Online Proceedings

Poster Session 2

MGH 241, Easel 138

1:00 PM to 2:30 PM

Interactions Between Chaperones and Disease-Associated Tau Mutants

Hau Pham, Senior, Biochemistry
Mentor: Hannah Baughman, Medicinal Chemistry
Mentor: Abhinav Nath, Medicinal Chemistry

Microtubules are critical for cellular and developmental functions, including neurite outgrowth and maintaining stable wiring of the nervous system. Tau, an intrinsically disordered protein, plays important roles in microtubule assembly and stabilization. However, it dissociates from microtubules and forms amyloid fibrils in a set of neurodegenerative diseases termed tauopathies, which includes Alzheimer's disease, and frontotemporal dementia. Mutations in the sequence of tau cause the disease FTDP-17T (frontotemporal dementia with parkinsonism linked to chromosome 17 and specially characterized by tau pathology), providing evidence that alterations in tau alone can cause tauopathies. Most mutations occur in or near the microtubule-binding domain of tau, which suggests that mutant protein may be deficient in its capacity to stabilize neuronal microtubules, yet efficient at speeding up the process of aggregation. In particular, disease-associated mutations such as ΔK280 and P301L appear to enhance tau's propensity to aggregate into fibers, and alter its pathological activity. Molecular chaperone proteins are responsible for maintaining protein solubility, promoting proper folding, and preventing atypical aggregation. HspB1, a member of the small heat shock proteins (sHSPs), has been shown to delay wild-type tau fibril formation by weakly interacting with early species in the aggregation process. Hsc70 is a constitutively expressed chaperone that inhibits tau fibrils formation substoichiometrically. Both chaperones are able to recognize aggregation-prone motifs within the microtubule binding repeat region of wild-type tau. Therefore, our interest is to test the affinity and activity of HspB1 and Hsc70 against tau constructs containing the ΔK280 and P301L mutations, to see whether these mutations alter interaction with these chaperones. We will use various biophysical methods, including fluorescence spectroscopy and electron microscopy to analyze these interactions. This will extend our understanding of the characteristics and behaviors of disease-associated mutations of tau and the ways in which chaperones target aggregation-prone tau species.

Poster Session 3

MGH 206, Easel 173

2:30 PM to 4:00 PM

Interactions between the HIV-1 Env Glycoprotein and DC-SIGN are Influenced by Env Glycan Presentation

Adam Nguyen, Senior, Biochemistry
Mentor: Kelly Lee, Medicinal Chemistry
Mentor: James Williams, Medicinal Chemistry

Interactions between HIV-1 and dendritic cells (DCs) have been suggested to play a role in HIV-1 pathogenesis. DCs are antigen presenting cells that take up, process, and present foreign material to T-cells. Previous research suggests that HIV-1 can exploit this process by binding to DCs, allowing HIV-1 virions to relocate to lymph nodes where infection of T-cells can occur. HIV-1 mediates this interaction through binding of the HIV-1 envelope glycoprotein (Env) to DC-SIGN, a glycan binding protein located on the surface of DCs. Env contains a high amount of oligomannose glycans, enabling Env to act as a binding partner for DC-SIGN. Due to high sequence variation, HIV-1 strains exhibit variability in glycan presentation. A gap remains in our knowledge of where DC-SIGN binding occurs and how glycan presentation across various isolates modulates these interactions. In this study, we applied a combination of biophysical and structural approaches to characterize Env:DC-SIGN interactions across multiple HIV-1 strains. Biolayer interferometry experiments measuring binding affinity demonstrate that DC-SIGN binds with strong affinity towards Env from different isolates. This suggests that DC-SIGN is capable of recognizing different oligomannose glycan presentations and may not have a well defined epitope. However, preliminary results using electron microscopy illustrate that Env glycoprotein structure can be disrupted and altered via binding to DC-SIGN. This appears to be an isolate-specific response, as some strains remain unchanged. Using single particle approaches, we identified potential epitopes in heavily glycosylated regions of Env where additional densities are attributed to DC-SIGN. We infer that in addition to binding HIV Env, DC-SIGN may shield key neutralizing epitopes within these glycosylated regions. Our results provide further insight into the interactions that occur between HIV Env and DC-SIGN, and suggest a mechanism where HIV-1 hijacks DC's normal immune function allowing

HIV-1 trafficking while shielding neutralizing epitopes.

POSTER SESSION 4

Balcony, Easel 115

4:00 PM to 6:00 PM

Comparing CYP2J2 Regulation between Heart and Liver Tissue

Justin Paul Ford, Senior, Biochemistry, Chemistry
Mary Gates Scholar
Mentor: Rheem Totah, Medicinal Chemistry
Mentor: Eric Evangelista

In humans, CYP2J2 is involved in both drug metabolism and converting arachidonic acid to epoxyeicosatrienoic acids (EETs), which then act as signaling molecules. EETs are involved in angiogenesis, vasodilation, opening of ion channels, and general protection against cardiotoxicity. Currently, the Totah lab is testing the hypothesis that CYP2J2 has a critical role in the heart as one of the main contributors to EETs production. This research project seeks to determine whether CYP2J2 regulation is similar among different tissues, specifically between the heart and the liver, under oxidative stress conditions. A critical function in the heart would mean that under times of stress, CYP2J2 expression will increase. In contrast, CYP2J2 expression in the liver is expected to decrease similar to other CYP proteins under oxidative stress. To test this, reagents that increase reactive oxygen species (ROS) levels have been incubated with hepatic cells (HepG2) and the levels of CYP2J2 mRNA were measured and compared to untreated control cells. In the heart, CYP2J2 has a more important function in creating protective EETs and the benefits from increasing production of EETs have been shown in our lab to protect against the harmful effects of ROS. A few of the conditions being tested are: varying concentrations of hydrogen peroxide, cobalt chloride, and hypoxic conditions. MTT, a tetrazolium based dye, assays were used to quantify cell viability and rt-PCR was used to determine gene upregulation or downregulation of CYP2J2. Afterwards, the results were compared to similar treatments and conditions in cardiomyocytes. If transcription in HepG2 cells is downregulated but increased in cardiomyocytes, it supports the hypothesis that CYP2J2 has a critical role in the heart compared to the liver, specifically under times of ROS stress.