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The therapeutic roles of ACE-overexpressing macrophages and resistance to structurally defined $A\beta_{1-42}$ forms

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Introduction: Previously, a fundamental role for monocyte-derived macrophages (Mo/MΦ) was implicated for the clearance of amyloid β-protein (Aβ) that is tightly associated with Alzheimer's disease (AD) pathology. Angiotensin-converting enzyme (ACE) can degrade neurotoxic $A\beta_{1-42}$ and mice overexpressing ACE in myelomonocytic cells (i.e. microglia, Mo, and MΦ; termed ACE10) have enhanced innate immune responses. We further demonstrated that targeted ACE-overexpression in myelomonocytes in $APP_{SWE}/PS1_{\Delta E9}$ transgenic mice modeling AD (AD^+) markedly attenuated AD-associated pathology and cognitive decline via enhanced recruitment of Mo/MΦ.

Aims: To further investigate the therapeutic potential of ACE-overexpressing (ACE10)-Mo/MΦ and their ability to eradicate and resist structurally defined forms of Aβ.

Methods: Peripheral blood enrichment with bone marrow (BM)-derived ACE10-Mo was achieved through BM transplantation (irradiation with head shielding) or adoptive transfer into the tail vein of AD^+ mice. *In vitro* studies were utilizing primary cultures of ACE10- *vs*. WT-MΦ to evaluate phagocytosis capacity, cell morphology, intracellular Aβ processing, and enzymatic degradation in response to structurally defined forms of $A\beta_{1-42}$.

Results: Peripheral blood enrichment of ACE10-Mo alleviated disease progression in AD^+ mice. We revealed that BM-ACE10 as compared to BM-WT or BM-AD^+ resulted in reduction of soluble and fibrillar Aβ as well as GFAP+ reactive astrocytes. Transplantation of GFP-labeled BM cells allowed us to track the cells in the brain and characterize them around Aβ plaques. We found increased infiltration of ACE10- vs. WT-Mo/MΦ and their reduced TNFα production. Adoptive transfer of ACE10-Mo derived from young donor mice into symptomatic AD^+ mice markedly attenuated cognitive decline assessed by the Barnes maze test and cerebral Aβ and hippocampal $GFAP^+$ levels. Our *in vitro* studies indicated the high capacity of BM-derived ACE10- vs. WT-MΦ to bind and uptake fibrillar (f) and oligomeric (o) Aβ1-42, especially at early time points (5-15 minutes). Accelerated rates of extracellular fAβ1-42 degradation by ACE10-MΦ were detected after 18, 20, and 23 hours. Both cellular uptake and extracellular degradation of fAβ1-42 were significantly reduced by inhibition of ACE catalytic domains (Lisinopril). Moreover, we discovered an unique, potentially 'protective', cell morphology associated with ACE10- as compared to WT-MΦ in response to fAβ1-42, along with increased scavenger receptors' expression.

Conclusions: These studies provide evidence to support powerful therapeutic effects to the genetically modified Mo/MΦ (ACE10) in curbing Aβ-induced toxicity and controlling neuroinflammation associated with AD.

Biography

Maya Koronyo-Hamaoui, Ph.D., Assistant Professor in the Department of Neurosurgery and the Department of Biomedical Sciences at Cedars Sinai Medical Center, is head of the Neuroimmunology and Retinal Imaging Laboratory in the Department of Neurosurgery. She has held research positions at the Danek Gertner Institute of Human Genetics at The Chaim Sheba Medical Center at Tel Hashomer and was a faculty adjunct lecturer at The Sackler School of Medicine at Tel Aviv University, in Israel. She earned her bachelor's degree cum laude and her master's magna cum laude at Tel Aviv University before receiving her Ph.D. in human molecular genetics and psychiatric genetics at the university's Sackler School of Medicine. She completed her postdoctoral fellowship in neuroimmunology at one of the world's leading neuroimmunology laboratories at the Weizmann Institute of Science, Rehovot. Dr. Koronyo-Hamaoui's laboratory focuses on various models of acute and chronic CNS-degeneration, with a great emphasis on Alzheimer's disease: retinal pathology, retinal imaging and immune-based therapies. Her pioneering work on imaging of beta-amyloid retinal pathology created the basis for translating this novel approach to the clinic for early detection of Alzheimer's disease through a non-invasive eye scanning; her team is committed to developing a definitive diagnosis early, when the disease is most likely to be treatable. Her other main focus is on immune-based mechanisms of repair and regeneration in the brain and developing immune-modulation therapies for Alzheimer's disease. In addition to the BrightFocus award, she has received the George S. Wise Faculty of Life Sciences recognition, the Wolf Fund and Sackler School of Medicine Faculty Dean's Honor & Prize for Best Achievements, a Pioneer in Medicine Award from the Brain Mapping Foundation, and the primary research award from the Coins for Alzheimer's Research Trust (CART) Fund.

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