Disease vs health

Dr Irving Vega, Associate Professor in Biology, is uncovering the molecular mechanisms underlying tauopathies such as Alzheimer’s disease by identifying and characterising brain region-specific biomarkers in the course of tau-mediated neurodegeneration.

To begin, could you provide a brief overview of your research?

Tauopathies are a family of neurodegenerative disorders characterised by the neuronal accumulation of tau protein. Our main objective is to understand how adaptive proteome responses contribute to the pathobiology induced by the presence of tau. To achieve this, we use a tauopathy mouse model that expresses the human protein tau bearing a mutation (P301L) found in human cases of tauopathy. The neurodegeneration phenotype in these mice is induced by the expression of the human tau mutant protein, allowing us to identify changes in the proteome in response to the progressive accumulation of pathological tau.

What role does tau pathology play in the context of neurodegeneration?

There are no doubts that tau plays a central aetiological role in neurodegeneration. Tau pathology was exclusively defined based on the detection of aggregated and hyperphosphorylated tau proteins in the somatodendritic compartment of neurons. The amount of hyperphosphorylated tau aggregation detected in specific brain regions after post-mortem analyses correlates with the severity of the clinical presentation. However, recent evidence suggests that aggregated tau may not be the main pathological form.

Could you summarise some of your methodologies?

Our scientific approach is based on the fact that the proteome (all proteins in the cell) is dynamic and adaptive. Proteome dynamics could be defined as transient changes in post-translational modification, interactions, function and/or subcellular localisation. Sustained proteomic changes through constant environmental or cellular stress could lead to cellular transformation or disease. The default response to cellular stress is survival. The induction of changes in the proteome leads to the activation of molecular processes that intend to avert the consequences of cellular insults. However, if the cellular insult continues, other cells can enter into the same paradigm of survival and death decisions. Therefore, the fitness of an ageing brain dealing with the accumulation of environmental insults could determine the fate of an individual: disease versus health.

What is the purpose of the EFhd2-knockout mouse?

Since EFhd2 is a novel protein, we have to develop all of the molecular tools required for its characterisation. In addition, we are close to finishing the characterisation of a mouse colony in which the EFhd2 gene has been deleted; both alleles of EFhd2 were deleted through homolog recombination in mouse embryonic stem cells. The EFhd2-knockout mouse can be used to directly test the effect of the absence of EFhd2 when a toxic tau molecule, such as the P301L mutant, is expressed in the central nervous system.

You have also worked to identify proteome changes induced by tau-mediated neurodegeneration in subcortical brain regions. How did this lead to the identification of amphiphysin-1 (AMPH1)?

AMPH1 is a protein involved in clathrin-mediated endocytosis that we identified in a brain region-specific proteomic analysis of regions affected by tau pathology. We showed that the abundance of AMPH1 is only reduced in brain regions that accumulate pathological tau in a tauopathy mouse model and brains affected by Alzheimer’s disease (AD). The results obtained from the mouse model that expresses the mutant tau protein indicate that the accumulation of pathological tau leads to a reduction in AMPH1, but not the mere expression of the mutant tau protein. We are now conducting experiments to determine the molecular mechanism that leads to the reduction of AMPH1 protein abundance in tau-mediated neurodegeneration.

Could you discuss the study of brain region-specific vulnerability observed in neurodegeneration among familial and sporadic tauopathies?

This is a baffling phenomenon. First, the neuropathology detected in an AD brain is the same whether it is a familial or a sporadic case. Moreover, the expression of human mutant tau proteins in mice, such as the P301L mutation found in frontotemporal dementia with parkinsonism-17 (FTDP17) familial cases, induces neurodegeneration in similar brain domains as in humans, suggesting that the tau mutation produces toxic species specific to particular brain regions. Interestingly, in the mouse model, and even in FTDP17 familial cases, the P301L mutant tau protein is present in all neurons of the nervous system, suggesting that there are brain regions that are resistant to toxic tau molecules. Therefore, we are conducting experiments to identify differences in the proteome of vulnerable and resistant brain regions to tau-mediated neurodegeneration.
Tackling tauopathies

Researchers at the University of Puerto Rico are seeking to identify the role of a novel tau-associated protein in neurodegeneration. The study may lead to improved biomarkers and effective therapeutics for Alzheimer’s disease and related neurodegenerative disorders.

TAUOPATHIES ARE A family of age-related neurodegenerative disorders associated with the pathological aggregation of the tau protein in the brain, and include Alzheimer’s (AD) and Pick’s disease among others. Due to its prevalence, severity and financial burden to healthcare, AD is the most common and intensively studied tauopathy. There is no cure, and AD becomes progressively worse over time, with symptoms including memory loss, confusion, speech problems and mood swings.

It has been suggested that up to 10 per cent of AD cases remain undiagnosed. At present, physicians can only diagnose the disease in its mid to late stages, often by using psychometric tests. Another diagnostic method is neuroimaging, although this is expensive and its accuracy remains unproven. It is also possible to diagnose AD by detecting disease biomarkers in a sample of cerebrospinal fluid collected by lumbar puncture; unfortunately, however, this procedure is invasive and painful and carries risk of serious health complications.

The inadequacy of these current diagnostic methods underlines the importance of developing more accurate techniques that can identify biomarkers of neurodegeneration without being invasive. Hence, molecular diagnostic tools that can enable the detection of pathological events in AD and other neurodegenerative tauopathies are essential for the development of effective therapeutics.

EF-HAND MOTIFS

In earlier work, Vega identified a protein that is expressed in the brains of non-transgenic mice and humans, and is associated with tau in the brains of JNPL3 mice – genetically modified mice that express a human tau protein with mutation P301L – that are terminally ill with AD. The function of this protein was unknown. Sequence analysis of the protein revealed the presence of two conserved calcium-binding motifs, known as EF-hand motifs. Initially known as swiprosin 1, Vega and his colleagues now refer to the novel amyloid protein as EFhd2. “The link between EFhd2 and tau has been validated in post-mortem AD brains, suggesting that the association between these two proteins may be a component of the molecular mechanisms elicited by pathological tau,” he elucidates.

In humans, the EFhd2 gene is located in chromosome 1, specifically in a region that has been linked to late-onset AD. EFhd2 has been conserved in evolution from invertebrates to vertebrates, which suggests the protein may play an important physiological or pathological role, although this is still poorly understood. Vega previously demonstrated that EFhd2 and tau combine in known tau-tangle structures within neurons. He and his team are now trying to determine whether EFhd2 plays a neuroprotective or a neurodegenerative role in AD.

EFHD2-KNOCKOUT MOUSE

The University of Puerto Rico researchers have developed a mouse colony in which the EFhd2 gene has been deleted to create EFhd2-knockout mice. Vega had initially expected the deletion of the gene to have a detrimental effect on the
INTELLIGENCE
THE ROLE OF A NOVEL TAU-ASSOCIATED PROTEIN IN NEURODEGENERATION

OBJECTIVES

• To understand how adaptive proteome responses contribute to the pathology induced by the presence of tau
• To identify and characterise biomarkers for use as diagnostic tools and to better understand disease pathogenesis

KEY COLLABORATORS

University of Puerto Rico: Yancy Ferrera-Acosta, PhD; Eva N Rodriguez Cruz, MS; Carlos J Nogueras-Ortiz, BS; Hector J De Jesus-Cortes, BS

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CONTACT

Dr Irving E Vega
Associate Professor
Department of Biology
University of Puerto Rico
PO Box 23360
Office JGD-120
San Juan
Puerto Rico
00931-3360
T +1 787 764 0000
E irvingvega@gmail.com
E irving.vega1@upr.edu

&cr=5&csb=default&css=ASC

DR IRVING VECA is an associate professor of biology at the University of Puerto Rico. His current research aims to unravel the mechanisms underlying tauopathies in neurodegeneration, with a focus on Alzheimer’s disease and related dementias by identifying and characterising brain regions specific biomarkers in the course of tau-mediated neurodegeneration.

nervous system. However, this hypothesis proved to be incorrect: “The EFhd2-knockout mice are viable and without any detectable cognitive or motor dysfunction, which is similar to the result obtained from the deletion of the gene (MAPT) that encodes the tau protein,” he describes.

JNPL3 mice were found to develop behavioural and motor deficits following the accumulation of tau in their brains as early as six months of age. As in humans with AD, the formation of tau aggregates in JNPL3 mice is dependent on age and are brain-region specific. The EFhd2-knockout mice will be used to test the effect of the absence of the EFhd2 protein when a tau molecule such as the P301L mutant is present in the animal’s central nervous system.

PROTEOME CHANGES

Vega uses tandem mass spectrometry to test his hypothesis of the adaptive proteome response in neurodegeneration. This powerful tool allows the team to identify proteins that deviate from their natural state in neurons at specific stages in the progression of tau-mediated neurodegeneration. In mass spectrometry, purified proteins are digested to produce peptides: these are ionised and fragmented, which provides the order of specific amino acids in the peptide’s sequence. Vega then subjects these molecular masses and fragmentation patterns to an algorithmic analysis. “Mass spectrometry-based proteomics allow us to directly identify proteins that may be involved in the cellular response to tau-mediated neurodegeneration,” he elaborates.

The group recently demonstrated that the usual abundance of Amphiphysin-1 (AMPH1) – a protein that is important for neurotransmission – is reduced in the central nervous systems of JNPL3 mice and humans suffering from AD. Hence, Vega wants to establish the causes and effects of lower levels of AMPH1, as this protein plays a key role in the synaptic functions of the neurons affected in AD.

AMPH1-knockout mice showed a decrease in AMPH2 (also known as BIN1). Single nucleotide polymorphism at BIN1 has recently been identified as one of the most important risk factors for late-onset AD. These results suggest there could be a link between AMPH1 and tau-mediated neurodegeneration.

Auto-antibodies against AMPH1 are found in the serum of patients that suffer a rare disease known as stiff-person-syndrome (SPS). Vega’s group hypothesised that the reduction of AMPH1 protein level in JNPL3 mice could lead to the release of peptides that elicit an auto-immune response. Recently, the researchers detected auto-AMPH1 antibodies in the serum of JNPL3 mice that correlates with the progression of tau-mediated neurodegeneration. Now, they are focusing on validating this result using human plasma and cerebrospinal fluid from confirmed cases of human tauopathies.

RESISTANT REGIONS

Vega’s research to date suggests that certain parts of the human brain are more vulnerable to AD than others, which in turn suggests that some brain regions are resistant to the toxicity of tau molecules. By dissecting the brains of JNPL3 mice, the researchers have been able to separate the regions that contain sarkosyl-insoluble tau from those that have the mutant human tau present but do not develop neurodegeneration. “We are convinced that the results obtained from this approach will not only provide insights into specific molecules that confer brain region vulnerability to tau-mediated neurodegeneration, but will also allow us to identify factors that contribute to toxic-tau resistance in specific brain regions,” Vega concludes.

Vega wants to establish the causes and effects of lower levels of AMPH1 and detection of auto-AMPH1 antibodies in AD sufferers