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ApoE4: an emerging therapeutic target for Alzheimer's disease

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Abstract

Background: The growing body of evidence indicating the heterogeneity of Alzheimer's disease (AD), coupled with disappointing clinical studies directed at a fit-for-all therapy, suggest that the development of a single magic cure suitable for all cases may not be possible. This calls for a shift in paradigm where targeted treatment is developed for specific AD subpopulations that share distinct genetic or pathological properties. Apolipoprotein E4 (apoE4), the most prevalent genetic risk factor of AD, is expressed in more than half of AD patients and is thus an important possible AD therapeutic target.

Review: This review focuses initially on the pathological effects of apoE4 in AD, as well as on the corresponding cellular and animal models and the suggested cellular and molecular mechanisms which mediate them. The second part of the review focuses on recent apoE4-targeted (from the APOE gene to the apoE protein and its interactors) therapeutic approaches that have been developed in animal models and are ready to be translated to human. Further, the issue of whether the pathological effects of apoE4 are due to loss of protective function or due to gain of toxic function is discussed herein. It is possible that both mechanisms coexist, with certain constituents of the apoE4 molecule and/or its downstream signaling mediating a toxic effect, while others are associated with a loss of protective function.

Conclusion: ApoE4 is a promising AD therapeutic target that remains understudied. Recent studies are now paving the way for effective apoE4-directed AD treatment approaches.

Keywords: Alzheimer's disease; Anti-apoE4 antibodies; Apolipoprotein E4; Human apoE-targeted replacement mice; apoE4 lipidation; apoE4 therapeutics.

Figures

Fig. 1 Possible therapeutic approaches targeting apoE4

Fig. 2 Schematic presentation of the apoE4-driven...

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