ICE-Cleaved alpha-Synuclein as a Biomarker for Neurodegenerative Diseases

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Technology description

Alpha-synuclein (αSyn) is primarily found in brain tissues making up to 1% of all cytosolic proteins in neurons and is predominantly expressed in the neocortex, hippocampus, substantia nigra, thalamus and cerebellum. Fibrillization, aggregation and overexpression of α-synuclein is believed to play a major role in the degeneration of dopaminergic neurons in synucleinopathy diseases such as Parkinson’ s disease, dementia and multiple system atrophy. Lewy bodies, which are the abnormal intracellular aggregates found in the dying neurons of Parkinson’ s disease patients, consist mainly of ubiquitin mixed with misfolded full-length αSyn and a truncated form containing only its N-terminal 120 amino acids generated by protease cleavage. Our opportunity is a diagnostic method to identify target patient populations having synucleinopathy diseases who are likely to respond favorably to treatment with caspase-1 inhibitors.

Based on the inventors’ novel finding that the 120 and 20 amino acid cleavage fragments of αSyn are generatedin vivoby the protease caspase-1 (also referred to as interleukin-1 beta converting enzyme or ICE), our opportunity available for licensing is a diagnostic method to identify target patient populations having synucleinopathy diseases who are likely to respond favorably to treatment with caspase-1 inhibitor drugs. Caspase-1 is a member of the cysteine protease family of enzymes and located in inflammasomes where it becomes activated in response to environmental toxins, oxidative stress and infections. Our method consists of analyzing a patient’ s tissue sample (e.g. blood) for the presence of the C-terminal 20 amino acid cleavage fragment of αSyn that typically is undetectable in normal subjects. Those patients found to have elevated levels of this cleavage fragment would be ideal candidates for treatment therapies using caspase-1 inhibitors.

Caspase-1 is the only known protease capable of cleaving αSynin vivointo its two protein fragments associated with synucleinopathies. The inventors identified caspase-1 as the responsible isozyme using RNAi knockdown experiments in yeast and human neuronal cell culture models. Caspase-1 proteolysis of αSyn, fragment aggregation and motor-function impairments were preventedin vivousing the ICE inhibitors VX765 (Vertex Pharmaceuticals) or NCGC00185682 (NIH) in mouse models of synucleinopathy diseases.

Summary

· Diagnostic method to determine which patients having a synucleinopathy disease would likely respond to treatments using caspase-1 (ICE) inhibitor drugs
· Methodology is based on detecting the presence of a 20 amino acid C-terminal proteolysis αSyn fragment in patient samples (which is normally absent in samples from unaffected subjects)
· Target patient populations for this method are persons with Parkinson’ s or Lewy body diseases

Publication

Wanget al.(2016) Caspase-1 causes truncation and aggregation of the Parkinson’ s disease-associated protein –synuclein.Proc Natl Acad Sci113(34)9587-92.
Bassilet al.(2016) Reducing C-terminal truncation mitigates synucleinopathy and neurodegeneration in a transgenic model of multiple system atrophy.Proc Natl Acad Sci113(34):9593-8.

Advantages

· Targets treatment based on disease causation from αSyn aggregation and neuronal cell toxicity

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