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On the evolution of microglia

Over the last three decades, microglia have been recognized as essential components of central nervous system (CNS) development, homeostasis, immune surveillance, and neurodegenerative pathogenesis (Lin & Wang, 2024; Prinz et al., 2019). Historically, microglia were regarded as exclusive to the CNS, based on the absence of cells bearing microglial morphology, transcriptional identity, and ontogeny in tissues outside the CNS in standard mouse and rat models. However, recent studies, including those from our group, have identified cells in peripheral tissues of humans and other vertebrates that share the transcriptomic signature and yolk sac-derived ontogeny characteristic of CNS microglia (Bao et al., 2024; Garcia-Alonso et al., 2022; Gopee et al., 2024; Wang et al., 2023; Wu, 2025). These findings suggest that the microglial lineage represents a broader spectrum of tissue-resident macrophages with specialized roles across organs.

Microglia constitute one of the most evolutionarily ancient macrophage subtypes, with IBA1-positive cells already identifiable in the brain of the annelid *Hirudo medicinalis* (Prinz et al., 2019). Our recent identification of microglial cells in the peripheral nervous system (PNS) provides compelling evidence supporting the notion that homologous cell types may evolve independently in distinct anatomical niches (Figure 1). In evolutionary biology, homology denotes descent from a common ancestor, irrespective of phenotypic similarity (Fitch, 2000). Conventionally, cell type homology within and between species has primarily been inferred from shared anatomical location, phenotype, or function (Arendt et al., 2016). However, phenotypic or functional similarity is neither necessary nor sufficient to establish homology (Arendt et al., 2016). Single-cell transcriptome profiles, which reflect molecular-level phenotypes, have become increasingly used to resolve previously obscured homologies among cell types. Recent developments advocate assessing cell type homology in a proper phylogenetic framework rather than relying on transcriptomic similarities alone (Mah & Dunn, 2024).

By integrating comparative single-cell transcriptomics, immunohistochemistry, and epigenetic profiling, we identified a distinct population of PNS-resident cells sharing transcriptomic, epigenomic, and ontogenetic features with canonical CNS microglia. Both populations originate from yolk sac-derived macrophage progenitors. In certain vertebrates, these PNS microglia directly enwrap neuronal soma, a role previously attributed solely to satellite glial cells (SGCs) based on rodent models. Our findings revealed a layered structure in larger vertebrates, including humans, with PNS neurons first enveloped by PNS microglia, followed by SGCs.

Phylogenetic analyses across 24 vertebrate species demonstrated that PNS microglia have an ancient evolutionary origin. After correcting for evolutionary relatedness, their presence showed a positive correlation with both body size and peripheral neuronal size. This suggests that the distribution of PNS microglia reflects functional adaptation related to neuron and body size rather than phylogenetic proximity. One plausible explanation is that larger vertebrates require PNS microglia to support the metabolic and structural demands of enlarged peripheral neurons. In contrast, smaller species with reduced neuronal dimensions and simpler metabolic needs appear to have lost this population entirely. Unlike CNS microglia, which were stably present across the vertebrate lineage, the discontinuous distribution of PNS microglia reflects tissue-specific evolutionary pressures. These findings support the hypothesis that ancestral cell types may diverge into paralogous subtypes through adaptation to distinct physiological niches. Moreover, if selective pressure diminishes—such as reduced body size—the derived cell type may subsequently undergo lineage-specific extinction. Indeed, this evolutionary turnover of cell types has been documented in some extant animal clades (Arendt et al., 2016).

The observed distribution of PNS microglia suggests that stronger selective pressures maintain this population in larger-bodied vertebrates with larger peripheral neurons. Functional analyses further demonstrated their direct role in soma enlargement and axonal growth during peripheral neuron maturation. Notably, depletion of PNS microglia in neonatal pigs resulted in smaller neuronal soma, reduced nerve density, and weakened mechanical sensitivity, indicating a direct fitness cost on neural development and sensory function. The occurrence of PNS microglia in larger vertebrates indicates that natural selection has shaped their divergence to fulfill niche-specific functional requirements, aligning cell type evolution with the increasing structural and metabolic demands imposed by greater nervous system complexity and body size.

Several important questions regarding these enigmatic cells remain unresolved. While the presence of PNS microglia in diverse vertebrates suggests they were already established in the last common ancestor of Osteichthyes, the depth of their evolutionary origin is unclear. CNS microglia have been identified in Annelida (Geirsdottir et al., 2019), a phylum that diverged from vertebrates approximately 708 million years ago. Further sampling of more basal metazoan lineages is required to reconstruct the ancestral states of microglial populations, clarify their original tissue niches, and elucidate the evolutionary dynamics driving their divergence in response

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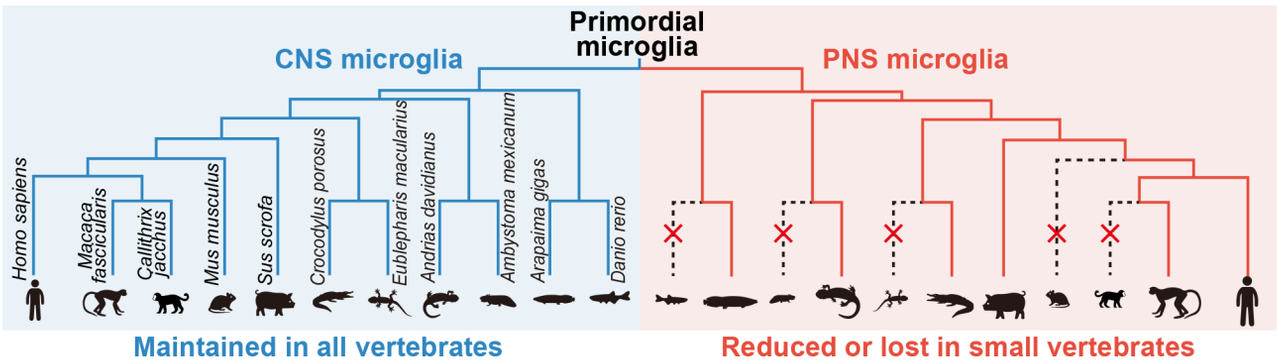

Figure 1 Schematic illustrating the evolution of microglia in the central and peripheral nervous systems (CNS and PNS)

Primordial microglia gave rise to CNS and PNS subtypes, which evolved as paralogous cell types through independent specialization under different selective pressures imposed by their respective tissue environments. CNS microglia were conserved across all vertebrates, whereas PNS microglia were reduced or lost in smaller species, likely due to relaxed selection associated with reduced neuronal and body size. Homologous cell types are defined as those descended from a common ancestral cell type, e.g., microglia in different tissues of all species, including both orthologous and paralogous cell types. Orthologous cell types are those that trace their most recent common ancestor (MRCA) to a speciation event, e.g., microglia in the same tissue across different species. Paralogous cell types share an MRCA due to a divergence event within a lineage, e.g., microglia occupying different tissues within the same species.

to nervous system elaboration.

In conclusion, this study demonstrated a causal relationship between the presence of PNS microglia and both body and neuronal size across vertebrates, providing insights into how homologous cell types diverge or become lost under distinct tissue-specific selective pressures. Expanding phylogenetic analyses to additional microglial lineage subsets in other tissues, such as skin, testis, and heart, across species will help reconstruct a more comprehensive view of microglial lineage evolution among vertebrate tissues.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

Z.W., R.C., and H.L. wrote the draft manuscript. All authors revised, read, and approved the final version of the manuscript.

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REFERENCES

Arendt D, Musser JM, Baker CVH, et al. 2016. The origin and evolution of cell types. *Nature Reviews Genetics*, **17**(12): 744–757.

Bao YZ, Wang GL, Li HJ. 2024. Approaches for studying human macrophages. *Trends in Immunology*, **45**(4): 237–247.

Fitch WM. 2000. Homology: a personal view on some of the problems. *Trends in Genetics*, **16**(5): 227–231.

Garcia-Alonso L, Lorenzi V, Mazzeo CI, et al. 2022. Single-cell roadmap of human gonadal development. *Nature*, **607**(7919): 540–547.

Geirsdottir L, David E, Keren-Shaul H, et al. 2019. Cross-species single-cell analysis reveals divergence of the primate microglia program. *Cell*, **179**(7)**:** 1609–1622. e16.

Gopee NH, Winheim E, Olabi B, et al. 2024. A prenatal skin atlas reveals immune regulation of human skin morphogenesis. *Nature*, **635**(8039): 679–689.

Lin C, Wang XH. 2024. Microglia in drug addiction: a perspective from neuroimmunopharmacology. *Zoological Research*, **45**(3): 704–706.

Mah JL, Dunn CW. 2024. Cell type evolution reconstruction across species through cell phylogenies of single-cell RNA sequencing data. *Nature Ecology & Evolution*, **8**(2): 325–338.

Prinz M, Jung S, Priller J. 2019. Microglia biology: one century of evolving concepts. *Cell*, **179**(2): 292–311.

Wang ZS, Wu ZS, Wang H, et al. 2023. An immune cell atlas reveals the dynamics of human macrophage specification during prenatal development. *Cell*, **186**(20): 4454–4471. e19.

Wu Z, Wang Y, Chen WW, et al. 2025. Peripheral nervous system microglia-like cells regulate neuronal soma size throughout evolution. *Cell*, **188**(8): 2159–2174.e15.