The potential of pathological protein fragmentation in blood-based biomarker development for dementia - with emphasis on Alzheimer's disease

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The diagnosis of dementia is challenging and early stages are rarely detected limiting the possibilities for early intervention. Another challenge is the overlap in the clinical features across the different dementia types leading to difficulties in the differential diagnosis. Identifying biomarkers that can detect the pre-dementia stage and allow differential diagnosis could provide an opportunity for timely and optimal intervention strategies. Also, such biomarkers could help in selection and inclusion of the right patients in clinical trials of both Alzheimer’s disease and other dementia treatment candidates. The cerebrospinal fluid (CSF) has been the most investigated source of biomarkers and several candidate proteins have been identified. However, looking solely at protein levels is too simplistic to provide enough detailed information to differentiate between dementias, as there is a significant crossover between the proteins involved in the different types of dementia. Additionally, CSF sampling makes these biomarkers challenging for presymptomatic identification. We need to focus on disease-specific protein fragmentation to find a fragment pattern unique for each separate dementia type - a form of protein fragmentology. Targeting protein fragments generated by disease-specific combinations of proteins and proteases opposed to detecting the intact protein could reduce the overlap between diagnostic groups as the extent of processing as well as which proteins and proteases constitute the major hallmark of each dementia type differ. In addition, the fragments could be detectable in blood as they may be able to cross the blood-brain barrier due to their smaller size. In this review, the potential of the fragment-based biomarker discovery for dementia diagnosis and prognosis is discussed, especially highlighting how the knowledge from CSF protein biomarkers can be used to guide blood-based biomarker development.