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Title: **Beta-Synuclein: A Dynamic Biomarker and Modulator in Neurodegenerative Dementia**

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Summary:

Beta-synuclein, more than a biomarker, may help trace, time, and shape dementia's evolving course.

Recent advances in neurodegenerative biomarker research shed light on **beta-synuclein** as a promising indicator of synaptic dysfunction in Alzheimer's disease (AD) and related dementias. Two noteworthy studies—**Barba et al.** on p XX and **Kong & Joon** on p XX — independently demonstrate that serum beta-synuclein levels are significantly associated with clinical staging and synaptic degeneration. **Barba et al.** showed that beta-synuclein levels progressively increase across the AD continuum, from preclinical to MCI and dementia, supporting its role as a marker of disease severity. This cross-sectional pattern provides a foundation for understanding beta-synuclein's potential as a **staging biomarker**.

Kong & Joon extended this perspective by identifying beta-synuclein as a predictive marker for longitudinal cognitive decline and dementia risk, thereby establishing a temporal relationship between beta-synuclein levels and AD progression. Interestingly, their analysis revealed a non-linear association between beta-synuclein tertiles and dementia risk in amyloid- β -positive individuals. While the overall difference in risk between the high and low tertiles was not statistically significant, the middle tertile showed a significantly increased risk compared to the low tertile. This trend suggests that beta-synuclein may reflect a transitional phase of synaptic vulnerability, rather than a simple linear progression. It also aligns with non-linear trajectories observed in other biomarkers such as tau and GFAP (Park et al., 2020), reinforcing the need for stage-aware interpretation of beta-synuclein levels.

In Lewy body dementia (LBD), beta-synuclein levels are also elevated, but notably independent of amyloid or tau pathology. **Barba et al.** found that beta-synuclein was increased in LBD patients even in the absence of classical AD biomarkers, pointing to a distinct mechanism of synaptic injury. This aligns with findings from Li et al. (2024) which revealed that beta-synuclein regulates the phase behavior of α -synuclein, promoting liquid-liquid phase separation while delaying its conversion into toxic amyloid aggregates. In this context, beta-synuclein acts as a modulator of disease progression, potentially buffering against α -synuclein toxicity in LBD.

While mechanistic studies suggest beta-synuclein may modulate α -synuclein aggregation, the clinical relevance of this remains to be fully established. More compelling, however, are the findings from

Barba et al. and **Kong & Joon**, which underscore beta-synuclein's value as a dynamic biomarker of synaptic integrity and cognitive decline. In LBD, elevated beta-synuclein levels occur independently of amyloid and tau pathology, pointing to a distinct mechanism of synaptic injury. Notably, **Barba et al.** observed increased beta-synuclein even in the absence of classical AD biomarkers, reinforcing its role in non-amyloidogenic neurodegeneration. These findings suggest that beta-synuclein may reflect a broader spectrum of synaptic vulnerability across dementia types, with potential implications for staging and prognosis.

In conclusion, beta-synuclein is more than a static biomarker—it is a dynamic indicator of disease progression and cognitive risk. **Barba et al.** and **Kong & Joon** research studies highlight its relevance not only in cross-sectional staging but also in predicting longitudinal decline. Its evolving profile across disease types and stages positions beta-synuclein as a key molecule in the future of dementia diagnostics, with potential utility in guiding stage-specific interventions and personalized treatment strategies.

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