

Podosome Loss and Impaired Phagocytosis in Primary Macrophages from an Alzheimer's Disease Patient

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Accumulation of fibrillar, amyloid beta (Ab) plaques in the brain of patients with Alzheimer's disease (AD) may be due in part to an inability of the innate immune system to clear the toxic protein deposits. Consistent with this, primary macrophages from AD patients have a reduced ability to internalize (Ab)₁₋₄₂ peptide compared with macrophages derived from age-matched control subjects. To investigate the basis of this internalization defect, we used live cell imaging approaches to examine the phagocytic pathway and the actin cytoskeleton of primary human macrophages from an AD patient and from an age-matched control subject. The ability of the macrophages to undergo phagocytosis was analyzed by testing whether they could internalize 2 μm beads coated either with Ab₁₋₄₂ peptide or rabbit IgG. Control macrophages effectively bound and internalized both types of beads, whereas AD macrophages showed lower affinity for the beads and an inability to internalize them. Fluorescently-labeled phalloidin was next used to examine actin organization within these cells. Whereas total F-actin staining was similar in the control and AD macrophages, a significant difference in the shape and distribution of F-actin was observed. AD macrophages displayed an overall rounded shape with less lamellopodia compared to the control cells. Most notably, AD macrophages lacked podosomes. These actin-rich, adhesive structures have been implicated in cell migration and invasion, and are a characteristic feature of macrophages. We discuss how podosome loss and impaired phagocytosis within AD macrophages could prevent these cells from removing toxic, fibrillar Ab deposits in the brains of AD patients.