mouse anti-Islet1 (1:100; Developmental Studies Hybridoma Bank, Iowa, USA), rabbit anti-BFABP (1:1,000; Chemicon, California, USA), mouse anti-BrdU (1:200; Calbiochem, Darmstadt, Germany). Species-specific secondary antibodies conjugated to Cy2 or Cy3 (1:1,000; Jackson ImmunoResearch, West Grove, PA, USA) were used to detect primary antibodies. Sections were observed under a Nikon BOi or a Zeiss LSM510 confocal microscope.

BrdU labeling and TUNEL staining

For BrdU labeling, a single BrdU pulse (60 μg/g of body weight) was delivered intraperitoneally to timed-pregnant females at E10.5, and embryos were fixed 2 hours later. Sections were processed for BrdU immunostaining as described above. TUNEL staining was performed according to the In Situ Cell Death Detection Kit instructions (Roche, Indianapolis, USA).

Statistical analysis

For cell counts in E10.0 and E10.5 TG, six sets of consecutive 12 μm-thick sections were made in each E10.5 embryo, and cell counts were done in one set of sections that had been processed for islet1/Sox10, P75/Sox10 double immunostaining, BrdU or TUNEL staining. For cell counts in E16.5 TG, eight sets of consecutive 12 μm-thick sections were made in each E16.5 embryo, and cell counts were done in one set of sections that had been processed for SCG10 in situ hybridization and BFABP immunostaining. Approximately five sections on one slide were counted. For each set of comparisons, at least three CKO mice and three littermate controls (e.g. wild-type, *Rbpj*$^{flox/+}$ or *Wnt1-Cre; Rbpj*$^{flox/+}$) were included. All data were analyzed using OriginPro7.5 software and

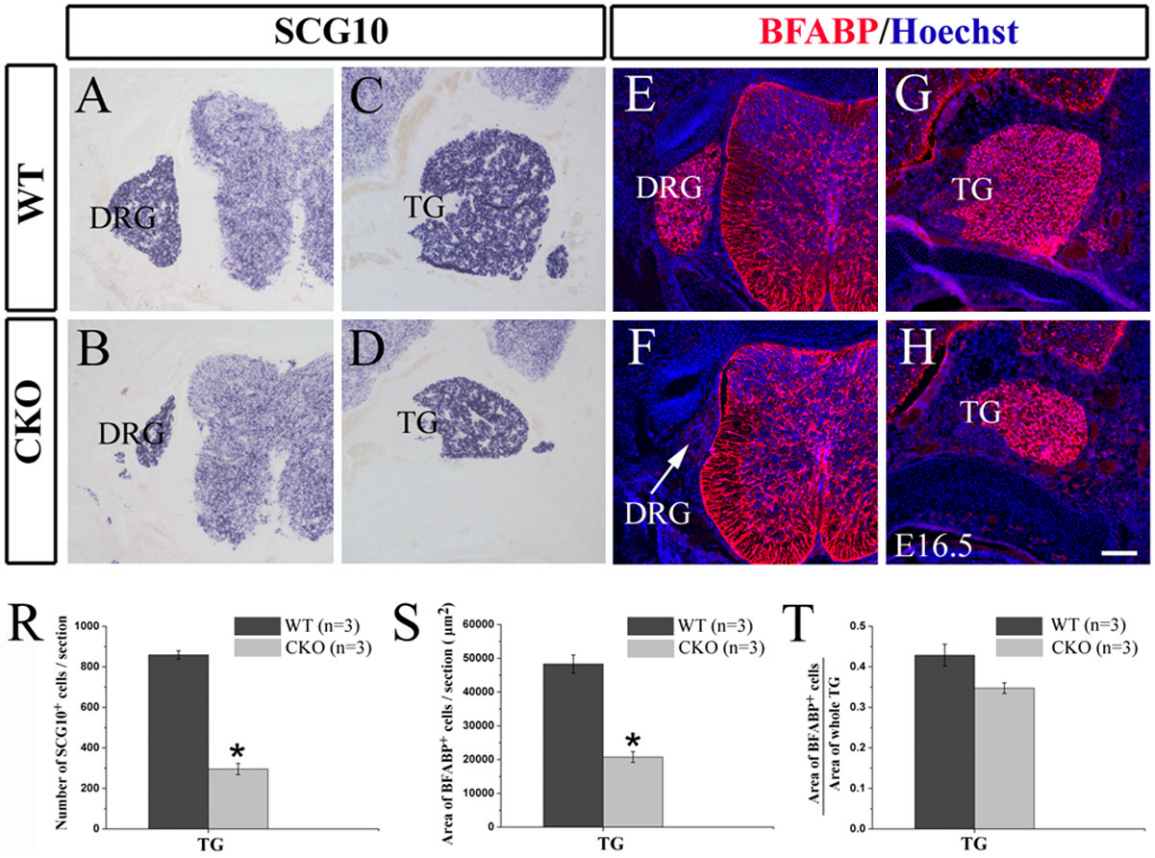

Figure 1. Complete loss of glial cells in *Rbpj*-deficient DRG but presence of glial cells in *Rbpj*-deficient TG at E16.5. A-D: Transverse sections through DRG and TG were *in situ* hybridized with SCG10 mRNA probe. The number of *SCG10* mRNA$^+$ neurons is decreased both in DRG and TG in *Rbpj* CKO mice. E-H: Transverse sections through DRG and TG were immunostained with BFABP (red) and counterstained with Hoechst (blue). BFABP$^+$ glial cells are completely lost in DRG, but dispersed throughout the whole TG in the absence of *Rbpj*. Arrow indicates DRG. R: Comparison of the number of SCG10$^+$ in the TG between the wild-type and *Rbpj* CKO mice. S: Statistical analysis of the area of BFABP$^+$ glial cells in the wild-type and CKO TG. T: The ratio of the area of BFABP$^+$ glial cells to the area of the whole TG in the wild-type and CKO mice. *P < 0.01. Scale bars: 100 μm.

are presented as mean ± standard error of the mean. Comparisons were made using an unpaired Student's *t*-test and statistical significance was set at $P < 0.05$.

Results

Presence of glial cells in Rbpj-deficient TG at late embryonic stage

In order to compare the function of Rbpj in the development of DRG and TG, we firstly examined the neurogenesis and gliogenesis of TG and DRG at E16.5 in the *Rbpj* CKO mice. The in situ hybridization of SCG10, a pan neuronal marker, showed the number of neurons in both TG and DRG was decreased dramatically in *Rbpj* CKO mice (**Figure 1A-D**, **R**). The immunostaining of the specific marker for glial cell, brain fatty acid binding protein (BFABP), revealed that the no BFABP$^+$ cells were detected in the *Rbpj*-deficient DRG (**Figure 1E**, **F**), whereas a large number of BFABP$^+$ cells were present in the *Rbpj*-deficient TG (**Figure 1G**, **H**). Since the BFABP protein existed in the cytoplasm of glial cells which was very small in size, it was difficult to precisely count its number. We thus measured the area of BFABP$^+$ cells and found the area of BFABP$^+$ cells in the CKO TG was significantly reduced compared with wild-type TG (**Figure 1S**). But there was no significant difference in the ratio of the area of BFABP$^+$ cells to the area of whole TG between wild-type and CKO TG (**Figure 1T**). In summary, in contrast to *Rbpj*-deficient DRG lacking glial cells, many glial cells are maintained in *Rbpj*-deficient TG at late embryonic stage.

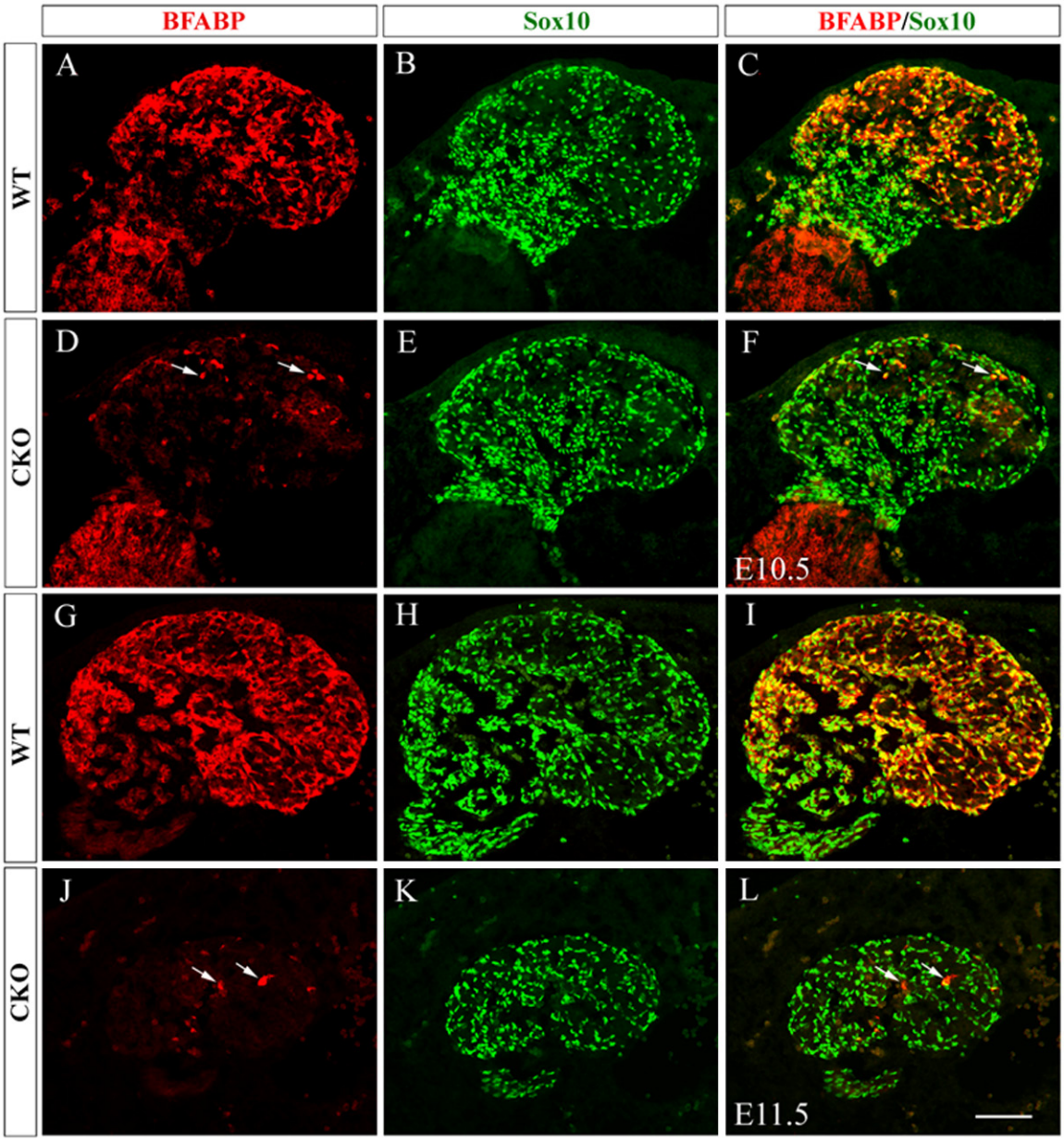

Figure 2. Defects of initial gliogenesis in *Rbpj*-deficient TG. Double immunostaining of BFABP (red) and Sox10 (green) was performed at E10.5 (A-F) and E11.5 (G-L). A-F: Only a few BFABP$^+$ cells are scattered in *Rbpj*-deficient TG at E10.5, whereas a large number of BFABP$^+$ cells are distributed throughout wild-type TG. Similar expression of Sox10 is observed in wild-type and *Rbpj*-deficient TG. G-L: Expression of BFABP in E11.5 *Rbpj*-deficient TG is unchanged relative to that at E10.5, but Sox10$^+$ cells are significantly reduced in E11.5 *Rbpj*-deficient TG compared with that in wild-type controls. Arrows point to BFABP$^+$ glial cells in *Rbpj*-deficient TG. Scale bars: 100 μm.

Initial gliogenesis is delayed in Rbpj-deficient TG

We next examined the progress of gliogenesis in the *Rbpj*-deficient TG by looking at the expression of BFABP and high-mobility group transcription factor SRY box10 (Sox10) at early embryonic stages. Sox10 was reported to be expressed in the NCCs, glia-restricted progenitors and differentiated glial cells [15, 16]. At E10.5 and E11.5, most Sox10$^+$ cells were co-labeled with BFABP in the wild-type TG (**Figure 2A-C**, **G-I**). In E10.5 *Rbpj*-deficient TG, although expression of Sox10 was not different from controls (**Figures 2E**, **4M**), only a few Sox10$^+$ cells were BFABP positive because of a drastic

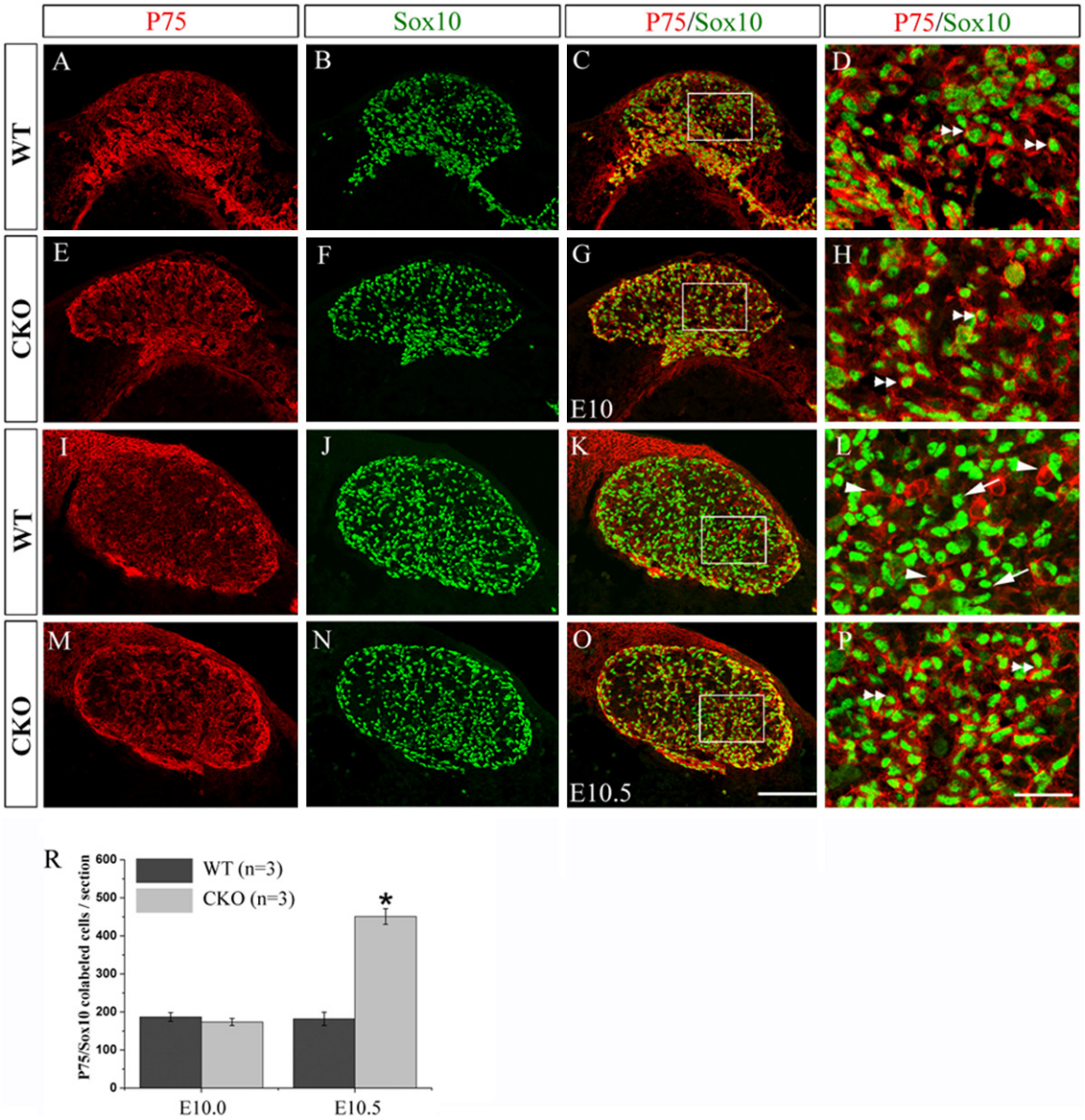

Figure 3. Segregation of P75 and Sox10 expression does not occur at E10.5 in *Rbpj*-deficient TG. Double immunostaining of P75 (red) and Sox10 (green) at E10 (A-H) and E10.5 (I-P) was performed. P75/Sox10 co-labeled cells are observed in both wild-type (C, D) and *Rbpj* CKO TG (G, H) at E10.5 and there were no obvious differences in the number of co-labeled cells between the wild-type and CKO. In wild-type TG at E10.5 (K, L), P75 and Sox10 are distinctly expressed in separate populations of cells, whereas many P75/Sox10 co-labeled cells are present in CKO TG at this stage (O, P). (D, H, L, P) High magnification views of the areas delineated by white rectangles in (C, G, K, O). Arrows indicate cells that express Sox10 alone, arrowheads indicate cells that express P75 alone, and double arrows indicate P75/Sox10 co-labeled cells. R: Comparison of the number of P75/Sox10 co-labeled cells in the TG between the wild-type and *Rbpj* CKO mice. *$P < 0.01$. Scale bars for A-C, E-G, I-K and M-O = 100 μm. Scale bars for D, H, L, P = 25 μm.

reduction of BFABP$^+$ cells (**Figure 2D-F**). On the other hand, in E11.5 *Rbpj*-deficient TG, Sox10-positive cells were reduced dramatically relative to controls (**Figures 2K**, **4M**), and like what observed at E10.5 there were few BFABP$^+$ cells scattered in TG (**Figure 2J-L**). Since there was no difference in the number of Sox10$^+$ cells at E10.5 between the control and *Rbpj*-deficient TG (**Figures 2B**, **E**, **4M**), the failure of initiation of BFABP expression in Sox10$^+$ cells suggests that NCCs in the *Rbpj*-deficient TG arrest their development at E10.5.

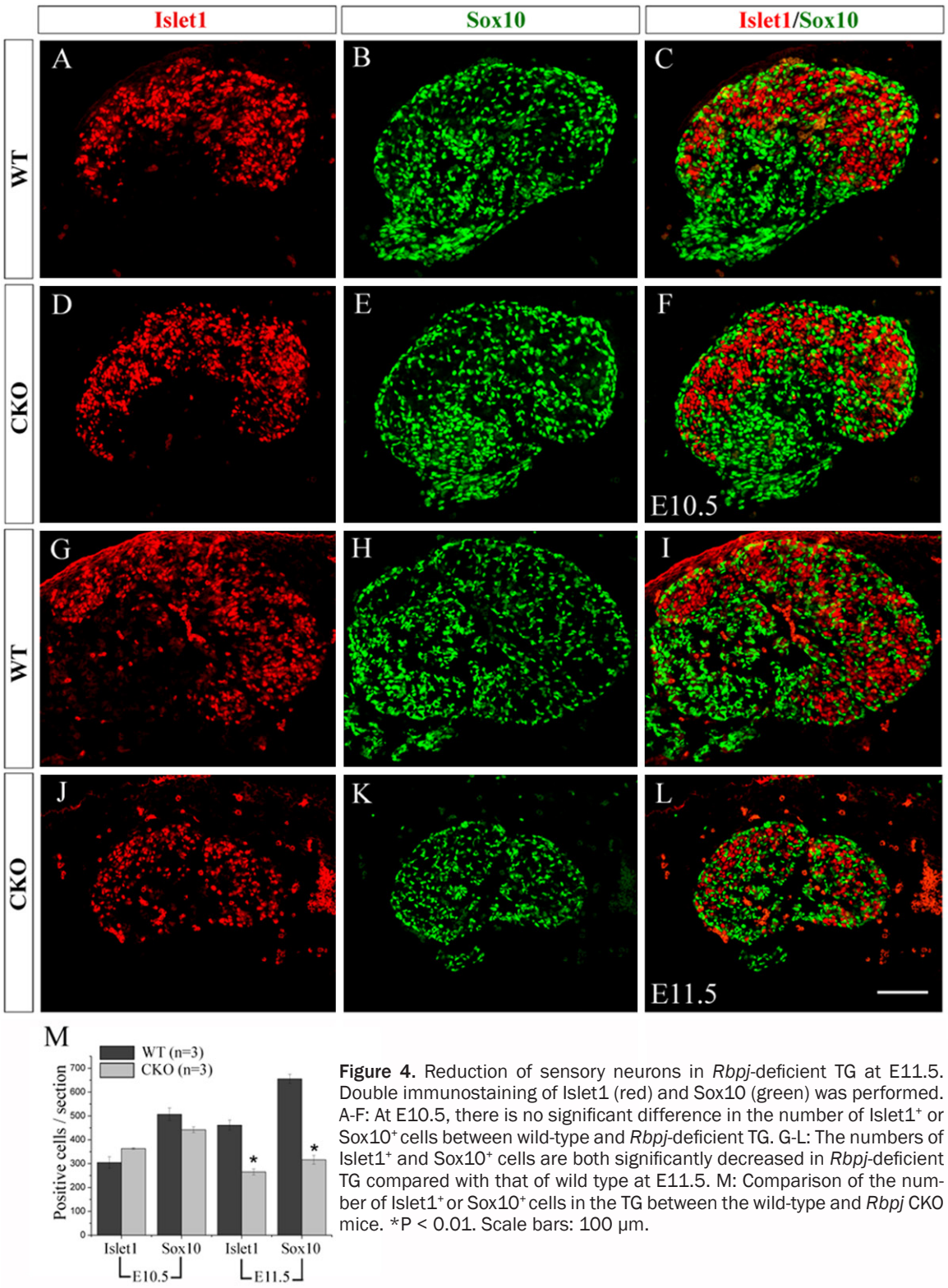

Figure 4. Reduction of sensory neurons in *Rbpj*-deficient TG at E11.5. Double immunostaining of Islet1 (red) and Sox10 (green) was performed. A-F: At E10.5, there is no significant difference in the number of Islet1$^+$ or Sox10$^+$ cells between wild-type and *Rbpj*-deficient TG. G-L: The numbers of Islet1$^+$ and Sox10$^+$ cells are both significantly decreased in *Rbpj*-deficient TG compared with that of wild type at E11.5. M: Comparison of the number of Islet1$^+$ or Sox10$^+$ cells in the TG between the wild-type and *Rbpj* CKO mice. *$P < 0.01$. Scale bars: 100 μm.

Then we tested our hypothesis by using the double immunostaining of Sox10 and another specific marker for NCCs, the low affinity neurotrophin receptor P75 [17]. In the wild-type mice, P75 and Sox10 are co-expressed in NCCs during early DRG development, but are subsequently become restricted to neuronal precursors and glial precursors, respectively [18]. At

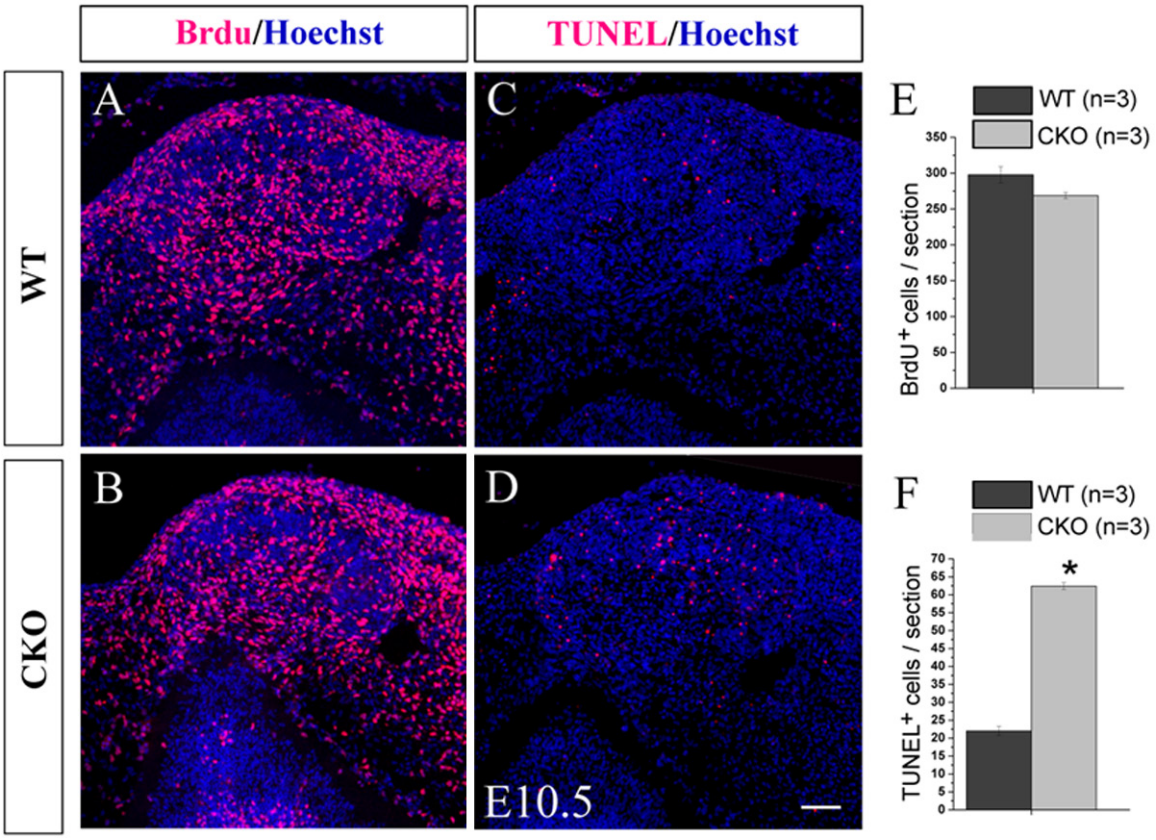

Figure 5. Inactivation of *Rbpj* results in increased cell death in *Rbpj*-deficient TG at E10.5. Wild-type (WT) and Rbpj CKO embryos were pulse labeled with BrdU 2 hours prior to fixation. A, B: BrdU incorporation in *Rbpj*-deficient TG is comparable to that in wild-type controls at E10.5. C, D: TUNEL staining shows that the number of TUNEL-labeled cells is significantly increased in *Rbpj*-deficient TG at E10.5. I, J: Statistical analysis of BrdU+ (I) or TUNEL+ cells (J). *P < 0.01. Scale bars: 100 μm.

E10.0 when the expression of BFABP has not been widely initiated in the TG, a large number of cells that co-expressed P75 and Sox10 were present in the TG of both wild-type mice and *Rbpj* CKO mice at a similar level (**Figure 3A-H**, **R**). At E10.5, separated expression of P75 and Sox10 was observed in the wild-type TG (**Figure 3K**, **L**), whereas this separation did not occur in *Rbpj*-deficient TG, as shown by the results that many P75/Sox10 co-expressing cells were distributed in the TG (**Figure 3O**, **P**, **R**). The presence of P75/Sox10-co-labeled cells further suggests that the restriction and bifurcation of NCC-fates from E10.5 fails to occur in *Rbpj*-deficient TG.

Increased cell death in Rbpj-deficient TG

Double immunostaining of LIM homeodomain transcription factor Islet1, an early sensory neuronal marker, and Sox10 was performed to examine the neurogenesis of *Rbpj*-deficient TG. There was no significant difference in numbers of Islet1$^+$ cells and Sox10$^+$ cells between the wild-type TG and *Rbpj* CKO TG at E10.5 (**Figure 4A-F**, **M**). However, their numbers were both significantly decreased in the *Rbpj*-deficient TG compared with the wild-type TG at E11.5 (**Figure 4G-M**).

To discover the reason that resulted in the reduction of Islet1$^+$ cells and Sox10$^+$ cells, we pulse labeled the E10.5 embryos with bromodeoxyuridine (BrdU) and analyzed the rates of proliferation of progenitor cells 2 hours later. There was no significant difference in BrdU incorporation between wild-type and *Rbpj* CKO TG at E10.5 (**Figure 5A**, **B**, **E**). Then we performed terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining to determine whether elevated rates of cell death may present in the absence of *Rbpj*. The number of TUNEL$^+$ cells was dramatically increased in *Rbpj* CKO TG relative to wild types at E10.5

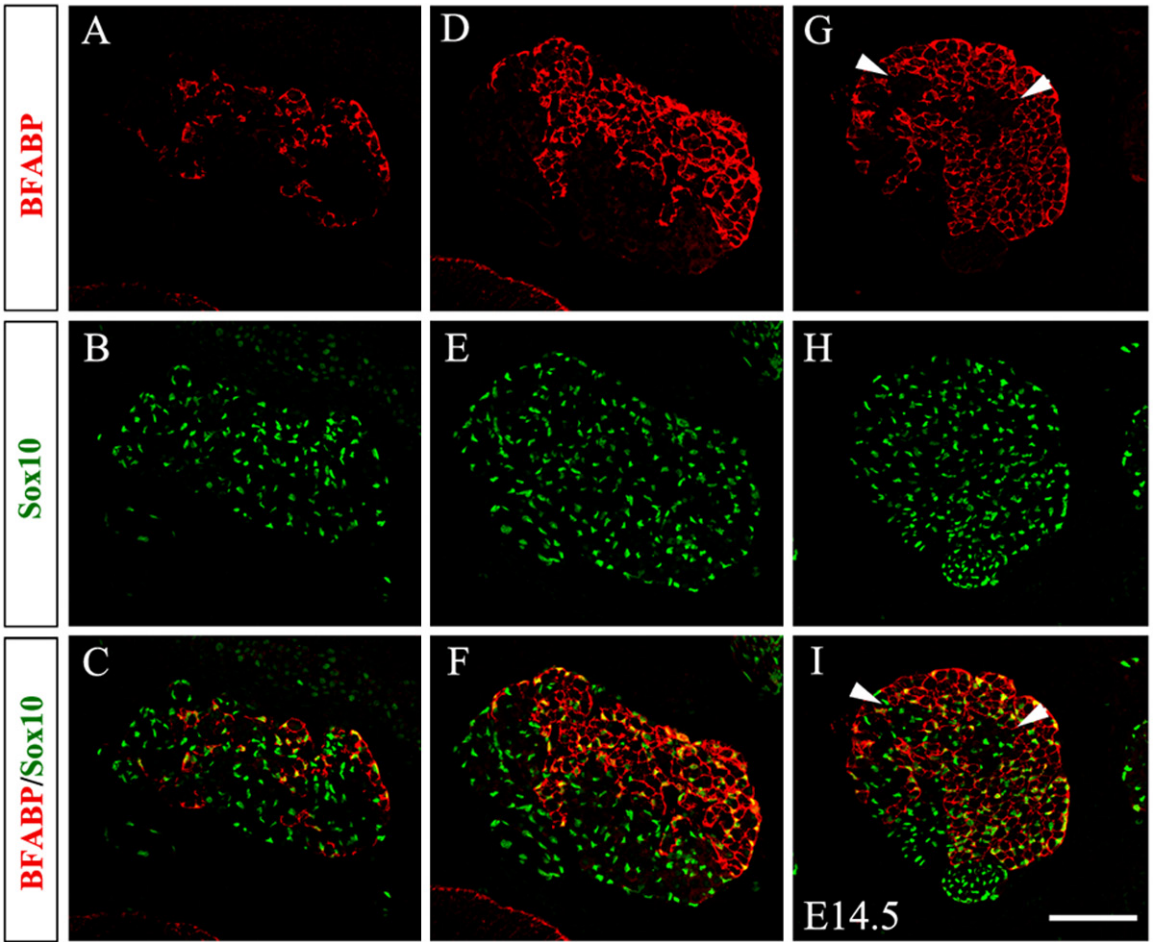

Figure 6. Recovery of gliogenesis is observed in *Rbpj*-deficient TG at E14.5. Transverse sections through TG were immunostained with BFABP (red) and Sox10 (green). The number of BFABP$^+$ cells was gradually increased from caudal part (A-C), middle part (D-F) to rostral part (G, H). At the most rostral part, BFABP$^+$ cells almost dispersed throughout the whole TG with several small patches left (arrowheads). Noted that most BFABP$^+$ cells in each part are co-labeled with Sox10. Arrowheads point to the small patches in the TG that are Sox10$^+$ and BFABP$^-$. Scale bars: 100 μm.

(**Figure 5C**, **D**, **F**), suggesting that increased cell death contributes to the reduction of sensory neurons as well as delayed gliogenesis in the TG of *Rbpj* CKO mice.

The gliogenesis is largely recovered in E14.5 Rbpj-deficient TG

In order to discover how the glial cells were recovered in the *Rbpj*-deficient TG, we examined the expression of BFABP and Sox10 at later developmental stages between E12.5-E16.5. The expression of BFABP was only restricted to a few cells until E14.5 in the *Rbpj*-deficient TG. At E14.5, the number of BFABP$^+$ cells was gradually increased along the caudo-rostral axis (**Figure 6**). In the caudal TG, a small number of BFABP$^+$ cells were clustered in the TG (**Figure 6A-C**), in the middle part their number was increased and distribution territory expanded greatly (**Figure 6D-F**), and in the rostral part more BFABP$^+$ cells were found and they almost dispersed throughout the whole TG with several patches of Sox10$^+$ cells left to be BFABP$^-$ (**Figure 6G-I**). Importantly, P75 and Sox10 were separately expressed in TG cells, which was consistent with what had happened in the wild-type TG (**Figure 7**). Taken together, these results suggested that the remaining NCCs in the *Rbpj*-deficient TG differentiate to BFABP$^+$ glial cells around E14.5.

Discussion

Here we focused on the developmental progress of primary sensory neurons and glial cells in the TG of *Wnt1-Cre; Rbp$^{flox/flox}$* CKO mice. The delay of BFABP expression and abnormal main-

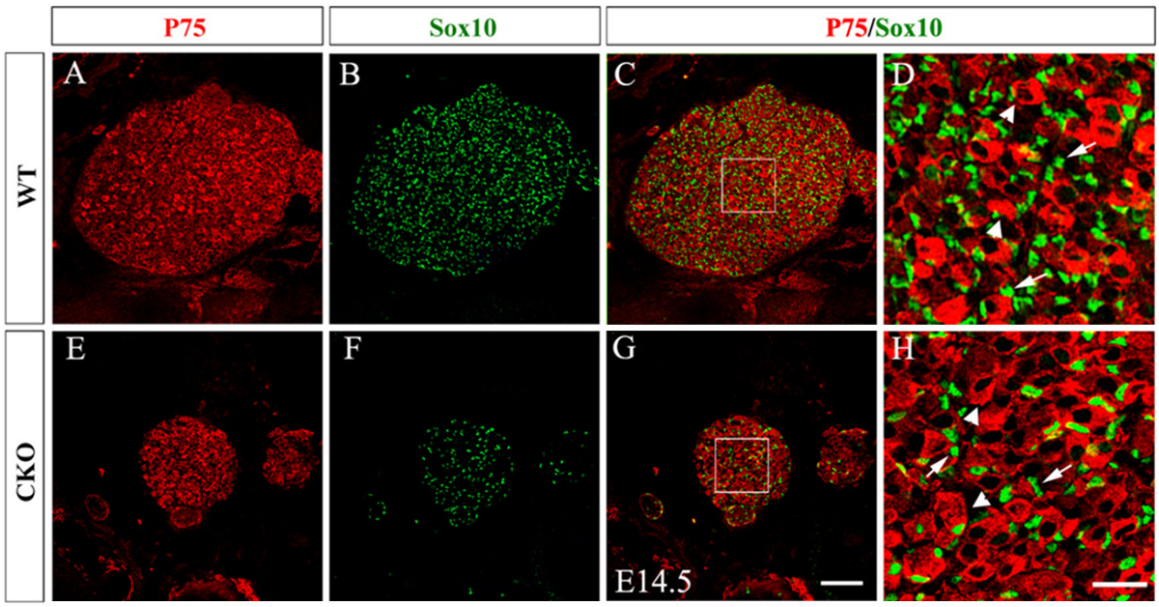

Figure 7. P75 and Sox10 expression is segregated at E14.5 in *Rbpj*-deficient TG. Double immunostaining of P75 (red) and Sox10 (green) at E14.5 was performed. In both wild-type (A-D) and *Rbpj* CKO TG (E-H), P75 and Sox10 are distinctly expressed in separate populations of TG cells. (D, H) High magnification views of the areas delineated by white rectangles in (C, G). Arrows indicate cells that express Sox10 alone, arrowheads indicate cells that express P75 alone. It is noted the density of Sox10$^+$ cells in *Rbpj*-deficient TG is lower than that in wild-type TG. Scale bars for A-C, E-G = 100 μm. Scale bars for D, H = 25 μm.

tenance of P75/Sox10 co-labeled cells were observed at E10.5 in the *Rbpj*-deficient TG, which is consistent with the early defects of gliogenesis in the *Rbpj*-deficient DRG. On the other hand, the gliogenesis was largely recovered in the *Rbpj*-deficient TG at later stage, and this is totally different from the phenotypes of *Rbpj*-deficient DRG in which all glial cells are lost at later stage.

What mechanisms caused the different phenotypes in gliogenesis between *Rbpj*-deficient DRG and TG? One possible reason was the difference of Cre recombination efficiency between DRG and TG. The incomplete deletion of *Rbpj* in NCCs of TG might result in differentiation of the scattered BFABP$^+$ glial cells (**Figure 2**), which proliferate gradually and disperse throughout the whole TG at later developmental stage. This explanation, however, is not supported by the fact obtained in *Rbpj*-deficient DRG. That is, similar to what observed in *Rbpj*-deficient TG, a very small number of BFABP$^+$ glial cells were also observed at early stage, but were lost completely in the Rbpj-deficient DRG at late stage [8]. In addition, the significant recovery of gliogenesis in the *Rbpj*-deficient TG was not detected until at about E14.5. Because the increase of BFABP$^+$ cells in the caudal part and rostral part was not synchronous, it was permitted to analyze where the glial cells came from by comparing the cellular components of caudal part and rostral part. Since most BFABP$^+$ cells were colabeled with Sox10 and the density of Sox10$^+$ cells was similar between the caudal part and rostral part at E14.5, it seemed that the Sox10$^+$/BFABP$^-$ cells differentiated to Sox10$^+$/BFABP$^+$ cells together at E14.5, instead of the scattered BFABP$^+$ cells observed at E11.5 (**Figure 2J**), proliferated and migrated throughout the TG gradually.

The other possible explanation might lie in the two cellular origin of TG. It was reported the neuronal precursors that generate TG derive from both the cranial neural crest and placodal ectoderm [19]. The proper formation of TG relied on the reciprocal interactions between placode- cells and neural crest-derived cells, which has been revealed in chick [20]. Although all the glial cells in TG are derived from the neural crest cells, whether the interactions between placode- and neural crest-derived cells affect the gliogenesis of TG is an open question. We speculated that difference in the cellular origin between the TG and DRG may contribute to the

distinct role of Rbpj in gliogenesis in the two somatosensory ganglia. Because of the lack of specific markers for trigeminal placode-derived cells in the mouse, it is technically difficult to address.

In addition, the differences in the developmental progress between DRG and TG might contribute to the differences of gliogenesis between DRG and TG in the absence of *Rbpj*. For the DRG [8], a small number of NCCs shown by co-expression of P75 and Sox10 existed and they are located at the periphery of DRG before they differentiated to glial cells at E10.5. Then the freshly differentiated glial cells that are derived from NCCs and labeled by BFABP begin to proliferate and populate the whole DRG. While for the TG, a large number of NCCs have already been present throughout the TG, and seemed to differentiate to BFABP$^+$ glial cells almost at the same time (**Figure 3**). Accordingly the developmental molecular mechanisms of these two sensory ganglia might be different that are remained to be explored.

Acknowledgements

We thank Dr AP McMahon for providing Wnt1-Cre mice and Dr Qiufu Ma for in situ hybridization probes. This work is supported by the Shanghai Committee of Science and Technology [grant 11DZ2260600] and China Postdoctoral Science Foundation grant [No. 2012M520844] to ZeLan Hu.

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