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PERSPECTIVE

Trogocytosis: An underappreciated but vital cellular process in the nervous system

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Trogocytosis is a process in which one cell nibbles part of the cellular structures of other cells, playing a crucial role in neuronal pruning and circuit formation. However, the lack of understanding of trogocytosis, especially in the field of neuroscience, poses significant challenges for data retrieval and the investigation of its underlying mechanisms. Notably, most studies related to trogocytosis have not explicitly identified the phenomena they observed as trogocytosis. We have compiled some representative research and categorized them into trogocytosis occurring in epidermal cells, retinal pigment epithelium, microglia, and oligodendrocyte precursor cells. We then discuss whether the pruning of entire synapses should be considered a type of trogocytosis and explore the molecular mechanisms that differentiate trogocytosis from phagocytosis. We anticipate that further research on trogocytosis in the nervous system will advance our understanding of neurodevelopment, motor learning, neurodegenerative diseases, and beyond.

INTRODUCTION

Trogocytosis, derived from the Greek word "trogo" meaning "nibble", is a cellular process in which one cell nibbles part of the cellular structures of another living cell.[1,2] Distinct from phagocytosis, which involves the complete engulfment of entire cells or cell debris, trogocytosis is characterized by the selective internalization of only portions of living cells,[1] occurring without the formation of large phagocytic cups.[2] Recent research indicates that trogocytosis is present not only in the immune system, where it was first identified, but also in the nervous and reproductive systems of metazoans. This suggests that trogocytosis is a prevalent and conserved phenomenon.

Recent studies of trogocytosis in the nervous system have revealed its significant role in neural physiology, such as circuit maturation during neurodevelopment,[2] maintenance of neural homeostasis,[3] and clearance of damaged neurons to prevent inflammation during neurodegeneration.[4] Despite its functional significance, the concept of 'trogocytosis' remains largely unrecognized in neuroscience. Consequently, many instances where portions of a living neuron are nibbled by nearby cells have been inaccurately described as partial phagocytosis or simply as cells gnawing bits of another cell.[2,5] This lack of precise terminology significantly impedes progress in this field, particularly in identifying conserved molecular mechanisms across species, and hinders research in neurodegeneration and neuro-regeneration. In this context, we have compiled and organized representative studies that describe the observations and molecular mechanisms of trogocytosis in various components of the nervous system, including epidermal cells, retinal pigment epithelium, and glial cells (Figure 1). Additionally, we discuss the role of trogocytosis in synaptic pruning, highlight the importance of distinguishing it from phagocytosis, and propose future perspectives on trogocytosis within the nervous system.

TROGOCYTOSIS OF SENSORY NEURONS IN EPIDERMAL CELLS OF FLIES

In fruit flies (*Drosophila*), the epidermal cells adjacent to the sensory neurons play a crucial role in engulfing their dendrites. Abnormal engulfment can affect the trimming of excess branches and connections during development, hinder the clearance of damaged neurons,[4] and disrupt the homeostasis of the nervous system.[3] The neuronal phosphatidylserine (PS) is normally localized in the inner leaflets of the cell membranes. However, in response to physical injuries, it translocates to the outer leaflets, acting as the "eat-me" signal recognized by epidermal cells. Conditions such as physical injury, neurodegeneration, and specific gene mutations in neurons can trigger PS exposure. To mimic these pathological conditions, studies have employed scramblase overexpression and flippase inactivation to induce PS exposure in distal parts of intact sensory dendrites. Upon detecting PS exposure, epidermal cells utilize physical force to nibble off the tips of these dendrites,[4] a process consistent with the definition of trogocytosis.

The molecular mechanisms underlying neuronal trogocytosis in *Drosophila* have been partially revealed. The engulfment receptor Draper (Drpr) on epidermal cells facilitates trogocytosis by recognizing exposed PS.[4] Orion, released by peripheral nonneural tissues, acts as a bridging molecule that helps Drpr recognize PS. The dosage of Orion determines the sensitivity of trogocytosis. Furthermore, while the presence of Orion on neurons aids in recognition and subsequent trogocytosis, its excessive existence on epidermal cells and interaction with Drpr can block the PS recognition function of Drpr.[3]

The cellular recognition mechanisms in *Drosophila* are conserved and may apply to other animals. The trogocytic receptor Drpr in *Drosophila* is homologous to the engulfment receptor CED-1 in *C. elegans* and Jedi-1 and MEGF10 in mammals. The CX_3C and RRY motifs in Orion are similar to the mammalian chemokine CX_3CL1 and are part of the neutrophil peptides in the human immune system. These motifs are crucial for the bridging function of the Orion in trogocytosis, suggesting the conservative characteristic of trogocytosis between the nervous and immune systems [3].

TROGOCYTOSIS OF THE RETINA AND MOLECULAR MECHIANISM OF SCISSION

Although research in *Drosophila* has advanced our understanding of the recognition mechanisms involved in trogocytosis, the molecular mechanism responsible for scission remains obscure. Scission, the mechanical force that cleaves the engulfed part from the cell undergoing trogocytosis, is one of the main characteristics of trogocytosis. Previous studies have shown that retinal pigment epithelium (RPE) engages in trogocytosis of retinal pigment cells. The retina is an extension of the central nervous system. In mice, RPE can nibble portions of the photoreceptor outer segment (POS), including light-damaged discs caused by phototransduction. This circadian process is vital for maintaining healthy vision and normal photoreceptor metabolism. It also plays a crucial role in preserving vision in severe autophagic defects of the RPE, such as those associated with macular degeneration, which can lead to blindness.[5]

The initial recognition process begins with the targeted exposure of PS at the distal ends of the POS, detected by the avb5 integrin and the activated Mer tyrosine kinase on RPE. Following recognition, the ubiquitinated POS is bound by Optineurin on the RPE cell membrane. Optineurin recruits the actin motor myosin VI (MYO6) to the pre-phagosome membrane, facilitating the scission process to detach the engulfed particles from the parent cell. The artificial block of either Optineurin or MYO6 leads to significantly fewer scission events on the photoreceptors, indicating the critical interactions of Optineurin and MYO6 in promoting trogocytosis.[5]

VARIOUS MICROGLIAL TROGOCYTOSIS AND ITS RELATION TO IMMUNITY

Although the studies on trogocytosis outlined above have revealed some

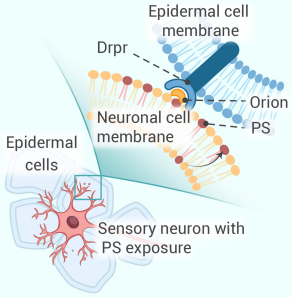
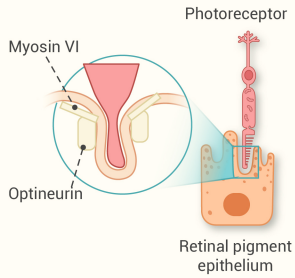
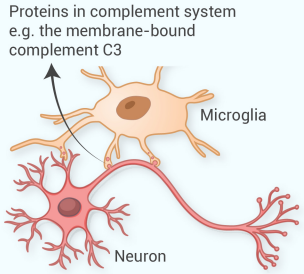
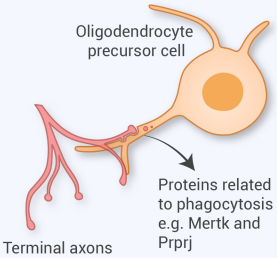
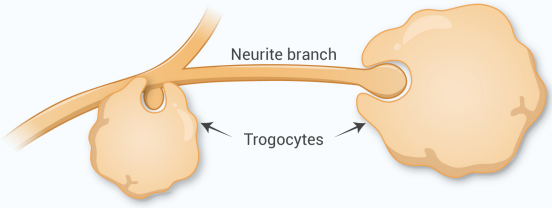
Trogocytes	Epidermal cell	Retinal pigment epithelium	Microglia	Oligodendrocyte precursor cell
Trogocytosed parts	Neurites of sensory neurons	Distal ends of the photoreceptor outer segment	Presynaptic terminals, neurites of neurons in the central nervous system	Terminal axons of neurons in visual cortex or in retinal ganglion cells
Model organisms	Fruit fly[3,4]	Mice[5]	Mice,[2] Xenopus,[6] Macaque[7]	Mice,[9] Zebrafish[10]
Biological functions	To trim excess branches and connections; clear damaged neurons to prevent inflammation; keep homeostasis	To maintain normal photoreceptor metabolism and healthy vision; secure healthy vision in severe autophagic defects of the RPE	To facilitate circuit maturation during development; keep normal visual function in adult stage	To control neural circuit refinement during development
Regulators and process				
Model				

Figure 1. A summary illustration depicting the process and function of trogocytosis of axons, dendrites and synapses by various types of trogocytes.

underlying mechanisms, they are not the only examples that characterize trogocytosis in the field of neuroscience. Trogocytosis in the nervous system was first identified in research involving microglia, which aimed to distinguish the engulfment of a portion of pre/postsynaptic materials, axons, or dendrites from the pruning of entire pre- and post-synapses.[2] Microglia can selectively engage in trogocytosis of axons and presynaptic terminals to limit synaptic materials, thereby promoting the maturation of neural circuits in the hippocampus of mice and the retinal ganglion cells (RGCs) of Xenopus while preserving the integrity of dendritic spines and postsynaptic materials [2,6]. In contrast, in the inner retinal neurons of the macaque (such as retinal ganglion cells, wide-field amacrine cells, and Bipolar cells), trogocytosis occurs on axons and dendrites but not the synapses themselves.[7] The variability of trogocytosed portions of neurons may stem from differences in species, age, and regions of the nervous system. However, future studies across various tissues and species may help to identify universal molecular mechanisms.

Microglial trogocytosis is closely linked to the immune system. Unlike other glial cells, microglia also functions as innate immune cells in the central nervous system. The study of RGC trogocytosis in Xenopus laevis has elucidated the involvement of complement regulatory proteins in modulating this process. The membrane-bound complement C3 fusion protein, known to mediate phagocytosis, has been proposed to enhance trogocytosis of the RGCs. In addition, amphibian complement activation 3 (aRCA3), a membrane-bound protein that shares homology with human CD46, can inhibit the activity of the membrane-bound complement C3 fusion protein, thereby preventing the synaptic and axon pruning of microglia.[6]

Although studies in mice have shown that the complement receptor CR3, required for the complement signaling pathway in microglial phagocytosis, is not involved in the trogocytosis of presynaptic elements,[2] further research has confirmed CR3's role in the synaptic remodeling of microglia in the retinothalamic system and the perinatal mouse cortex.[8] The involvement of the phagocytic signaling pathway in trogocytosis may differ across species. Trogocytosis may confer neuroprotective benefits to microglia. One hypothesis suggests that microglial trogocytosis facilitates retinal antigen presentation to regulatory T cells, thereby suppressing immune response. Unlike other microglia in the eye, retinal microglial cannot be activated by systemic inflammation. However, when the blood-retinal barrier is impaired, allowing circulating immune cells to infiltrate the retina, the retinal microglial gains the capacity for antigen presentation to regulatory T cells. This process likely involves antigens derived from portions of retinal cells that have been engulfed through microglial trogocytosis.[7]

TROGOCYTOSIS OF THE OLIGODENDROCYTE PRECURSOR CELLS IN THE VISUAL SYSTEM

Oligodendrocyte precursor cells (OPCs) exhibit a form of trogocytosis similar to microglia. Although the OPCs in the central nervous system can differentiate into myelinating oligodendrocytes, most remains undifferentiated and are found in regions without myelin. These OPCs contribute to the pruning of neural circuits during neurodevelopment, which is crucial for the normal functioning of the visual system. In the visual cortex of mice, trogocytosis of OPCs engulfs terminal axon branches and presynaptic terminals. This is supported by 3D imaging, which shows that a small portion of the axon branch engulfed by OPC remains connected to its parent axon. RNA sequencing of OPCs demonstrates a high-level expression of genes associated with phagocytosis, such as Mertk and Ptprj, which are also expressed in microglia.[9] Similarly, in zebrafish, the absence of OPCs in the optic tectum contributes to ectopic branching during early development and the enlarged arbor size of RGC once the visual system is established. This highlights the persistent role of OPCs in fine-turning neural circuit formation to support normal visual functions.[10] However, further evidence, such as specific gene expressions related to phagocytosis and lysosomal activity in OPCs, is needed to further substantiate the process of trogocytosis and its contribution to the function of the visual system.

DISCUSSION

Based on the definition, it is essential to delineate and broaden the scope of trogocytosis in the nervous system. Recent research on trogocytosis has often conflated it with phagocytosis, and studies addressing trogocytosis in the nervous system are limited to microglia. We propose that trogocytosis should include not only the specific engulfment of pre-/post-synaptic materials, axons, and dendrites, but also the pruning of the entire synapse. However, the main text does not introduce examples such as synaptic pruning of astrocytes due to a lack of supporting evidence in the literature mentioning

'trogocytosis'. Firstly, the normal size of the synapse is much smaller than the average width of phagocytosis, which is approximately 1 μm.[2] Secondly, synaptic pruning does not involve engulfing entire neurons or causing neuronal death. As highlighted in previous examples, trogocytosis plays a vital role in self-clearance or neurodevelopment, thereby maintaining the normal function of the nervous system. Incorporating the pruning of entire synapses into the definition of trogocytosis allows for the inclusion of astrocytes and broadens the research scope to cover learning, memory, and neurodegenerative diseases.

In addition to the size of swallowed objects and the viability of cells, the molecular mechanisms underlying trogocytosis are crucial for validating this cellular process. Scientific efforts have focused on characterizing genes that regulate trogocytosis, with many identified genes also involved in phagocytosis or autophagy. However, there may be indispensable candidate genes specific to trogocytosis that have not yet been identified in phagocytosis. One key aspect is the scission process that disconnects the engulfed material from cells involved in trogocytosis, such as the recruitment of MYO6 in the retinal pigment epithelium, as previously mentioned.[5] Moreover, conserved genes related to trogocytosis in the immune system could be selected as candidate genes in the nervous system, given that research on trogocytosis in immunity is more advanced and has unveiled various recognition molecular mechanisms. The nervous system is also closely linked to immune processes, exemplified by aRCA3, which prevents microglial pruning.[6] Importantly, trogocytosis involves not only intercellular mechanisms within the nibbling cells but also the critical intercellular interactions. A notable example is the PS exposure on sensory neurons, which can lead to the change of physical force of adjacent epidermal cells.[4] Moreover, nibbled cells may promote the scission process during trogocytosis. Signals from the nibbling cells could induce the budding process, which might be further facilitated by the nibbled cell itself through cytoskeletal movements or increased membrane flexibility in the nibbled area to enhance stretching.

FUTURE PERSPECTIVES

The study of trogocytosis in the context of the nervous system is still in its infancy due to the limited research history and the misuse of terminology. The molecular mechanisms behind trogocytosis, such as recognition signals beyond PS exposure, the regulation of the engulfment process, and the signaling pathways involved in engulfment and scission, remain largely unexplored. Glial cells, in particular, require a deep understanding of these molecular mechanisms, as only a few candidate genes associated with phagocytosis have been demonstrated to regulate trogocytosis. Moreover, investigating the features and conserved genetic pathways of trogocytosis, specifically in the nervous system, could be crucial for understanding processes such as the pruning of axons, dendrites, presynaptic and postsynaptic materials, and even entire neuronal synapses. Previous research on neuronal trogocytosis has primarily focused on neurodegeneration, circuit remodeling, and antigen presentation. However, its broader functions, resembling those found in the immune system or amoebas, such as cell-cell communication, the spread of intracellular bacteria, evasion of therapeutic interventions, and the formation of structures similar to immunological synapses, remain unexplored in the nervous system. Additionally, the potential benefits to both trogocytosed cells and recipient cells during the trogocytosis process have been largely overlooked and warrant further investigation. In summary, the study of trogocytosis in the nervous system is still at an early stage, and future research is needed to unravel its complexities.

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DECLARATION OF INTERESTS

The authors declare no competing interests.