Enhancement of innate immunity by curcuminoids and hormones as a therapeutic strategy in neurodegenerative disorders

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'...adaptive and innate immunity components need to work in unison. Future therapies will need to pay attention to improving both innate and adaptive immunity.'

Despite impressive advances in the understanding of the neuropathological basis of Alzheimer's disease (AD) as being related to neuronal toxicity of amyloid- β (A β ; 1-40 and 1-42) in fibrillar, soluble or oligomeric form according to the amyloid hypothesis [1], there is as yet no clinically successful strategy to remove A β deposits from the brain. In sporadic cases of AD, amyloidosis of the brain may be related to defective clearance of A β [2]. Several groups have shown diligent interest in microglial clearance of A β [3,4], leading to the development of an A β vaccine [5] and a clinical trial, which was, however, abrogated due to adverse encephalitic complications [6]. On the other hand, microglia, with the help of complement and astrocytes, have been shown to be a perpetrator of inflammatory damage in neurodegenerative diseases [7,8], and anti-inflammatory therapies with different nonsteroidal anti-inflammatory drugs have had a continuing vogue [9]. The role of microglia in A β clearance was initially proposed as being due to Fc-receptor-mediated phagocytosis and A β degradation by microglia [4]. Another strategy for A β clearance purports that antibodies can dissolve A β deposits [10] and immunoglobulin administration may have beneficial effects in AD patients [11]. In a third scenario, peripherally administered anti-A β antibody creates a sink that drains A β from the brain [12]. In this editorial we will present our proposals on new strategies for A β brain clearance by natural substances to bolster the innate immune system. According to our hypothesis, the normal innate immune system, with the help of adaptive immunity, should be able to clear A β from the brain unless there is overproduction of A β . We must advise the general readership that the concepts presented below are not yet in the mainstream but are receiving further support from our ongoing studies and those of other investigators.

The first issue is the identity of the innate immune cells responsible for A β clearance. Traditionally, activated microglia are considered to be responsible for both brain inflammation and A β phagocytosis [13,14] through various receptors, including the class B scavenger receptor [15]. Our immunohistochemical studies of AD brain demonstrated that inducible nitric oxide-synthase-positive and cyclooxygenase-2-positive bloodborne monocytes/macrophages penetrate across brain microvessels (with destruction of interendothelial zonula occludens-1 protein) and significantly infiltrate perivascular and parenchymal sites, but only partially clear neuritic plaques [16-18]. These observations suggested that, in addition to microglia, in the human brain with AD, peripheral monocytes/macrophages are the cells involved in A β clearance. Our neuropathological results received recent support from studies in animal models of AD. Two groups have demonstrated the ability of peripheral blood macrophages and T cells to invade the brain of aged amyloid-precursor protein transgenic mice [19] and to clear A β deposits [20]. We also noted that the density of macrophage infiltration of neuritic plaques was not (inversely) related to residual A β (as would be expected if AD macrophages could efficiently clear A β) and speculated that the cardinal problem in AD lies specifically in the dysfunction of macrophages. Our studies of over 100 patients and approximately 40 control subjects are revealing unsuspected pathophysiology of AD monocyte/macrophages, which is probably not explained by serum factors since they are noted even in the presence of fetal bovine serum. We are detecting heterogeneous defects in macrophage differentiation *in vitro*, A β uptake and trafficking to lysosomes, and apoptosis on exposure to A β . In addition, patients' monocytes overexpress interleukin-12 and patients' CD4 T cells overproduce interleukin-10 and interferon- γ , the cytokines belonging to both T helper (Th)1 and Th2 sets. Thus, the adaptive and innate immune system components of AD patients seem to be in various stages of disharmony and dysfunction. In stark contrast, macrophages of control subjects voraciously ingest A β and appear to degrade it (probably without the

help of antibodies) [17]. In conclusion, we believe that the whole innate immune system (including macrophages and microglia) in AD patients may be defective and its pathological state can be evaluated by studying peripheral blood monocyte/macrophages.

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The second issue is the classical controversy between the benefits of therapeutic strategies targeting inflammation versus A β removal by the immune system. This subject has recently been elegantly reviewed from the point of view of transgenic animal models, with the conclusion that inflammation may induce both beneficial A β phagocytic responses and adverse neurotoxic responses [21]. However, the problem is that although current transgenic animals do model brain amyloidosis, albeit iatrogenically, they do not reproduce the immune problem of patients with AD. Therefore, we have been studying the benefits of enhancing immune responses to A β using peripheral blood leukocytes of patients and control subjects.

Following the demonstration of defective phagocytosis of A β by macrophages of a majority of AD patients [17], we have investigated the substances previously shown to be effective in clearance of A β plaques in transgenic animals, that is to say curcuminoids [22] and insulin-like growth factor [23]. In cultured macrophages of AD patients *in vitro*, curcuminoids improved the defect in macrophage phagocytosis of A β in 50% of patients in a small study [24]. The responding patients were younger and had higher minimal mental scores, suggesting that patients in the less advanced stages of AD may respond better. This mechanism of action of curcuminoids is novel

and seemingly not in line with the anti-inflammatory and proapoptotic effects of curcuminoids. However, the multitude of regulatory effects of curcuminoids on cell-signaling pathways lends credence to the concept that curcuminoids may be returning the cell to a physiological balance [25]. In addition, we have observed that treatment of AD macrophages with insulin-like growth factor improved A β phagocytosis in some macrophages, but we have not yet determined whether hormonal and curcuminoid effects are synergistic or additive. It is tantalizing to speculate whether the effects of immunomodulating and anti-inflammatory therapies could be evaluated *in vitro* and individualized according to each subject's innate and adaptive immune responses.

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In addition to our novel approaches, classical immunological approaches have been proposed to mitigate the encephalitic problem. Microglia have been activated with beneficial and adverse effects using lipopolysaccharide [26] or a proteosome-based adjuvant (Protolin[®]) [27]. A strong consideration has been given to the possibility that a Th1-cell response against A β was responsible for encephalitis in vaccinated subjects and, therefore, strategies to circumvent this complication have been designed using mucosal immunization or using only the B-cell epitope of A β for vaccination [28]. In all of these approaches, the adaptive and innate immunity components need to work in unison. Future therapies will need to pay attention to improving both the innate and adaptive immunity.

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