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Commentary

A specific immunity brain aging gene with a future

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The paper by James et al. [1] here extends previous work from the Minnesota group [2] on the protective effect of certain Human Leukocyte Antigen (HLA) genes on age-related brain atrophy to dynamic brain function and the concomitant evaluation of the effects of apolipoprotein E (apoE) in a large sample of 178 healthy women. Using magnetoencephalography, a high-fidelity method for assessing brain function [3], and more specifically, the variability of neural interactions as an estimate of neural network integrity, they found that the integrity of brain networks remained stable over decades in women carrying the HLA gene DRB1*13 and/or the apoE2 genotype, whereas participants lacking DRB1*13 and/or carrying the apoE4 genotype (a risk factor for Alzheimer's disease) showed a significant increase in network variability (i.e. gradual loss of integrity) over a similar time period. A key finding of the study is that the presence of either one of the protective genes (DRB1*13 or apoE2) is sufficient to prevent aging-related increase in neural network variability, and thus preserve healthy brain functioning over the years. The differential effects of apoE2 and apoE4 on neural network variability have been documented previously [4], and are attributable to differential stability of the apoE2 and apoE4 molecules [5] and the toxicity of apoE4 and its fragments [6,8]. On the other hand, the protective effect of DRB1*13 has been attributed to the hypothesized presence of pathogenic persistent antigens [2] for the elimination of which the specific immunity HLA DRB1*13 gene would be essential, and which therefore, would persist causing low-grade neuroinflammation. The detrimental effects on neurons of such inflammation would be enhanced by the presence of toxic apoE4 fragments and, conversely, would be prevented in the presence of apoE2. These considerations point to a common final path for neuronal protection effected by DRB1*13 and apoE2. The cell biological, biochemical and molecular mechanisms of this cascade open a rich new field of basic research.

The involvement of DRB1*13 in protecting brain structure [2] and functional integrity [1] over the years has some intriguing and potentially far-reaching implications for clinical medicine. These implications stem from the fact that this gene belongs to HLA which is necessary for antigen presentation to CD4+ lymphocytes and subsequent production of specific antibodies to external pathogens. The detrimental effects of its absence on brain aging suggest that the damage is, at least partly, done by persistent antigens that would have been eliminated if it were present: this is the "persistent antigen" hypothesis of James et al. [2]. In that light, the finding of this study that the presence of HLA DRB1*13 overrides the harmful effects of apoE4 on the brain, acquires special significance, since it implies that those effects are only exerted when persistent antigens are present and, therefore, that the apoE4 effects are exerted downstream. In keeping with this idea is the corresponding finding that the presence of apoE2 prevents the harmful effects of the hypothesized persistent antigens: thus both the apoE4 and the apoE2 effects are similarly exerted downstream. Although the mechanisms of some of the toxic effects of apoE4 are understood [6,8], the protective effects of apoE2 remain to be elucidated. Finally, it should be noted that, unlike other genes that have been reported to be associated with accelerated brain aging (see, e.g. [7]), DRB1*13 possesses a specific immune function that lends itself to a testable hypothesis as to the nature of the protection conferred by it and, by extension, the nature of the damaging agents and their possible elimination. Indeed, the future identification of the hypothesized persistent antigens might well open new avenues for preventing "normal" brain aging – a misnomer!

Disclosure

The author declared no conflicts of interest.

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