Secretion, Autophagy and their role in Neurodegeneration

Reporting

Project Information

SAND

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Periodic Reporting for period 1 - SAND (Secretion, Autophagy and their role in Neurodegeneration)

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Summary of the context and overall objectives of the project

Neurodegenerative disorders (NDs) such as Huntington disease (HD), Parkinson's Disease (PD), and Alzheimer's disease (AD) represent a major health problem of the continuously aging society and are among the leading causes of mortality. Most NDs are characterized by the accumulation of cytotoxic protein aggregates (e.g. amyloid plaques and Lewy bodies) and neuronal death in specific regions of

the central nervous system. Such protein aggregates can form as a result of familial or sporadic genetic mutations in the aggregating proteins but are often a result of an imbalance between protein production, sorting, and turnover (commonly referred to as cellular proteostasis). The secretory and the autophagic pathways are two major regulators of cellular proteostasis and their dysfunction can therefore lead to NDs. The main research focus of SAND is to obtain a deeper understanding of these pathways and their role in NDs. The specific research objectives of SAND are therefore aimed at 1) elucidation of the fundamental mechanisms underlying the autophagy and secretory pathways and their crosstalk, 2) characterization of the role of these pathways NDs, and 3) identification of novel drug targets and diagnostic markers with the potential to target NDs. SAND will train a new generation of early-stage researchers (ESRs), who will obtain core scientific skills through work on various projects related to these research objectives, in addition to an extensive repertoire of transferrable skills needed for their future careers in academia or the industry.

Work performed from the beginning of the project to the end of the period covered by the report and main results achieved so far

The research activities of SAND are divided into three areas; 1) Fundamental, 2) Neuro, and 3) Drugs and Biomarkers, with close collaborations between research groups of the three areas to bridge fundamental discoveries with translational neuroscience approaches. The five ESRs of SAND Fundamental are all working on projects focused on the mechanisms linking secretory trafficking and autophagy to protein aggregate and stress granule formation and how alterations of this crosstalk relate to neurodegeneration. The seven ESRs working on projects within SAND Neuro are using cellular and animal (Drosophila, zebrafish, and mouse) models of amyotrophic lateral sclerosis (ALS), PD, and AD to investigate how alterations in protein secretion and their crosstalk with autophagy affect neurodegeneration. SAND Drugs and Biomarkers include three ESRs working on projects related to screening approaches aimed at identification of the machinery regulating the autophagy-secretion crosstalk and their possible relevance as therapeutic targets or biomarkers for NDs. All SAND ESRs have obtained training in core scientific skills, through training and supervision in their individual research projects, at annual meetings, via secondments to other labs, and by participation at workshops and conferences.

Progress beyond the state of the art and expected potential impact (including the socio-economic impact and the wider societal implications of the project so far)

The SAND ESRs have obtained results that go beyond the state of the art, as evident from their propject presentations at our two annual meetings (202 and 2021). These include identification of novel players involved in regulation of autophagy and secretion, mechanisms underlying protein aggregate formation, characterization of interaction partners and post-translational modification of aggregate-prone proteins, establishment of novel cell and animal models to study NDs and characterization of new chemical compounds that modulate autophagy and secretion. We expect that the results obtained within SAND will provide a deeper mechanistic understanding of autophagy,

secretion and their crosstalk and how these pathways regulate protein aggregate formation and eventually development of NDs.
SAND brings together expertise from several different research disciplines (such as vesicular trafficking, autophagy, chemical biology, neuroscience, computational sciences, systems biology and clinical neurology) and we expect that the extensive interactions and collaborations within SAND will bridge fundamental discoveries to translational research, hopefully paving the way for development of therapeutic approaches to treat NDs. This is important, as NDs are predicted to become the second leading cause of death in the next two decades with a continuously aging society. Thus, the results obtained in SAND will be of considerable interest to the research industry sector and for the clinical fields, in addition to the research community. Importantly, the training program of SAND will equip the ESRs with a valuable combination of skills essential to careers in academia or industry.

SAND - two first annual meetings

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