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New Perspective in Alzheimer's Disease: Theranostic Strategy

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ABSTRACT

Alzheimer's Disease (AD) is the most common dementia among older adults; it causes neuronal loss and cognitive impairment. The number of people with Alzheimer's disease is expected to rise to about 152 million people by 2050 with a significant impact on the economy and society. In the last decade scientific community is apply his efforts towards a new approach for AD challenge, the theranostic strategy: a single agent useful for diagnosis and therapeutic treatment. In this mini review a screenshot of this new possibility is presented.

Keywords: Alzheimer's Disease; Theranostic; Nanoparticles

Introduction

The term "theranostic" defines a single agent with both therapeutic and diagnostic properties [1]. Unlike the traditional clinical approach where two different compounds are deputies to achieve the two objectives, theranostic agents combine these features in a single package. The great potentials of theranostic strategy allow overcoming of possible discrepancies in the biodistribution and selectivity profiles that instead exist when separate diagnostic and therapeutic agents are used [2,3]. The final objective in the context of theranostics is, therefore, to develop the ability to monitor at the same time the affected tissue, the kinetics of release and effectiveness of therapeutic treatment in the way to calibrate in a very precise way the type and dosage of the therapeutic treatment to be used for a specific individualize therapy [4]. Theranostic strategy has been successfully exploited in oncology, [5] and is now emerging as a possibility for Alzheimer's disease [6].

Alzheimer's Disease (AD) is the most common neurodegenerative disease and causes dementia in the elderly and represents a serious social and economic problem for society [7]. According to World Alzheimer Report 2018, [8] the number of people with Alzheimer's disease is expected to rise to about 152 million people by 2050 due to the increase in the population aged 65 and over. Many studies demonstrated that AD is mainly caused by the accumulation of misfolded proteins that triggers brain tissue degeneration [9].

One of the main pathological characteristics of AD in the brain of patients is the extracellular deposition of beta-Amyloid plaques (Aβ), composed mainly of Aβ1-40 and Aβ1-42 [10]. Such aggregates promote formation of intracellular neurofibrillary tangles and other neurotoxic effects until neuronal death and onset of dementia. The deposition of Aβ aggregates has a critical role in AD pathogenesis and therefore the cerebral Aβ plaques represent a promising and predictive biomarker for the early diagnosis of AD [11]. Moreover agents able to inhibit the aggregation of Aβ monomers represent useful therapeutic agents for the treatment of AD [12]. A molecule that can perform in vivo imaging of Aβ / plaque species and inhibition of Aβ aggregation would represent a useful and innovative agent in the development of theranostic strategy [13].

Discussion

In the last decade several probes for specific labeling, detection, imaging of Aβ plaques both in vitro and in vivo have been developed [14] Mostly, these probes are exploitable in imaging techniques such as Positron Emission Tomography (PET) [15,16] Single-Photon Emission-Computed Tomography (SPECT) [17] and Magnetic Resonance Imaging (MRI) [18]. Moreover, these techniques are expensive, lack specificity and radioactive compounds and specialized facilities are required. In contrast, in the last few years, optical imaging techniques has emerged an attractive tool

in the study of neurodegenerative diseases due to low cost, wide availability, high resolution and specificity [19]. In particular, Near Infra-Red (NIR) fluorescent probes (600-900 nm) have been designed initially for Aβ imaging [20,21] and later as theranostics, which could simultaneously perform Aβ aggregation inhibition [22]. Within this framework, extended π-conjugated systems was found as requirement to obtain compounds in a suitable spectral range of the absorption and emission bands useful for Aβ imaging by NIRF and for Aβ binding and interfering [23].

In 2016, starting from carbazole-based cyanine derivative as fluorophores able to bind Aβ, DBA-SLOH has been developed [24]. This compound displayed high affinity and selectivity towards Aβ species and, due to the incorporation of lipophilic alkyl chains with moderate length into the charged skeleton; it possessed an excellent BBB permeability overcoming the limited penetration of several probes through the BBB [25]. Hence it has been considered as a new starting point in the development of more effective theranostic due to its biocompatibility for NIR imaging of Aβ species in vivo and inhibition of Aβ aggregation.

Yang, et al. also contributed in the design of NIR probes and they developed a fluorescent Cu^{2+}chelator namely TBT with the aim of reducing metal-induced Aβ aggregation and neurotoxicity by regulation of metal ions [26]. TBT is composed of a metal-chelating moiety linked to an Aβ recognizing portion. It displayed high binding affinity towards Aβ aggregates and ability in attenuation of this aggregates through Cu^{2+} ions capture, that it is possible to visualize by fluorescence imaging of the chelator. Moreover, TBT displayed high ability to enter BBB of mice in vivo. Although its short fluorescence wavelength, which could be a limitation in *in vivo* imaging, it could be a promising theranostic tool, after appropriate structural changes for longer fluorescence emissions or NIR emissions.

Recently, Dao, et al. developed phenothiazine-based derivatives and among them compound 4a1 showed high affinity towards Aβ aggregates (Kd = 7.5 nM), in addition fluorescence staining of Aβ plaques in brain slices in vitro demonstrated a good targeting ability [27]. In addition, this set of phenothiazine derivatives was found able to inhibit Aβ aggregation showing a promising potential as theranostic agents for the diagnosis and therapy of AD. The recent development of nanotechnology has allowed the development of new agents in which diagnosis and treatment are combined in a single solution [28-31]. The interest in nanotechnology-based strategies has grown thanks to the good prospect of overcoming the limits inherent BBB crossing.

Nanoparticles-based therapies were studied with the aim of subsequently developing theranostics; [32-34] have the advantage of high versatility, allowing ultrasensitive imaging by attaching imaging agent, ability to absorb and transport various drugs, fluorescence properties (due to quantum dots), however they still have some limitations in ability to cross BBB and related to accumulation in other district body [35].

It has been demonstrated that lectin-modified PEG-poly(lactic-co-glycolic acid) nanoparticles (PEG-PLGA NPs) have an increased BBB crossing ability [36]. Based on these findings dual functional PEG-PLGA NPs have been recently developed [37]. In particular, TGN and QSH were used at the NPs surface: TGN specifically targets ligands at the BBB, and QSH for its good affinity to Aβ42. These NPs were found able to prevent A¤¤¤¤¤¤ and results obtained by ThT-binding assay, cellular uptake assay, in vivo imaging, and SPR showed that they could be considered a valuable targeting system for AD diagnosis and therapy.

Although nanotechnology-based approaches seems promising in theranostic development, they have not yet been successful in clinical translation and further studies will be needed [38,39]. Nucleic acid-based technologies have gained interest in recent years as novel theranostic strategies for several pathologies an also for AD. These approaches are based on the use of synthetic oligonucleotides, which bind to RNA and alter the expression of the targeted RNA and protein [40]. Recently, an aptamer complexed with ruthenium able to selectively bind and inhibit Aβ oligomers formation have been designed. The luminescence intensity of Ru-complex is increased due to the strong interaction of aptamer with Aβ monomer or oligomers [41].

Also Farrar, et al. developed a fluorescently tagged anti-Aβ RNA aptamer, β55, which binds amyloid plaques in ex vivo AD brain tissue and in vivo transgenic mice [42].

Conclusion and Perspectives

In conclusion, even several attempts have been made in the search for a single agent able to diagnose and treat AD in a therapeutic way; a theranostic agent for the clinical study is not yet available. And while theranostics approach is gained interest as the new frontier in the challenge of Alzheimer's disease, hopes come from anti-Aβ- immunotherapies. Aducanumab (phase III trials) is a potent monoclonal antibodies that have shown encouraging signals in AD therapy: it binds selectively and with high affinity Aβ oligomers and fibrils and, in the meantime, the reduction of plaques has been correlated to slow decline in clinical measures in patients with acceptable safety and tolerability. However, further studies are needed to better clarify whether this drug can be used in MCI or AD patients.

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