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CELLULAR NEUROPHYSIOLOGY

ER cargo confinement influences dendritic plasticity

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The dendritic tree of hippocampal pyramidal neurons is highly branched, allowing a high degree of functional compartmentalization. Such compartmentalization involves local protein synthesis and the regulated delivery of proteins, such as AMPA receptors, to specific regions of the plasma membrane of the dendritic tree by a secretory pathway involving the endoplasmic reticulum (ER) and Golgi apparatus. Changes in the functional properties of dendritic segments involve the specific targeting of newly synthesized proteins to dendrite subdomains, but little is known about how this process is regulated. A new study by Cui-Wang *et al.* indicates that variations in the complexity of ER structure affect the spatial domain of the delivery of nascent cargo, including receptors and membrane, which in turn influences dendritic morphology.

First, the authors investigated the rates and spatial range of diffusion of newly synthesized membrane cargo within the ER. Using quantitative photobleaching and super-resolution imaging, the authors determined that nascent secretory cargo including AMPA receptors are highly mobile within the ER, but that their motility is impeded in areas of increased structural complexity. Computational analysis of cargo diffusion in the ER supported tightly controlled spatial scales of new membrane protein delivery. Furthermore, the authors found that ER complexity is greater in older neurons compared with younger neurons. Importantly, ultrastructural analysis revealed that ER complexity was highest in areas adjacent to sites of dendritic branching, and that these dendritic branch points have a higher density of ribosomes and Golgi outposts. This suggests that ER complexity, by retarding diffusion, might localize ER cargo at sites where it can be exported via the Golgi to areas of new branch formation.

As ER complexity increases as the nervous system matures, the authors reasoned that it might be driven by the emergence of synaptic activity. Consistent with this hypothesis, they found that the stimulation of postsynaptic group I metabotropic glutamate receptors (which mimics emergent synaptic activity) resulted in increased ER structural complexity and, as a result, restricted diffusion and clustering of ER cargo. Microtubules are important for ER morphology, and it is known that CLIMP63 (also known as cytoskeleton-associated protein 4), a microtubule-binding protein that is expressed in the ER, is regulated by protein kinase C (PKC)-mediated phosphorylation. In addition, at a time during development of dendritic tree elaboration, CLIMP63 was shown to be clustered where new dendrites form. Group I metabotropic glutamate receptors signal via PKC, and this led the authors to hypothesize that phosphorylation of CLIMP63 might be involved in the regulation of ER complexity. Expression of a mutant CLIMP63 that mimicked either the unphosphorylated or the phosphorylated form caused a decrease or an increase in ER complexity, respectively. Moreover, expression of the phosphomimetic form of CLIMP63 led to enhanced export and delivery of AMPA receptors and increased synaptic strength.

In summary, these data implicate the ER as an important regulator of dendritic plasticity because its structural complexity indirectly creates zones of restricted diffusion that leads to the clustering of cargo and enhanced export. This in turn influences the spatial scales of cargo transport to the dendritic membrane, which may contribute to the regional control of synaptic plasticity on specific dendritic branches.

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ORIGINAL RESEARCH PAPER Cui-Want, T. *et al.* Local zones of endoplasmic reticulum complexity confine cargo in neuronal dendrites. *Cell* **148**, 309–321 (2012)

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