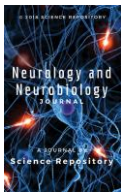

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Review Article

Can Repurposed Polyvalent Vaccine Boosters (like BCG) Limit Dementia Progression by Modifying Microglial Activation Phenotypes?

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ABSTRACT

This article sets out a case for considering generally available polyvalent vaccines such as BCG, MMR and DPT to be repurposed for treating emerging cognitive decline in elderly people through reducing neuroinflammation via microglial activation. Up to now, treatments to reduce parenchymal oligomers such as Amyloid beta in Alzheimer's disease have been clinically unsuccessful. Therefore, an alternative approach to try and directly attenuate microglial activation has utility.

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Physiology of Microglial Activation

Microglia are the scavenger cells in the brain, with multiple roles of phagocytosing cell debris, viral particles and unused synaptic dendritic spines [1]. Resting or quiescent microglia maintain contact with neurones, astrocyte (support) cells and the intracellular environment via cellular projections. When noxious stimuli are detected, these projections are withdrawn, and microglial activation takes place with the cell morphology changing to an amoeboid form, suitable for phagocytic functions. Microglial activation can be measured via Positron Emission Tomography (PET) using radioactive ligands binding to benzodiazepine receptors [2]. Qualitative analysis of microglial activation is also possible using a ligand PK11195 [3].

Microglial activation is not a single pathway; there are 2 pathways quiescent microglia can proceed to in the face of pathogens (like viral particles) or when presented with neuronal damage (for example following traumatic brain injury). Firstly, conversion to the M1 phenotype can result in an inflammatory response with cytokine release (IL6, TNF Alpha). Alternatively, a conversion to a variety of M2 activation cells can provide a neuroprotective effect [4]. These 2 phenotypes are mutually inhibitory; similar to the peripheral T helper cells proceeding to either TH1 (inflammatory and cytotoxic) or TH2 (antibody producing) cell lines [5]. However, unlike the peripheral adaptive immune pathway, microglia also provide the phagocytic function carried out by macrophages.

On, precipitants of microglial activation, studies in mice show that rapidly replicating neurones produce a signalling protein call fractalkine, which binds to the microglial receptor CX3CR1, causing activation [6]. Animal studies have shown that microglia can also be activated in the prefrontal cortex by chronic stress [7]. The relationship between stress and microglial activation is based on the release of cytokines such as IL6. This cytokine penetrates the blood brain barrier and activates microglia in the central nervous system and plays a key role in the pathogenesis of mood disorders [8]. T helper cells can also penetrate the blood brain barrier via the choroid plexus, especially during systemic inflammation led by the TH1 pathway [9]. On the adoption of the M1 or M2 phenotype, microglia can be stimulated by Interferon gamma (IFN-γ) to an M1 phenotype for expression of pro-inflammatory cytokines or

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by Interleukin 4 or Interleukin 13 to an M2 phenotype for resolution of inflammation and tissue repair [10].

Link with Neurodegeneration

The association between microglial activation and clinical manifestations of neurodegenerative diseases has been noted in Alzheimer's, Lewy Body and Fronto Temporal Dementias [11-13]. Furthermore, there appears to be a 'dose response' relationship in early Alzheimer's disease with extensive microglial activation leading to a more rapid clinical decline [14]. It is known that microglial activation is supressed by atypical antipsychotics such as Olanzapine, Risperidone and Quetiapine independent of its anti-dopaminergic potential; this might partially explain their mode of action in psychoses and other neuropsychiatric features in these conditions, although most of the studies have been conducted on mice (with the exception of 16) and requires continuous dosing with the associated metabolic risks due to non-specific Glucose Transporter (GLUT) blockade [15-18].

Regards the pathognomonic late feature of neurodegenerative disease; accumulation of oligomers such as Amyloid Beta in Alzheimer's disease, the consensus opinion is that an inflammatory milieu activates microglia, but inhibits its phagocytic capability, leading to increasing accumulation and formation of solid plaques [19]. It is known that activated microglia do not phagocytose soluble amyloid beta, but partially degrades these proteins by secreting an Insulin Degrading Enzyme [20]. However, at an earlier stage in the neurodegenerative process, activated microglia phagocytose synaptic dendritic spines, commencing the pathological cascade [21].

Alternatives to Psychotropics for Attenuating Microglial Activation

Recently, researchers using a polyvalent vaccine including an 'anti-GA' antigen, demonstrated attenuation of microglial activation in mice carrying a genetic mutation for Amyotrophic Lateral Sclerosis [22]. This team found that the vaccine provided protection from motor features alongside attenuated microglial activation. The vaccination also appeared to clear the pathogenic poly-GA aggregates (similar to Amyloid in Alzheimer's disease). However, vaccination with antigenic Amyloid beta 1-42, despite clearing parenchymal Amyloid deposits, resulted in downstream perivascular amyloid deposition with associated micro-haemorrhages in animal studies, consistent with findings in subsequent human trials; which had to be terminated prematurely due to a number of deaths due to angiopathic encephalopathy [23-25].

Subsequent post-mortems of patients who were vaccinated with amyloid beta antigens and thereafter died of natural causes later in life also showed evidence of parenchymal beta amyloid clearance, but not Tau based neurofibrillary tangles within neuronal bodies [26]. Consistent with this finding, these subjects also continued in their pre vaccination pattern of cognitive decline over the subsequent years. Despite this, researchers are returning to this field by injecting mice predisposed to Alzheimer's pathology with a tetanus epitope (platform) to transfer Amyloid Beta antigen producing RNA strands; expected to move to human trials imminently, despite ethical concerns on premature deaths of subjects due to angiopathic encephalopathy [27].

Rationale for Using Repurposed Polyvalent Vaccine Boosters (Such as BCG)

A repurposed polyvalent vaccine, such as the Bacillus Calmette-Guérin (BCG) booster has a proven record of safety across the age range; currently the latest iteration named VPM1002 from the Max Planck institute is undergoing trials involving elderly subjects (a phase III study) in India for attenuating infection with SARS-CoV-2 utilising 'trained immunity' of the innate immune system; such as Macrophages, Monocytes and Natural Killer cells [28]. Back up evidence on the protective effect of BCG vaccination against other viruses in humans is also available, alongside epidemiological data suggesting that individuals vaccinated with BCG has less mortality associated with SARS-CoV-2 infection [29-31]. Recent research in Alzheimer's disease has identified both Herpes Simplex and *Candida* species infiltration of the brain parenchyma, stimulating a joint microglial and beta amyloid response [32, 33].

If BCG vaccination can boost the innate immune system, it would be reasonable to examine the effects of this vaccine on microglial activity; for example, if it can encourage phagocytosis of oligomers without causing perivascular deposition in patients with established neurodegeneration such as Alzheimer's disease. Alternatively, if this vaccine produces microglial deactivation, the possibility of reduced synaptic destruction at an early stage of the disease process also needs to be considered. The overriding rationale is that these hypotheses can be examined safely due to this vaccine already having been tested regards safety in humans. There is no contraindication for using a vaccine booster alongside Acetylcholinesterase inhibitors which have anti-inflammatory properties in any case [34].

Future Research Strategy

It would be helpful to carry out further studies of mice predisposed to Alzheimer's, Lewy Body or Frontotemporal neurodegeneration to see if a polyvalent vaccine can prevent synaptic destruction by microglia at an early stage of the disease process and / or increases microglial phagocytosis of oligomers at a later stage. Further clarification of M1 / M2 ratios in neurodegenerative processes and how a polyvalent vaccine alters this ratio (or not) will also be helpful using animal studies prior to human trials. On human studies, it seems most appropriate to focus on early stage mild cognitive impairment with a high risk of conversion to pathological neurodegeneration (as evidenced by family genomic, imaging and cerebrospinal studies), to compare the effects of the soon to be tried m-RNA Amyloid Beta vaccine versus a polyvalent vaccine such as the newly developed BCG variant VPM1002 [27]. It is unlikely that a monovalent vaccine will produce a strong enough immune reaction, especially in older subjects; but this is also worth confirming.

Conclusion

A case has been made to consider a repurposed polyvalent vaccine such as BCG in order to reduce microglial activation the consequent loss of synaptic processes in early onset neurodegenerative conditions such as Alzheimer's, Lewy Body and Fronto Temporal dementias. Alternatively, use of this type of vaccine at a later stage could increase

microglial phagocytosis of oligomers such as beta Amyloid in Alzheimer's disease. This approach seems safer than utilising antibodies against oligomeric proteins which has resulted in deaths and also not provided efficacy in human trials. If repurposed vaccinations are successful, this would be a significantly cheaper and safer alternative compared to novel drug (and vaccine) development.

Conflicts of Interest

None.

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