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Microglia clearance of single dying oligodendrocytes is mediated by Cx3cr1

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Abstract

Myelin sheath, generated by oligodendrocytes, plays a vital role in ensheathing axons for efficient neural communication. Degeneration of myelin sheath is associated with several neurodegenerative diseases and aging. When myelin sheaths are damaged or degenerated, the resulting debris needs to be efficiently cleared to allow for regeneration and remyelination. The causes of myelin degeneration in various diseases vary, but the inability to effectively remove the myelin debris contributes to disease development and prevents tissue healing. Microglia are highly specialized phagocytic cells capable of recognizing and engulfing myelin debris. The *Cx3cr1* gene, which is primarily expressed on microglial cells, plays a significant role in the process of debris clearance. To investigate the role of *Cx3cr1* on clearance of single dying oligodendrocytes, we used a technique called 2Phatal. Longitudinal *in vivo* imaging revealed that microglia lacking the CX3CR1 receptor took on average 3 days longer to clear the targeted oligodendrocytes compared to controls. This suggests that *Cx3cr1* plays a critical role in facilitating the rapid and efficient removal of dying oligodendrocytes.

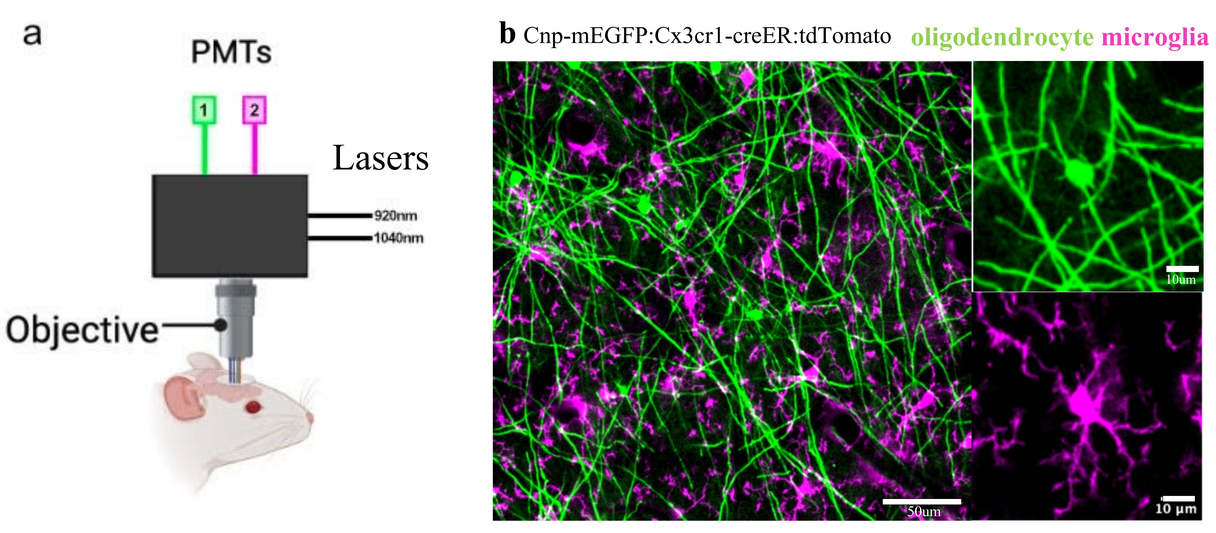

Figure 1. *In-vivo* imaging of oligodendrocytes and microglia in the mouse cortex.

(a) A 3 mm diameter portion of the skull is removed during a cranial window surgical procedure to expose the cortex. To label nuclei of cells, Hoechst nuclear dye is administered topically. The section of skull that was removed is replaced with a cover glass. The glass is fixed in place by dental cement being applied all around it. **(b)** Representative images taken *in-vivo* of oligodendrocytes and microglia in the mouse cortex.

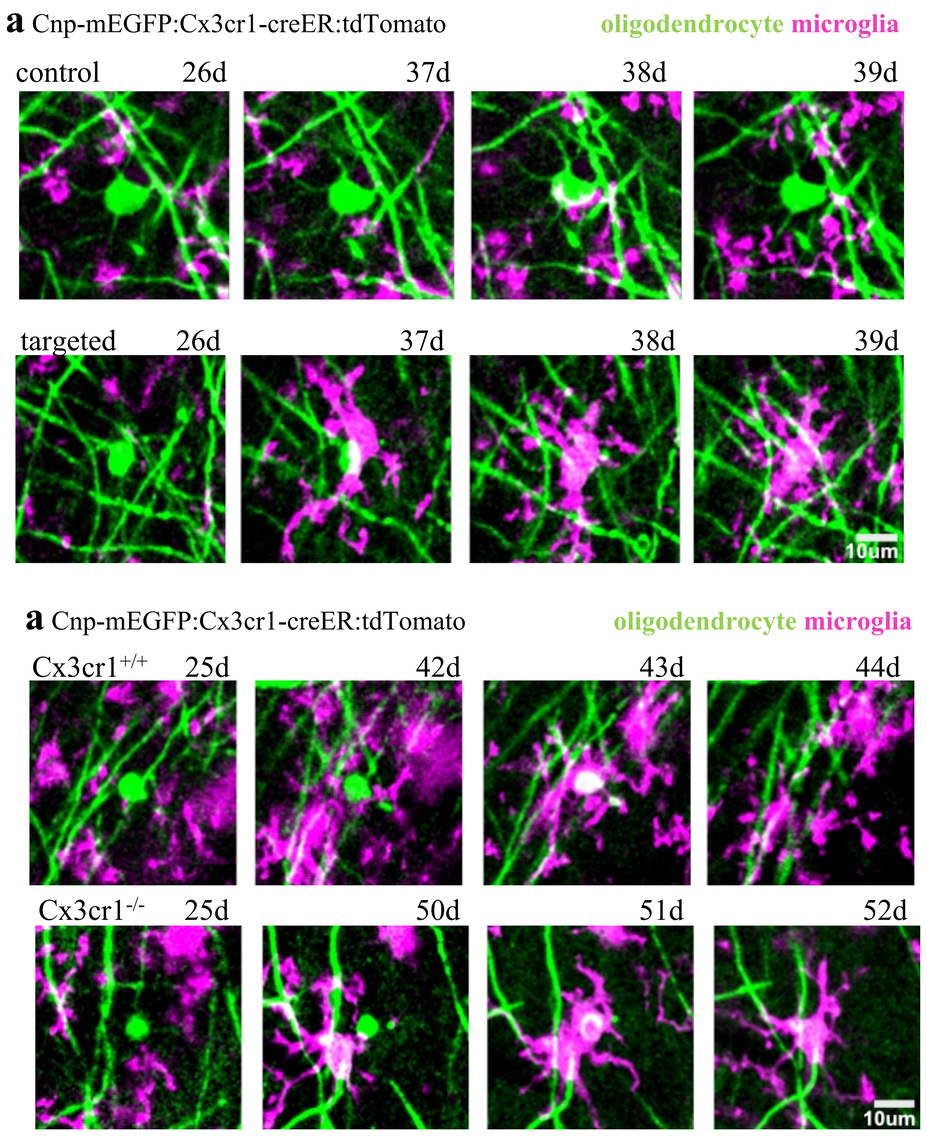

Figure 2. *In-vivo* imaging of oligodendrocyte and microglia following 2Phatal. In vivo images were captured from the cortex of a mouse with oligodendrocytes labeled with GFP and microglia labeled with tdTomato. **(a)** Representative timeseries images showing microglia dynamics around a nontargeted oligodendrocyte (top) and phagocytosis of an oligodendrocyte targeted with 2Phatal (bottom).

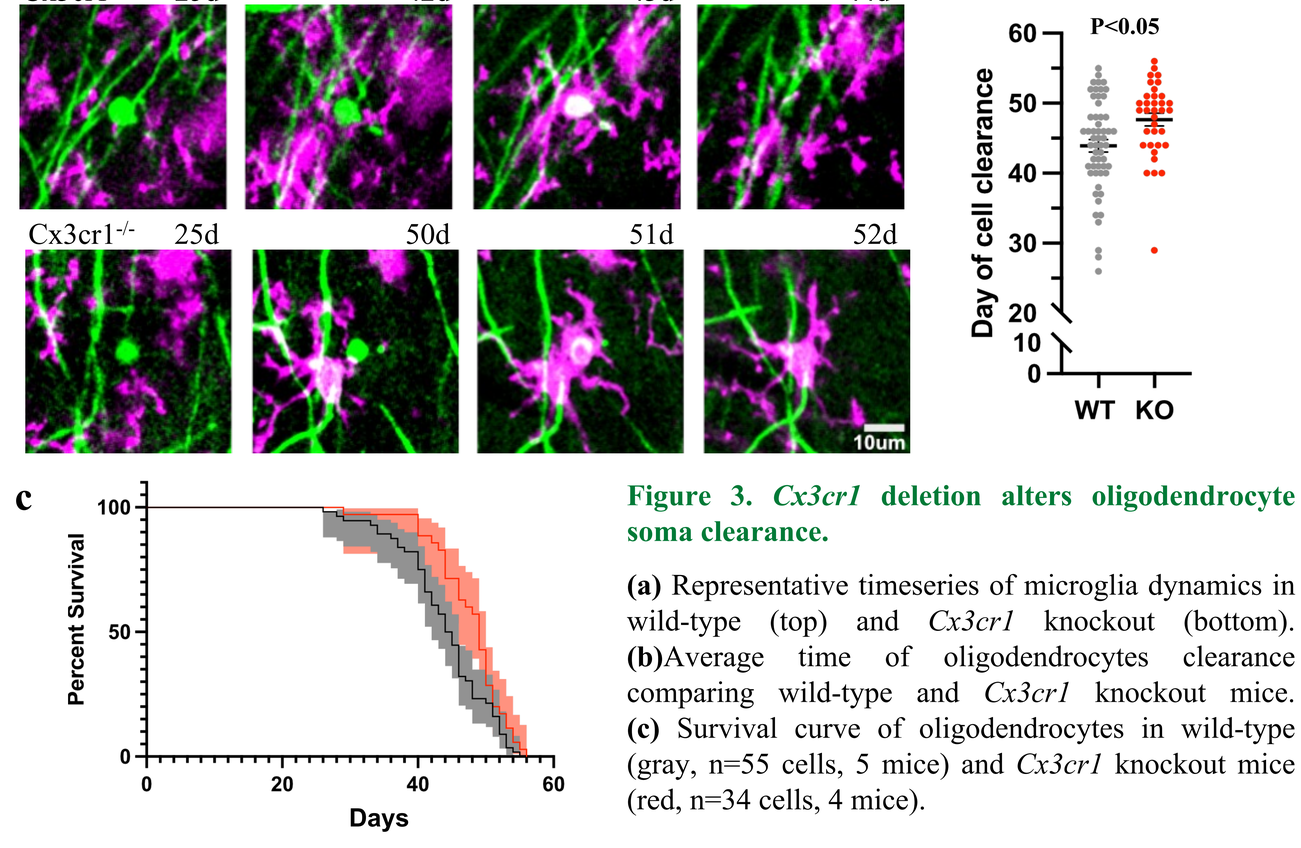

Figure 3. *Cx3cr1* deletion alters oligodendrocyte soma clearance.

(a) Representative timeseries of microglia dynamics in wild-type (top) and *Cx3cr1* knockout (bottom). **(b)**Average time of oligodendrocytes clearance comparing wild-type and *Cx3cr1* knockout mice. **(c)** Survival curve of oligodendrocytes in wild-type (gray, n=55 cells, 5 mice) and *Cx3cr1* knockout mice (red, n=34 cells, 4 mice).

Conclusions

- **Dying oligodendrocytes are cleared by microglia**
- **Deletion of the CX3CR1 receptor results in a delay of oligodendrocyte clearance by 3 days**

Acknowledgements

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