Molecular mechanisms of ganglion cell loss in Alzheimers disease

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Research Abstract

PROJECT SUMMARY Visual impairments are quite prevalent in patients suffering from Alzheimer’s disease (AD). Amyloid beta (A?) deposits can often be seen in retinas of AD patients early in the disease process, and chronic deposition of these amyloid plaques

progressively leads to degeneration and loss of retinal ganglion cells (RGCs) and their axons. Importantly, AD-related pathological changes in the retina closely resemble AD-related pathological changes in the brain, making the retina an outstanding alternative tissue for AD research. In this multidisciplinary study, we combine our multiyear research on retinal degeneration and RGC loss (in multiple neurodegenerative conditions) with new ideas from the published literature to propose an innovative model for AD pathogenesis. We note that the Tlr4 and Rage signaling cascades mediate AD-related pathological damage in both the retina and the brain parenchyma proper. We also observe that A? deposits in the retina stimulate RGC death not only by apoptosis, but also by necrosis. Programmed RGC necrosis (necroptosis) contributes to retinal injury through direct loss of RGCs and induction (via release endogenous factors such as Hmgb1 and Hsp70) of an inflammatory response. Our data also indicate that NF?B signaling is significantly suppressed in RGCs exposed to neurotoxic conditions, usually resulting in RGC death, chiefly by necrosis. In contrast, glial cells and infiltrating leukocytes subjected to neurotoxic conditions do activate NF?B signaling; these cells demonstrate not only increased survival but also increased production of neurotoxic pro- inflammatory factors. Our model proposes that, following A? binding, Tlr4 and/or Rage receptors mediate NF?B activation in glial cells and infiltrating leukocytes, facilitating survival of these cells but also initiating production of neurotoxic pro-inflammatory factors such as TNF. But in RGCs exposed to A? and TNF, a lack of NF?B activity contributes to cell death, mostly by necroptosis. Endogenous factors liberated from necrotic RGCs go on to augment the effects of A? deposits, reactivating glial and leukocyte Tlr4/Rage signaling and therefore upregulating the pro-inflammatory response. These events form a positive feedback loop that ultimately results in significant tissue damage. We will employ animal models of AD and a wide range of biochemical, molecular, and cell biological techniques to test our model in hypothesis-driven mechanistic experiments, outlined in the following specific aims: to test the hypotheses that 1) the Tlr4 and Rage signaling cascades coordinate the neurotoxic pro-inflammatory response and increased blood-retinal barrier permeability in retinas of mouse models of AD; 2) A? deposition mediates retinal damage by promoting RGC necroptosis; 3) increased activity of the NF?B signaling cascade supports the survival of damaged RGCs and regulates the regrowth of axons in models of AD. Upon completing these specific aims, we expect that the results will provide substantial insights and novel strategies for regulating AD pathogenesis, ultimately contributing to innovative therapies for improving vision and quality of life in AD patients.

Further information available at:

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