SHORT COMMUNICATION

Targeting amyloid beta in Alzheimer`s disease-time for a paradigm shift

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DESCRIPTION

Since its discovery in 1984, Amyloid beta (Aβ), the main component of plaques in Alzheimer`s Disease (AD) brains, has been the central target molecule for the design of disease modifying therapies. After more than 20 years of mostly clinical failures in Aβ related therapies, it is time to analyze the reasons and to challenge basic scientific assumptions.

While the validity of Aβ as a target by the well described role of PSEN and Amyloid beta mutations in Familiar AD is undisputed, two fundamental misconceptions about the role of Aβ led to a series of more than 20 insufficient clinical candidate's tor AD treatment during the last two decades:

1. Amyloid Beta, generated by subsequent Gamma- and Beta secretase cleavage, per se is an unphysiological, pathogenic product of APP bioprocessing.

Following this statement, Aβ was regarded as an evolutionary relic compared to the benign non-amylogenic alpha secretase pathway that avoids any formation of aggregation prone Amyloid beta monomer. This dogma of a general isoform independent Amyloid Beta pathology is still widely accepted, not admitting a highly regulated physiological Amyloid Beta turnover in synaptic regulation of healthy human neurons. Clinical failures of a series of beta and gamma secretase inhibitors as well as pan Amyloid beta immunotherapies in the last two decades have been explained by singular deficiencies of individual compounds or trial design rather than challenging the underlying imprecise concept.

2. Fibril type dense plaques are the culprit of AD pathology and thus are the main clinical target for therapy.

We already knew for a long time about poor correlation of distribution of dense plaques in Alzheimer Disease brains and the lack of clinical efficacy of merely dissolving plaques in AD patients in the early AN1792 trial. Recently a mechanistic study in APP/PS overexpressing mice demonstrated a scavenger function for fibril type deposits that questions the rationale of dissolution of plaques in brain parenchyma [1] as a treatment concept in AD.

A number of mechanistic studies have dealt with essential and benign effects of physiological Aβ monomer. If we build on a physiological role for Amyloid beta monomer as a key molecule in synaptic transmission, protection and preservation of the functional well regulated turnover bioprocessing will become the main target for any meaningful Amyloid beta related therapy.

There is substantial evidence from more than 20 years of science that the disturbance of amyloid beta homeostasis is due to appearance of early misfolded Amyloid beta oligomers [2] as soon as folding control is becoming incorrect (Figure 1).

The Beta Amyloid Dysfunction (BAD) Hypothesis [3] distinguishes from the classical Amyloid Beta Cascade Hypothesis by major characteristics (Table 1).

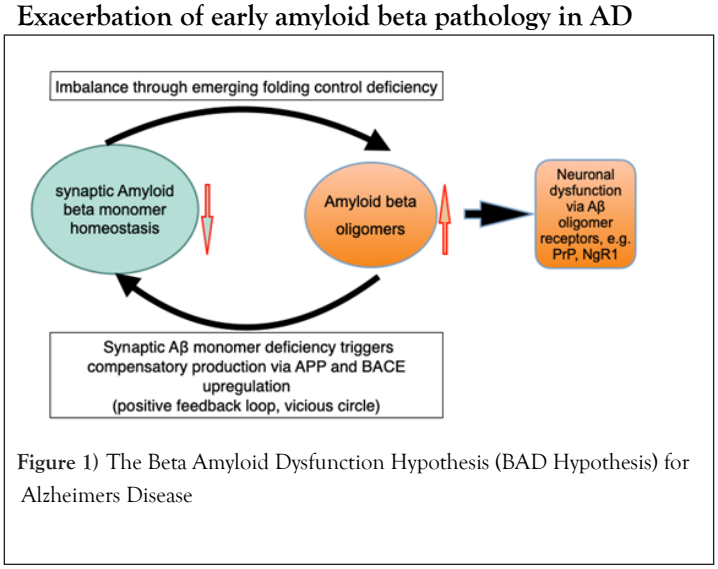

Figure 1) The Beta Amyloid Dysfunction Hypothesis (BAD Hypothesis) for Alzheimers Disease

	Beta amyloid cascade hypothesis	Beta amyloid dysfunction hypothesis
Physiological role for monomer	-	.
Distinction of isoform functionality (Monomer, oligomers, fibrils)	-	.
Dense plaque pathology	on target	not primary target
Therapeutic concept	Beta and Gamma Secretase inhibitors Pan Amyloid beta immunotherapies	Highly oligomer selective therapies; Gamma secretase modulators; Normalization of BACE as target engagement biomarker

TABLE 1:

Basic features for cascade versus dysfunction hypothesis

The BAD hypothesis is compliant to explain clinical failures of most amyloid beta drugs in terms of lack of efficacy and behavioral side effects.

The new concept guides us to design potent and highly oligomer isoform selective and specific therapies, that will enable sufficient CNS drug levels to neutralize early steadily formed misfolded species at synaptic sites of MCI or sporadic AD patients brains. Strict monomer selectivity, e.g for antibodies, is essential also from a pharmacokinetic perspective to enable effective immunotherapies, since wasting drug for neutralizing excess monomeric Aβ will need unrealistic high doses, as exemplified by poor efficacy for monomer and oligomer binding crenezumab in clinical studies [4,5].

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CONCLUSION

Albeit with too many negative clinical results for pan Aβ isoform targeting compounds, we are still far away from taking final conclusions for Amyloid beta as a disease target. The Amyloid hypothesis so far was not precisely specified for the physiological versus pathophysiological part of this molecule. Accordingly all current drug candidates, which inhibit either production or beneficial effects of Aβ monomer and neurotoxic oligomers at the same time, could not be successful so far.

So the future therapeutic focus needs to be dedicated to highly Amyloid beta oligomer specific compounds, antibodies and designed vaccines. Those have already been described preclinically.

In the past the main practical argument against developing specific oligomer directed antibodies was the unavailability of robust mechanistic biomarker to take these antibodies to a decision point in early clinical studies with limited number of patients, time and costs. With the recent breakthrough biomarker developments for some p-Tau species and BACE normalization, we should now have reliable and simple readouts to test the on-target efficacy of moving these early aberrant Tau species induced by Amyloid beta oligomers in a relevant clinical setting.

CONFLICT OF INTERESTS

The author declares that he has no conflict of interest.

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