Immunology of aging and immunotherapy of aging-associated diseases

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Country

USA

Title of project or programme

Immunology of aging and immunotherapy of aging-associated diseases

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 600,677.98

Start date of award
Total duration of award in years

13

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Biotechnology... Brain Disorders... Dementia... Immune System... Immunization... Neurodegenerative... Neurosciences... Prevention... Vaccine Related

Research Abstract

Aging significantly dysregulates the immune system affecting both composition and function of immune cells. However, mechanism of this process remains poorly understood. Here, to

understand this process we characterized B cells in aging hosts, as their impairment not only increases risk of serious complications from seasonal infections in the elderly, but also renders vaccines ineffective in reduction of flu-related deaths and hospitalizations. We previously reported that this problem can be circumvented by modifying a vaccine formulation (Olkhanud et al, Vaccine, 2011). For example, our Alzheimer's disease (AD) vaccine formulation, termed Abeta-CoreS, induces a potent humoral response and alleviates AD even if used at the onset of the disease in old mice when traditional vaccines are ineffective. On the other hand, our studies in cancer demonstrate that B cells can also directly regulate cellular immune responses (AG000443-09), suggesting that their dysregulation upon aging may also lead to the induction of autoimmune T cells. Indeed, we recently confirmed this possibility by discovering potentially pathogenic B cells of unknown origin that accumulate in elderly humans, monkeys and mice. These cells termed 4BL cells induce the generation of granzyme B (GrB) and perforin CD8+T cells (Lee-Chang et al., Blood, 2014). We now report that 4BL cells are derived from innate B1a cells that produce natural antibody. Thus, contrary to current assumption that innate B cells do not change upon aging, our result indicate that the aging renders B1a cells to lose their immune suppressive function and to become superb inducers of cytolytic T cells. We also found that this conversion is induced by aging human monocytes and murine peritoneal macrophages. By utilizing 4-1BB and CD40L, elderly human and murine myeloid cells convert young host B1a cells to upregulate 4-1BBL, IFNR1, CD86 and membrane TNF. This enables activated B1a cells (4BL cells) to induce expression of granzyme B in CD8+T cells by targeting TNFR2 via mTNF while providing co-stimulation with CD86. This finding has been recently reported (Lee-Chang et al., 2016). Overall, the project is progressing well as planned. It continues generating novel insights with significant scientific and clinical implications. The immune cells also play important role in proper function of the central neural system (CNS). However, their role in Alzheimer's disease (AD) remains poorly understood despite the fact that a risk for dementia and AD increases together with the dysregulation of immune cells in the elderly. Although our previous results suggest that that B cells can alleviate AD symptoms via generation of Ab plaque-neutralizing antibody (Olkhanud et al, Vaccine, 2011), here we explored whether aging B cells can also have pathogenic activity in AD. For this purpose we used 2 types of mice that develop AD in young and old age, 2xTgAD and 3xTgAD mice, respectively. The mice were crossed with B-cell deficient (BKO) mice to generate 2xTgAD/BKO and 3xTgAD/BKO mice. Our preliminary study indicates that the loss of B cells in 2xTg-AD mice is lethal, as they die by 2-3 month of age. In contrast, no lethality is detected in 3xTgAD/BKO mice. Although 3xTgAD/BKO mice are still young and did not yet develop the AD symptoms, they already exhibit skewed immune cell responses. Thus, this study for the first time has started revealing a new and interesting insight in the role of B cells in pathogenesis of AD. It suggests that pathogenesis of AD depends on B cells exerting age-dependent opposing functions, such as protective (in young age) and pathogenic (in old age) roles. The first part of the study will be completed in one year.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

Database Tags:
N/A