Seminar

"Cell Autonomous and Non-cell Autonomous Neurodegeneration in Parkinson's Disease"

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- **Date: 2:00PM/May. 21(Tues.)/2019**
- **Place: Conference room(476), Postech Biotech Center**
- **Inquiry: Prof. Jiwon Jang (279-2321)**
- **Abstract:**

Parkinson's disease (PD) is the second most common neurodegenerative disorder. Intracellular protein aggregates composed primarily of α-synuclein lead to neuronal dysfunction throughout the nervous system, ultimately accumulating in structures designated, Lewy bodies and neurites. During the pathogenesis of PD, monomeric α-synuclein assembles into higher ordered structures that ultimately become pathologic and drive neuronal cell death in a cell autonomous fashion. Pathologic α-synuclein can spread from cell to cell contributing to the progressive pathogenesis of PD, which causes microglia- and astrocyte-mediated neuroinflammation in a non-cell autonomous fashion. However, what drives the abnormal assembly of pathologic α-synuclein and death in neurons as well as the neuroinflammation in non-neuronal cells that are activated by pathologic α-synuclein are not known.

We first identified poly (ADP-ribose) (PAR) polymerase-1 (PARP-1) activation and the generation of PAR as a key mediator of pathologic α-synuclein toxicity and transmission in neurons. Activation of parthanatos is the primary driver of pathologic α-synuclein neurodegeneration. Inhibition of PARP and depletion of PARP-1 substantially reduces the pathology induced by the transmission of pathologic α-synuclein. In a feed-forward loop, PAR converted pathologic α-synuclein to a more toxic strain and accelerated neurotoxicity both in vitro and in vivo. Consistent with the notion that PARP-1 activation plays a role in PD pathogenesis, PAR levels were increased in the CSF and brains of PD patients. Thus, strategies aimed at inhibiting PARP-1 activation could hold promise as a disease modifying therapy to prevent the loss of dopamine neurons in PD and related α-synucleinopathies. Moreover, assessment of PAR levels in the CSF could serve as a theranostic biomarker for disease modifying therapies in these disorders.

Growing evidence suggest that neuroinflammation is another major patho-physiological process in PD. There is a new paradigm that activation of microglia by classical inflammatory mediators can convert astrocytes into a neurotoxic A1 phenotype in a variety of neurological diseases. We found that α-synuclein aggregates induce microglial activation and facilitate A1 astrocyte formation by secreting IL-1α, TNFα and C1q, thus killing dopaminergic neurons. Moreover, we developed a Glucagon-like peptide-1 receptor (GLP1R) agonist that protects against the loss of dopaminergic neurons induced by α-synuclein through the direct prevention of microglial-mediated conversion of astrocytes to an A1 neurotoxic phenotype. In light of its favorable properties, GLP1R agonist should be evaluated in the treatment of Parkinson's disease and related neurologic disorders characterized by microglial activation.

***This seminar will be given in English.**

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