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Designer vaccine for Alzheimer's?

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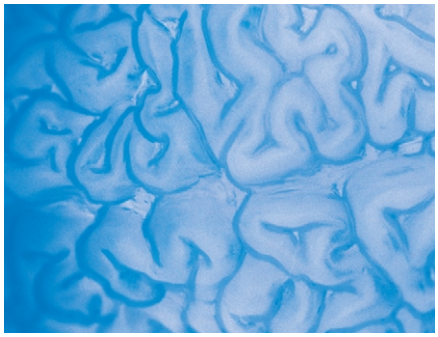
Recruiting the best immune system 'personnel' to combat Alzheimer's disease (AD) customizes the immune response to thwart disease progression: this important step to create a vaccine against AD has finally been achieved [1]. Scientists at the University of Rochester Medical Center (http://www.urmc.rochester.edu/) have used herpes simplex virus (HSV)-derived amplicons expressing peptides of amyloid beta (Aβ) to elicit distinctive immune responses that specifically combat AD pathogenesis in mice.

The ageing disease

AD is the most common cause of dementia in ageing people. A hallmark of AD pathology is the aggregation and accumulation of Aβ peptides (proteolytic cleavage products of the amyloid precursor protein) in cognitive regions of the brain. Although accumulation of Aβ might be part of the normal ageing process, clinical symptoms of AD possibly result from Aβ levels increasing above those which can be tolerated or controlled by clearance mechanisms within the brain. However, the factors that trigger this accumulation remain unknown.

Lost potential?

Aβ peptides accumulate in the brain, forming amyloid plaque deposits, which then undergo fibrillogenesis, during which neurotoxic intermediates are formed. These processes lead to synaptic dysfunction and eventually neuronal cell death. It is this role in the progression of AD pathogenesis that has led to therapeutic strategies being targeted towards preventing Aβ fibrillogenesis and accumulation.



Another goal is to remove plaque deposits already present in the brain.

Initial experiments using Aβ-based approaches in the mouse model showed great promise and raised the hopes of AD sufferers worldwide. Active immunization of transgenic mice with $A\beta_{1-42}$ (the predominant constituent of Aβ found in amyloid plaques) prevented the development of plaque formation and markedly reduced the extent and progression of AD-like neuropathologies in mice with established AD [2]. In addition, Phase I trials in AD patients following $A\beta_{1-42}$ (AN-1792) immunization demonstrated that the vaccine was safe to use. However, a major setback called a halt to the development of this vaccine when severe meningoencephalitis (inflammation in the brain) was reported in AD patients during a Phase II trial with $A\beta_{1-42}$ [3].

Customizing the Alzheimer's vaccine

Howard Federoff and colleagues [1] set out to design a vaccine that would shape the immune response in such a way that adverse side effects, such as inflammation, would not occur.

William Bowers, Assistant Professor of Neurology at the University of Rochester, said; 'From our studies and those of others, it appears that you need to induce specific immune activity to clear existing plaque or prevent the formation of new plaque deposits. In essence, we want the beneficial effects of the vaccine without the toxicity.'

Two vaccine vectors were constructed using the HSV amplicon system [1]. One expressed $A\beta_{1-42}$ alone and was most similar to the previous form used in the Phase II clinical trial [3]. The second vector expressed $A\beta_{1-42}$ fused with the molecular adjuvant tetanus toxin Fragment C, which aimed to overcome Aβ tolerance in the transgenic mice and to alter the type of immune response elicited. 'The herpes vector system gives us the flexibility to fine-tune the nature of the immune response so we can possibly create an effective vaccine that has a more optimal safety profile,' said Bowers.

Both types of vaccines elicited humoral responses to Aβ and reduced its accumulation in the CNS of transgenic mice. However, four of the six mice inoculated with the vector expressing solely the Ab_{1-42} peptide died and, upon examination, showed a marked inflammatory response within the brain. In stark contrast to this observation, all six mice inoculated with the vector that expressed the tetanus toxin in addition to Ab_{1-42} survived and, importantly, the amount of amyloid plaque formation in the brain was also reduced. Inclusion of the tetanus toxin specifically altered the immune response in such a way that the harmful side effects of the original vaccine disappeared.

'This work provides a platform to shuffle the immune response, a flexibility to modify the approach to create a vaccine that is safe and efficacious,' says Howard Federoff,

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Professor of Neurology and Director of the Center for Aging and Developmental Biology at Rochester.

Although this study was performed in mice and not in humans, it shows that a level of control over the immune response to an AD vaccine can be attained and paves the way for a brighter future for those suffering from this disease.

References

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Surprise at genotoxicity findings for childhood leukaemia therapy

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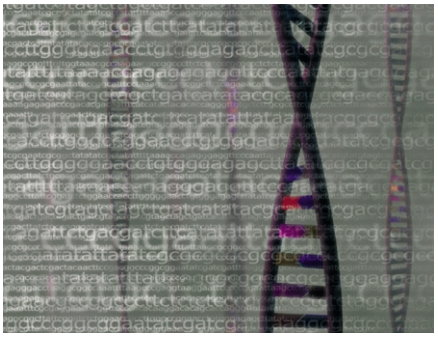
Children who survive acute lymphocytic leukaemia (ALL) thanks to standard chemotherapy are left with higher than expected rates of genetic damage, researchers have found. Chemotherapy is so successful that almost 80% of children with ALL now survive at least five years. However, the powerful antineoplastic drugs damage normal as well as cancerous cells, in some cases leading to organ damage and leaving survivors with a 5–20-times greater risk of developing secondary cancers in later life.

Barry Finette and colleagues at the University of Vermont, Burlington (http://www.uvm.edu), analyzed 130 blood samples from 45 children on standard treatment protocols for ALL, starting at first diagnosis and continuing during, and for five years after, treatment [1]. To measure the genotoxic effect of the drugs they looked at the frequency of somatic mutations in the *HPRT*-reporter gene, a widely used biomarker for mutation rate.

Surprise mutations

They found that the number of mutations carried by the children rose



during each phase of therapy, culminating in a 200-fold increase on completion. This is between 10 and 100 times higher than the increases in *HPRT* somatic mutation frequency recorded in survivors of nuclear bombs and workers involved in the cleanup of Chernobyl, and is thought to be the greatest increase ever recorded after exposure to genotoxins. Furthermore, the mutation frequency failed to drop back in the years after treatment, instead remaining high and increasing at the normal age-related rate.

'We were surprised at the degree of the increase, and at the fact that the mutation frequency remained elevated after cessation of treatment,' says Finette. The few studies done in adults exposed to genotoxins have shown a decrease in mutation frequency once exposure ends. He believes the increase found in the children is real: 'We've been doing this [measurement] for years with hundreds of patients,' Finette says. 'We don't believe it's an artefact.' Nor do they think that the treatment simply selects for existing cells with *HPRT* mutations.

However, Alan Kinniburgh, Senior Vice President for Research at the Leukemia and Lymphoma Society in the USA (http://www.leukemia.org), is cautious about the high numbers of mutations recorded. 'A selection effect by chemotherapy on HPRT mutations cannot be ruled out,' he says. 'But this does not detract from the finding that [these] therapies are mutagenic, and that this is the most likely explanation for the increased incidence of secondary malignancies.'

Another surprising finding, Finette says, was that the increase in mutation frequency was the same whether the children were on low-intensity or high-intensity regimens, despite significant differences in the respective dosages and clinical toxicity involved.

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