Page 475 to 479

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Regulating the Brain Autoimmune System: The End of All Neurodegenerative Diseases?

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In this article, I submit that the root cause of neurodegenerative diseases (NDs) is the brain's autoimmune system that had run amok in its unsuccessful attempts to maintain "brain homeostasis", i.e., the state of equilibrium (balance between opposing pressures) in the brain with respect to various functions and to the chemical composition of the fluids and tissues therein. In the case of Alzheimer's disease (AD), for example, the pressures are the synaptoblastic and synaptoclastic signals. The cure would be to temper and regulate this system to tolerate rather than fiercely combat the synaptoclastic signals such as by the use of regulatory chimeric antigen receptor (CAR)-T-cells (T_{reg}),

There are approximately 400 known NDs, some of which classified as mental disorders. A number of these disorders are mediated by a disruption or failure of the blood brain barrier (BBB) such as, for example: meningitis; epilepsy; multiple sclerosis (MS); AD; possibly prion and prion-like diseases such as Parkinson's disease (PD) and AD; HIV encephalitis (HIVE), a precursor of HIV-associated dementia (HIVAD); and systemic inflammation (sterile or infectious) that may lead to effects on the brain, cause sickness behavior and induce or/and accelerate brain diseases such as MS and PD. Understanding the nature of the role of the BBB in NDs is one imperative in their treatments, but the fundamental question of whether the compromised integrity of the BBB is a component of the etiology of the diseases or a consequence of it remains unanswered [1-2]. Further, drug resistance (DR) and the possible role of the BBB remain another important imperative [3]. However, the convergence between BBB studies and clinical investigations has historically been limited.

Our current state of knowledge of three major NDs (epilepsy, Parkinson's, and Alzheimer's) is illuminating in what we do not know. In epilepsy, studies of the interactions between putative anti-epileptic drugs (AED) and the endothelium have shown that many promising AEDs are excluded by the BBB. They are thus clinically unusable in spite of their significant potency and selectivity, as revealed by *in vitro* screening or animal models. It has become apparent that multiple drug resistance (MDR) is only one of the aspects in BBB research that may impact how we define, prevent and treat seizure disorders [4]. A compromised BBB has been associated with seizures in a number of other disorders. Not only congenital defects, such as GLUT1 deficiency, but acquired deficiencies, like those resulting from brain tumors, head trauma, etc., often result in seizure disorders. More recently systemic and immune triggers have been implicated in a leaky BBB and neuroinflammation.

In Parkinson's, we have learned that dopamine does not cross the BBB so it cannot be taken as a medicine to boost the brain's depleted levels of dopamine. However its precursor, levodopa, can pass through this barrier to the brain where it is readily converted to dopamine.

Administration of this drug temporarily diminishes the motor symptoms of PD. Unfortunately, only 5–10% of the drug crosses the barrier with much of the remainder being metabolized to dopamine elsewhere in the body, where it causes a variety of side effects [5].

Over the past few decades, AD, once considered a rare disorder, has emerged from obscurity to become a major public health problem. It is an irreversible, progressive brain disease that slowly destroys memory and thinking skills, eventually even the ability to carry out the simplest tasks. It is a chronic ND of poorly (or not) understood cause(s). Based on identified risk factors, several theories (hypotheses) have been propounded for its cause(s): genetic (early onset familial disease, late onset sporadic disease), cholinergic, amyloid, fungal infection, tau, neurovascular, neuroinflammation, neurodevelopment, cardiovascular, gum disease infection, dysfunction of oligodendrocytes, and others related to lifestyle, diet, and the environment [6-8]. Such a wide array of hypotheses is by itself indicative of our lack of true understanding and knowledge of the disease notwithstanding the fact that the disease has been identified since 1901 and despite the considerable number of publications dealing with it (in excess of 50,000). Indeed, there are no known treatments to stop or reverse the progression of AD, though some may temporarily improve symptoms. Research emphasis has been placed on diagnosing the condition before symptoms begin. A number of biochemical tests have been developed to attempt earlier detection including analysis of the cerebrospinal fluid for beta-amyloid (Aβ) or tau proteins and preventive anti-body vaccination. Neuroprotective agents (e.g., Al-108, PBT2 and TNFα receptor-blocking fusion protein etarnacept) have also been designed. Among the more than 400 pharmaceutical treatments having been investigated or in advanced clinical trials, putative pharmaceutical therapies attempt to treat the underlying disease pathology such as by reduction of Aβ levels (e.g., by apomorphine, investigational immunotherapy, or vaccination) and inhibiting tau aggregation (e.g., with methylthioninium chloride and dimebon). Still other "softer" methodologies involve meditation and anti-fungal infection of the brain.

Immunotherapy has been applied in both PD and AD. Putative immunological therapies are based on the concept of training the immune system to recognize, attack, and reverse the deposition of amyloid. However, immunotherapeutic agents have been found to cause some concerning adverse drug reactions. The immunotherapeutic strategy for PD therapy relies on the assumption that (a) alpha-synuclein is accessible in the extracellular space (trans-synaptic spreading), (b) antibodies against alpha-synuclein reach the brain in sufficient quantity, and (c) they trap alpha-synuclein aggregates when these are released ("spread") into the extracellular synaptic space. However, one important limitation of active and passive immunotherapy is the low amount of antibodies passing the BBB, which may be overcome by coupling antibodies to the peptide penetratin. Lastly, modulating the aggregation of alpha-synuclein aims to block or reduce the aggregation of its monomers to oligomers or later on to fibrils. In distinction with the antibodies employed, several small molecules have been designed to readily pass the BBB while delivering therapeutic compounds at the right locations in the right dosage amounts would herald a new treatment approach [11-12]. This is also what nanomedicine (NM) and nanotechnology (NT) promise to do. However, while the technology is now well known, its application to NDs has not yet been undertaken. While palliative treatments are available, NDs have generally been declared as incurable. The reason being that we truly have not yet been able to identify the etiology and biology of their root cause(s).

The above situation is reminiscent of that for other diseases, particularly cancer. It was not until after we came to the realization that cancerous cells like healthy cells from which they evolved are braided in our genome, and that cancer is not an organ disease but the result of multiple genetic mutations, i.e., understanding the biology of cancer, that we have made great strides in cancer treatment and cure. Witness the emergence of immuno-oncology and the recent FDA-approved use of chimeric antigen receptor (CAR) T-cells [13-15]. Immunotherapy has been successful in inducing long-term remissions of hard-to-treat cancers. The early identified protein receptor on the surface of T-cells (cytotoxic T-lymphocyte antigen 4, CTL-4) and a molecule (programmed death 1, PD-1) led to astonishing tumor shrinkage and increased survival, particularly in metastatic melanoma. Thus, anti CTL-4 and anti PD-1 have opened up new vistas in tumor treatment. Beyond that, genetically modified patients' T-cells and PD-1 molecules promise to be even more effective in specifically tailoring the treatment to the patient along the precepts of personalized medicine.

Owing to the presence of the brain's protective barriers (BPBs) at the interface between the central nervous system (CNS) and the periphery, and their muted response to neuroinflammation, it has been widely assumed heretofore that the brain (and, more generally, the CNS) is immune-privileged. However, in contrast to this earlier dogma, it is now evident that the CNS does contain immune capabilities. In addition, the BPBs contribute to the development of inflammation through either normal immune signaling, or disruption of the basic physiological barrier mechanisms. The brain's vaguely understood component of the immune system, as distinct from the rest of the body's immune system, is generally able to handle, treat, and overcome any adverse pathologies developing therein. Despite the protective mechanisms of the BPBs, the capacity for immune-surveillance of the brain is maintained, and there is evidence of inflammatory signaling at the brain barriers that may be an important part of the body's response to damage or infection. This signaling system appears to change both with normal aging and during disease. Changes may affect organic phenomena (or diapedesis) of immune cells and active molecular transfer, or cause rearrangement of the tight junctions and an increase in passive permeability across barrier interfaces. In parallel with immunotherapy as an emergent therapy of cancer, I advanced earlier the opinion that brain immunotherapy should also become a similar therapy for brain cancers and neurological disorders, providing a paradigm shift in our therapeutic approach to brain cancer and NDs.

I now posit that the root cause of NDs is the brain's very autoimmune system that had run amok in its attempts to maintain "brain homeostasis", that is the state of equilibrium (balance between opposing pressures) in the brain with respect to various functions and to the chemical composition of the fluids and tissues therein. For example, in AD, this process has been described as follows: Neurons sport receptors called amyloid precursor proteins (APP). When APPs grab hold of netrin-1 (molecules floating by in the intercellular environment), they send signals (so-called "synaptoblastic signals") to the neurons to keep them healthy and functional. This is the synapse-building phase. When this process fails, it defaults to opposite signals (so-called "synaptoclastic signals") instructing the neurons to commit suicide and to APPs to produce more Aβ thereby outnumbering netrin-1. This is the synapse-dismantling phase. As a consequence, the APPs are less likely to grab netrin-1 and more likely to keep grabbing Aβ. Any effective treatment for AD should therefore include a method to rebalance the synapse building and dismantling phases. One such approach would be to identify all different contributors to APPs (or AD's risk factors) and to address all (or as many) of them [8]. However, risk is not causation!

A different approach, and the one advocated here, would be to tame and regulate the underlying autoimmune system to tolerate rather than fiercely combat the synaptoclastic signals. This idea builds upon work done in diabetes type I, an incurable disease so far, in which the autoimmune system is taught to tolerate the insulin-producing cells of the pancreas so that it does not destroy the diabetic patient's ability to produce the glucose-regulating insulin [16]. The similar idea forms the basis of various clinical trials for treating other incurable diseases such as multiple sclerosis and Graves's disease. The overarching purpose is to tame down the hyperactive autoimmune system by employing molecules that can induce an immune response (antigens) or engineered immune cells that can train the autoimmune system to tolerate the process or tissue it is on track to damage. This idea has the potential to cure a range of autoimmune disorders, including especially NDs. As stated earlier in the case of cancer and brain tumors, this requires a deep understanding of the molecular basis of autoimmunity as well as advances in genetic engineering and cell-based therapy. Caution must nonetheless be exercised as deploying the immune system to treat certain diseases can also trigger autoimmune diseases, e.g., in the case of cancer, it may trigger autoimmune diseases, including rheumatoid arthritis and colitis.

The main immune players are the regulatory T-cells (T_{reg}), which act as the brakes of the immune system. Similarly to other T-cells, T_{reg}-cells rein in the immune cells that are doing damage. It has been suggested that the body can be made to produce the T_{reg}-cells required to dampen a certain autoimmune response, by dosing people who are affected with the same antigen or antigens that the immune system wrongly interprets as a reason to attack. This was tested [17-18] for multiple sclerosis, demonstrating less brain inflammation. This is similar to vaccination which, if administered without the immune-system stimulants called adjuvants that are usually included in vaccine formulations, antigens can induce a calming effect through T_{reg}-cells.

There may be other ways to temper a rogue autoimmune system. In cell- based therapy, a patient's Treg-cells can be removed from the body, engineered to respond to specific antigens that have been wrongly recognized by the immune system as being foreign, and

then returned. This is the very principle of chimeric antigen receptor (CAR) T-cells (here T_{reg}-cells) that have been FDA-approved and now applied to cancer treatment [15]. They can be used to dampen harmful inflammation.

In conclusion, a number of known NDs are mediated by a disruption or failure of the BBB. While understanding the nature of the BBB's role in NDs (and also the role of multi-drug resistance) is imperative in designing treatments, the fundamental question of whether the compromised integrity of the BBB is a component of the etiology of the diseases or a consequence of it remains unanswered. Like in other diseases (diabetes, cancer, etc.), we have been hampered by our imperfect understanding of the underlying biology and, in desperation, have too soon declared such diseases as "incurable". However, the realization that the brain and the central nervous system are endowed with their own immune system, accompanied by the greater understanding of the mechanism of autoimmunity, and the advent of cell-based therapy have empowered us to conceive other treatment strategies and even cures. The main immune players, the regulatory T-cells (T_{reg}), which act as the brakes of the immune system, can be so manipulated (engineered) as to temper and regulate the autoimmune system and train it to tolerate (rather than fiercely combat) the opposing pressures to achieve brain homeostasis. There may be additional ways to temper a rogue autoimmune system such as, for example, emulating cancer immunotherapy with CAR-T cells but with CAR-T_{reg} cells for the neurodegenerative diseases of interest.

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