Novel strategies for the prevention of dementia from Alzheimer's disease

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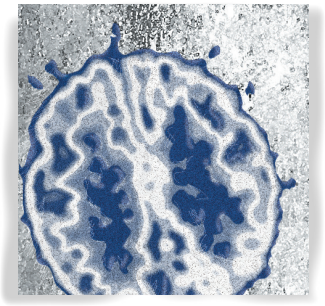

Understanding early changes in Alzheimer's disease and mild cognitive impairment

While many of today's cutting-edge Alzheimer's disease (AD) research programs focus on understanding and targeting the molecular mechanisms underpinning this disease, the ultimate goal for researchers and clinicians is the treatment of dementia, preventing the cognitive decline and loss of quality of life that can be so devastating, not just for the individual, but also for the families so greatly affected by the suffering of a loved

As the world's population continues to age, Alzheimer's disease presents a looming public health crisis that, left unchecked, threatens to overwhelm health care systems throughout the developed world. In order to significantly tackle the most catastrophic and devastating symptom of Alzheimer's disease (AD)—dementia—we must be able to detect the disease prior to the onset of clinical symptoms, and be able to offer patients preventative treatments that block or significantly slow disease progression. This review summarizes a variety of the most promising early detection methods for Alzheimer's disease (AD) and mild cognitive impairment (MCI) that could be used to identify those at high risk of developing the disease and used for monitoring disease progression and response to investigational treatments. In addition, treatment research programs that could be developed into disease-modifying treatments that significantly delay the development of dementia are highlighted. These potential treatments target many different pathways, and may one day be dosed in combination to increase efficacy and prevent cognitive deterioration in patients with AD. While we still face numerous challenges, AD researchers have made great progress in understanding disease mechanisms. As we have seen in the treatment of heart disease, even modest preventative treatments can have hugely significant clinical outcomes and drastically reduce disease prevalence on a population scale. Therefore, there is hope that the development of prophylactic treatments, combined with improved early detection methods, will provide dramatic relief for millions of aging individuals threatened by the specter of Alzheimer's disease.

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one with AD. With a continuously aging population, the number of people with AD is projected to increase by more than 50% by 2030, resulting in a tremendous drain to families, caregivers, and health care systems.[1] The development of treatments that delay disease progression by even a few years could drastically reduce disease prevalence.[2] Since AD is a late-life disease, slowing the disease progression may be sufficient to keep patients from the debilitating stages of AD before they succumb to other causes.

For most individuals with AD, symptoms emerge slowly, beginning with minor memory problems. A diagnosis of mild cognitive impairment (MCI) is made when an individual exhibits cognitive problems that are more severe than the normal cognitive changes associated with aging. MCI is often considered a prodomal phase of AD, and almost 50% of MCI patients convert to AD within 5 years.[3-5] It is currently unclear what pathological changes in the brain underlie the cognitive changes seen in MCI; however, it is clear that therapeutic intervention at this stage, or ideally even earlier, will have the best hope of arresting disease progression and preventing further cognitive decline.

In order to develop therapies that target the earliest stages of AD, we need a greater understanding of the pathological changes underlying initiation of the disease. Our current understanding of the disease comes from the analysis of post-mortem brain tissue, providing an invaluable window into the pathological state at the end stage of the disease. Through these studies, scientists have identified the major hallmarks of late-stage Alzheimer's disease, including amyloid plaques, neurofibrillary tangles, neuronal cell loss, and gliosis.[6] We now know that amyloid plaques are composed of aggregated amyloid-β (Aβ) peptides, largely Aβ42 peptides, that are cleaved from a precursor protein, amyloid precursor protein (APP), through sequential proteolytic cleavage reactions.[7] A-β peptides accumulate in the extracellular space and cause damage to surrounding cells, resulting in inflammation and gliosis. Neurofibrillary tangles reside within the cells and are composed of hyperphosphorylated tau proteins.[8] The tau protein is a microtubule-associated protein that is predominately found in axons of the central and peripheral nervous system. Upon hyperphosphorylation, tau loses its affinity for microtubules and aggregates into filaments resulting in cell death.[9] Even though we have made great progress in understanding the components that makeup the pathological lesions seen in Alzheimer's disease, to this day we do not fully understand the initiating mechanisms that trigger disease onset and drive its progression.

While many valuable studies have been performed in in vitro and in vivo models of AD, our ability to monitor disease progression in real-time or analyze pathological changes at early stages of the disease in humans is quite limited. Efforts to understand and track the early changes associated with AD and MCI will greatly increase our understanding of disease-causing mechanisms and lead to the identification of novel targets for pharmaceutical intervention. Developing methods for early detection and diagnosis will also allow scientists to more accurately measure responses to novel therapeutics in clinical trials. These efforts can reduce the cost and time of clinical trials, allowing the quicker identification of drugs that efficaciously slow or halt disease progression.

Developing surrogate markers for AD and MCI

Currently, AD research is greatly limited by a lack of validated surrogate markers and the fact that a true diagnosis of the disease can only be made post-mortem. Research trials are hamstrung by their reliance on cognitive testing and pathological end-point analysis to assess treatment efficacy. Clinically meaningful surrogate markers are sorely needed for the identification of at-risk or diseased individuals, and are essential tools in pharmaceutical development and clinical practice. In the case of heart disease, for example, cholesterol has long served as a surrogate for heart-attack risk. Individuals with high cholesterol are placed on prophylactic therapy, often statins, to reduce their cholesterol. This type of therapy has been demonstrated to reduce cardiovascular events and increase lifespan in patients followed in clinical trials.[10,11]

For Alzheimer's disease, many potential biomarkers are under investigation for their potential utility as surrogates for disease progression. Cerebrospinal fluid (CSF) Aβ42 levels are decreased with amyloid plaque formation and may be a useful surrogate for amyloid pathology in the brain, although individual variability is still high.[12] Variability can be reduced and sensitivity increased by combining CSF Aβ42 with CSF phospho-tau measurements.[13] While Aβ42 levels are lower in the CSF of patients with Alzheimer's disease, phosho-tau levels are increased and are thought to reflect an increase in

neuronal cell death. This combined analysis was demonstrated to be highly predictive of MCI to AD conversion. In addition, studies in human patients where Aβ is repeatedly measured in CSF overtime within an individual have provided valuable information about Aβ fluctuations and may serve as an experimental tool to measure immediate response to experimental treatments.[14,15]

The clinical utility of these approaches is limited, however, by the invasiveness required to sample CSF. Therefore, minimally invasive brain imaging technologies may prove to be a useful alternative to monitor changes within an individual over time. Like biochemical measurements, neuroimaging has the potential to be used for early diagnosis, to monitor disease progression, or to measure effectiveness of experimental treatments. While many neuroimaging methods are under development for use in AD, there are presently no validated methods available in a clinical setting. Longitudinal volumetric magnetic resonance brain imaging can be useful in predicting MCI to AD conversion by providing estimates of progressive whole brain atrophy over time and/or determining the rate of ventricular enlargement.[16] Alternatively, measurements of regional distribution of atrophy may be a more sensitive method to track early changes in the disease.[17,18] Fludeoxyglucose (FDG)-positron emission tomography (PET) scans, where blood flow and glucose utilization over different brain regions can be measured, may also provide useful information as to disease progression over time.[19] Further, methods are improving to image amyloid plaques in living patients using PET ligands that bind Aβ.[20] These methods have been used to measure significant changes in amyloid deposition in patients with MCI.[21] The most promising of these neuroimaging techniques and biochemical readouts could in time be used together as surrogate markers to provide an accurate assessment of disease state over time within an individual or across a population.

There is a risk, however, of focusing too heavily on surrogate markers. In studies of rosiglitizone for diabetes, negative outcomes on disease appeared despite expected positive effects on the surrogate.[22] Cholesterol has long been used as a surrogate for heart disease; however, in clinical trials of high-density lipoprotein-modifying drugs (such as torceptrabib) for prevention of heart disease, a positive effect on the surrogate was seen even though clinical outcomes were worsened.[23] As in AD, these other chronic degenerative diseases have complex, multifactorial causes that are not necessarily reflected in the surrogate marker. Therefore, while using surrogate markers can be quite a meaningful method to monitor aspects of disease progression, it is crucial to keep in mind the limitations of this approach.

Understanding genetic risk factors for AD is another method to facilitate early detection of high-risk individuals, while also providing insight into disease mechanisms. The discovery of genes underlying risk for AD has provided us with many of our most promising drug targets. Individuals with the apolipoprotein E4 allele (ApoE4), for example, have a significantly greater risk of developing Alzheimer's disease, and often exhibit an earlier age of onset and a more aggressive form of the disease.[24] While ApoE4 is a known risk factor for AD, we still do not fully understand its mechanism of function in AD pathogenesis. Identifying genetic subtypes of AD could allow for the development of more individualized therapies, as well as aid in clinical trial design for novel drug therapies. In fact, in the Phase II trial for Bapineuzumab, a monoclonal antibody to β-amyloid developed by Wyeth and Elan, ApoE4 carriers were separated from noncarriers in the analysis. Only noncarriers demonstrated a significant benefit from the treatment, which would not have been detected had the population been analyzed as a whole.[25]

It is our hope that in the near future early detection techniques, such as measurements of Aβ load, neuroimaging analysis, and/or genetic testing will function much like cholesterol testing does for heart disease. If the tests show individuals to be at high risk, doctors may suggest a regimen of preventative treatments, along with lifestyle changes, designed to decrease the likelihood of disease progression. Therapeutic strategies for chronic prophylactic dosing, analogous to lipid-lowering treatments for heart disease, are needed to prevent cognitive decline and the development of dementia in patients at the beginning stages of Alzheimer's disease. This strategy has been relatively effective in the management of cardiovascular disease and may prove a successful strategy for preventing the development of dementia from Alzheimer's disease as well.

Approaches for interventional treatment

The only drugs currently on the market for AD provide primarily symptomatic relief. While the identification of surrogate biomarkers and novel imaging technologies provides the framework to identify high-risk individuals or individuals with early stage disease pathology, paral-

lel approaches are also needed to develop disease modifying drugs to effectively treat these individuals. In terms of AD pathogenesis, it is thought that Aβ aggregation into amyloid plaques is the causative agent that initiates the disease cascade, leading to neurofibrillary tangles and neuronal cell loss. This hypothesis has become known as the amyloid cascade hypothesis.[7] This hypothesis was strengthened by human genetic studies identifying mutations in the APP gene in inherited familial early onset AD.[26-28] These mutations stimulate APP processing, resulting in increased Aβ42 production. By this hypothesis, therapies capable of reducing Aβ42 levels or preventing its aggregation may block the disease cascade, making this approach extremely attractive as an early-stage disease intervention. In addition to Aβ-targeted therapies, other therapeutic strategies that would protect neurons from injury are discussed below. This discussion is by no means a comprehensive list of ongoing treatment research programs, but is meant to highlight some of the key areas that are potentially applicable to preventative treatment development.

There are many research programs dedicated to disrupting Aβ pathology, including directly inhibiting Aβ aggregation, enhancing Aβ clearance, or blocking its production. Inhibiting Aβ aggregation has proven quite challenging; however, many groups are continuing to work on developing small molecule inhibitors of this reaction.[29] Investigators are targeting to a wide range of mechanisms to promote the clearance of Aβ from the brain. Included in this are research programs aimed at activating the efflux pumps at the blood-brain barrier, upregulating Aβ degradation enzymes, and immunotherapy methods that target disease-specific Aβ species, among other strategies.[30-32] There are also numerous efforts focused on reducing Aβ production by targeting the enzymes that generate Aβ from its precursor, APP. These strategies include developing γ-secretase inhibitors or modulators, β-secretase (BACE) inhibitors, and α-secretase stimulators, as well as targeting pathways that affect APP biogenesis or metabolism.[33-36]

In addition to antiamyloid therapies, many other strategies are under development that would be relevant to the early-stage disease processes, not only for AD, but also for other neurodegenerative diseases. These approaches include anti-inflammatory and antioxidant approaches, as well as general neuroprotective strategies or methods to enhance the pathways involved in learning and memory. For example, a small peptide that is derived from a neuroprotective protein is being developed by Allon Therapeutics as a drug candidate and has been shown to protect neurons from Aβ-induced insults.[37] In addition, investigators are working to develop peptidomimetic compounds that activate neurotrophin receptors and protect neurons from cell death.[38] Other strategies that increase brain-derived neurotrophic receptor (BDNF) receptor signaling have progressed into nonhuman primates and have shown promising results, including restoring cognitive function and protecting neurons from death.[39] Finally, the mitochondria has gained attention recently as a compelling target for preventing neuronal degeneration. Dimebon, a drug originally developed as an antihistamine, showed promising clinical benefit in a recent AD clinical trial in Russia and is thought to function through stabilization of the mitochondria.[40,41]

While the focus of this review is on preventing dementia at its earliest stages, in MCI, or even earlier, later-stage disease interventional therapies will also be necessary. As in heart disease, preventative therapies are not 100% effective, and strategies need to be developed to protect these patients from further disease progression. The amount and distribution of tangle pathology has been correlated with neuronal cell death and clinical disease severity,[42] therefore preventing tau aggregation and tangle formation may prevent cell death from occurring. Currently, investigators are working on a number of therapeutic strategies to disrupt tangle formation in AD, including directly disrupting tau aggregation and/or targeting numerous pathways that regulate tau phosphorylation.[43,44] In addition, many investigators are working on helping patients regain lost functionality by replacing injured neurons, either through the induction of pathways that stimulate neurogenesis or through exogenous stem cell therapies.[45,46]

Alzheimer's disease in perspective

These various treatment approaches should not be considered in isolation. The future of Alzheimer's disease therapy might be viewed as a combination approach or multitargeted therapeutic "cocktail." In the case of cardiovascular disease, even though we have good surrogate markers like cholesterol, we still do not fully understand the underlying disease mechanisms, nor do we have a cure for the disease. We do, however, have relative effective preventative treatments, such as statins, that reduce disease prevalence. Therefore, it is possible to achieve a

highly significant clinical result for AD through the development of validated surrogate markers combined with proven preventive therapy, even if the true cause of AD remains elusive and a cure is not yet found. Ultimately, AD could become a manageable chronic illness. Our hope that the combination of early disease diagnosis and intervention with novel disease-modifying therapeutics will allow individuals to age free from the scourge of dementia, able to retain their valuable memories and self-identity. ❑

Nuevas estrategias para la prevención de la demencia en la Enfermedad de Alzheimer

Ya que la población mundial sigue envejeciendo, la Enfermedad de Alzheimer presenta una crisis inminente para la salud pública, que si se descuida, amenazará con sobrecargar los sistemas de atención de salud en el mundo desarrollado. Para abordar significativamente el síntoma más catastrófico y devastador de la Enfermedad de Alzheimer (EA), la demencia, debemos ser capaces de detectar la enfermedad antes de que aparezcan los síntomas clínicos, y ofrecer a los pacientes tratamientos preventivos que bloqueen o retrasen significativamente la progresión de la enfermedad. Esta revisión resume varios de los métodos más prometedores de detección precoz para la EA y el deterioro cognitivo leve (DCL) que podrían ser utilizados para identificar a los pacientes con alto riesgo de desarrollar la enfermedad y para monitorear la progresión de ésta y la respuesta a tratamientos en investigación. Además, se destacan algunos de los programas de tratamiento en investigación que podrían llegar a constituir terapias modificadoras de la enfermedad, que retrasen significativamente el desarrollo de la demencia. Estos potenciales tratamientos están dirigidos a muy diversas vías, y un día podrán ser administrados en combinación para aumentar la eficacia y prevenir el deterioro cognitivo en pacientes con EA. Aunque todavía se enfrentan numerosos desafíos, los investigadores de la EA han realizado grandes progresos para la comprensión de los mecanismos de la enfermedad. Como se ha observado en el tratamiento de la enfermedad cardíaca, incluso modestos tratamientos preventivos pueden tener un gran impacto en la evolución clínica y reducir drásticamente la prevalencia de la enfermedad en un subgrupo de la población. Por lo tanto, hay esperanzas en que el desarrollo de tratamientos profilácticos combinado con una mejoría en los métodos de detección precoz, proveerá un dramático alivio para millones de individuos que están envejeciendo amenazados por el espectro de la Enfermedad de Alzheimer.

Nouvelles stratégies pour la prévention de la démence de la maladie d'Alzheimer

Alors que la population mondiale vieillit, la maladie d'Alzheimer présente un problème imminent de santé publique qui, non maîtrisé, menace de submerger les systèmes de santé des pays développés. Afin de lutter significativement contre le symptôme le plus catastrophique et le plus terrible de la maladie d'Alzheimer (MA), la démence, nous devons être capables de dépister la maladie avant l'apparition des symptômes cliniques et d'offrir aux patients des traitements préventifs pour arrêter ou ralentir significativement la progression de la maladie. Cet article résume les différentes méthodes les plus prometteuses de détection précoce de la MA et du déficit cognitif léger (DCL) qui pourraient permettre d'identifier les patients à haut risque de développer la maladie et qui permettraient de surveiller la progression du trouble et la réponse aux traitements étudiés. Il met de plus en lumière certains des programmes de recherche thérapeutique comme des traitements modifiant la maladie qui ralentissent significativement l'évolution de la démence. Ces traitements potentiels ciblent beaucoup de voies différentes et pourraient un jour être prescrits ensemble pour augmenter l'efficacité et prévenir la détérioration cognitive chez les patients atteints de MA. De nombreux défis nous attendent encore mais les chercheurs sur la MA ont beaucoup progressé dans la compréhension des mécanismes de la maladie. Comme nous l'avons vu avec le traitement de la maladie cardiaque, des traitements préventifs même modestes peuvent avoir de grands effets cliniques et réduire de façon importante la prévalence de la maladie à l'échelle d'une population. Il y a donc un espoir que des traitements préventifs associés aux méthodes améliorées de détection précoce, apportent à des millions de sujets âgés menacés par le spectre de la MA un soulagement remarquable.

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