Spring Seminar Series Educates Students on What's New in Research

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Clockwise: from Left *Dr. Sarita Lagalwar, Dr. Anne Houde, Dr. Robert Lamb, Dr. Carole Ober and Dr. Gloria Meredith.*

Continuing the tradition of teaching students both in and out of the classroom, Lake Forest College presented a spring semester filled with intelligent speakers from around the Chicago area. Sponsored by the Biology department, Eukaryon, Tri-Beta and the Center for Chicago Programs, the seminar series featured topics ranging from protein misfolding to guppy polymorphisms.

Protein Deposits in the Brain: Friendly or Deadly?

Dr. Sarita Lagalwar, Department of Cell and Molecular Biology, Northwestern University

In the first seminar of the semester, Dr. Lagalwar discussed her research on a protein with a simple name: tau. What this protein is capable of, however, is far from simple. Tau is found in the brain cells of those with Alzheimer's disease. The problem arises when this protein forms tangles within the brain. As the disease progresses, the tangles follow a predictable path, affecting different areas of the brain as they move. These affected areas correlate to the advent of symptoms seen in Alzheimer's patients, first moving to the area responsible for memory, then language, and finally, abstract thought.

Another protein called p-SAPK-JNK assists in the cascade of cell death seen in Alzheimer's disease. Tau has a very large number of sites available for phosphorylation. Problems arise when tau is hyperphosphorylated, as is seen in Alzheimer's patients. P-SAPK-JNK is capable of phosphorylating tau at a large number of sites, leading to cell death. When activated, caspase 3 has the ability to cleave the tau protein at a site that eliminates a peptide sequence controlling against polymerization of the tau protein. If tau is cleaved, the protein is polymerized. Therefore, both caspase 3 and p-SAPK-JNK cause tau to form tangles and this leads to the cell death cascade seen in Alzheimer's disease.

Dr. Lagalwar also spoke about GVDs, granules that build up in cells in the brain over time. Patients at different stages of disease progression were examined; the amount of GVDs present was identified. Alzheimer's patients in the later stages of the disease were found to have large numbers of granules: Those in stage four had four times the number of granules as those in stage three. The timing of this increase in granules correlates with the first presence of tau tangles within the hippocampus.

Research on this disease is far from finished. While Dr. Lagalwar's research has provided some new insights into the possible mechanisms of this disease, it has also raised even more questions: Are granules protective against the formation of tangles? Is tau present within granules? Does the composition of the granule change over time?

Polymorphism Persists: How Guppies Got Such Different Spots

Dr. Anne Houde, Professor of Biology, Lake Forest College

Lake Forest's own Dr. Anne Houde presented her research on the guppy at Eukaryon's inauguration ceremony. Speaking to an audience with varied scientific and non-scientific backgrounds, Dr. Houde emphasized the importance of Darwin's theory of natural selection in all aspects of biology, even those that may seem meaningless. On the northeast coast of South America, guppies live in streams found in Trinidad. Guppies reproduce through internal fertilization and give birth to live young. Mate choice is driven by female choice: thus, intersexual selection occurs, with females choosing to copulate with the most attractive males. This can be a complicated task because males display a wide array of very detailed polymorphic color patterns. These color patterns are genetic, with fathers passing on their specific colorations and unique spots to their sons. The vivid orange spots are most strongly inherited, as they are linked to the Y chromosome.

With strong female preferences, how is it that the processes of natural selection don't evolve all males into the same cookie-cutter pattern? Here, Dr. Houde introduced the concept of frequency dependent selection. This form of selection controls the phenotypes, maintaining everything at a certain level of rarity and allowing no one trait to become too common in the population.

Is this how guppies maintain such a strong polymorphism? Three experiments looked into this possibility. In the first, all of the guppies within one pool were removed, and males were sorted by their color patterns. When returning the fish to the pool, the rarity of certain color patterns can be controlled. By doing so, it was found that rare phenotypes had a high survival rate while common ones did not, perhaps because predators learn the color patterns of the common guppies. This is good evidence for frequency dependent selection.

The second experiment looks at a female's tendency to mate multiply. Females are able to control which male's sperm fertilizes their eggs, meaning that

there are usually multiple fathers within each brood and thus multiple phenotypes. Once a female has mated with a male, she will not mate with him again. What's more, she also ignores all males that look like him, ensuring that each brood contains a variety of genotypes to increase the likelihood that at least some survive.

The third experiment places one female in a tank with four males: two of the males were twins, and two who were completely unique from the others. In Dr. Houde's lab, it was observed that the females ignored the redundant males while preferring to mate with the unique males. Maybe the female had already mated with a male that resembled him, or maybe she had even just grown tired of sexual displays from males of that phenotype.

Each of these three experiments provides positive evidence into the idea that polymorphism in guppies is maintained through frequency dependent selection. In the future, the actual mating success of each male will be studied by looking at the proportion of babies who were fathered by each male.

Extreme Nanomachines: Protein Refolding Drives Membrane Fusion by the Paramyxovirus Fusion Protein

Dr. Robert Lamb, John Evans Professor of Molecular and Cellular Biology, Northwestern University; Investigator, Howard Hughes Medical Institute

Dr. Lamb presented his research in a very interesting and visual seminar. A professor at Northwestern University, Dr. Lamb looks at the elaborate structural folding of specific proteins, paying specific attention to the changes in shape that some proteins rapidly undergo.

In the past few years, the number of viral diseases in the world has increased remarkably, from West Nile to AIDS to Avian influenza. One particular family of viruses, *Paramyxoviridae*, includes such viruses as the human parainfluenza virus. This family of viruses has a particular structure: They are all enveloped. Attachment of the virus to the host cell occurs when the virus' lipid bilayer fuses with the host's plasma membrane. Two proteins assist in this process: HN and F. The receptor binding protein (HN) works together with protein F, which harpoons the host's plasma membrane to enable fusion. When the HN proteins bind to the plasma membrane, the fusion proteins are signaled. The F proteins can then change their shape, allowing them to send out a spike to the other membrane.

Robert Lamb and the rest of his lab wanted to determine the pre- and post-fusion structure of the F protein. Using X-ray crystallography, they were able to determine the two different conformations of the F protein. The pre-fusion protein had an interesting structure: hollow in the center with a trimeric alpha helix stalk and a head. Each monomer of the trimer was twisted together with the fusion peptide in the middle. This metastable structure, however, is simply waiting to drop to its much lower energy state; after fusion, the structure changes dramatically. This change in structure creates the fusion of membrane, does not require ATP and is an irreversible process. To change its shape, the helix of the pre-fusion protein opens up, releasing the fusion peptide. Multiple peptides can then fuse to the membrane and, by changing their shape, effectively fuse the two membranes together. This post-fusion structure contains a large alpha helix made of six helical bundles. Because the resulting helix is so different from the helical structure of the pre-fusion protein, it is suggested that this protein rearrangements is one of the most extensive known, possibly even more akin to a refolding. These deep insights shed light on just how specialized these viral proteins can be. The fact that one amino acid sequence can create two completely different secondary structures, all based on certain triggers within the virus, is indeed extreme.

Genetic Studies of Common Diseases in a Founder Population

Dr. Carole Ober, Professor of Human Genetics, The University of Chicago

The success of the Human Genome and HapMap projects has engendered a whole new era in the world of genetics. Dr. Carole Ober of the University of Chicago presented some of her research to a group of interested students and faculty, focusing on her work to link particular genes to specific diseases or quantitative traits. While the idea that a phenotype is the result of a single genotype and environment is relatively simple, in reality the relationship between genes and diseases is much more complex. Due to compounding heterogeneous effects (clinical, genetic and environmental), it is incredibly difficult to determine both what gene(s) is/are the cause of a disease and how they result in the observed phenotype, the disease symptoms.

In order to study these interactions more carefully, heterogeneity must be minimized. To do this, Dr. Ober uses a founder population. The small number of founders beginning the population decreases the genetic heterogeneity while the uniform communal lifestyle limits environmental heterogeneity.

The Hutterites, a Protestant population, were forced to migrate all over Europe; the small remaining population came to the United States. Of the 1,200 people that left Russia for the U.S., 400 left for non-communal living. The remaining 800 Hutterites created three different colonies. As each colony grew bigger, it divided into a new branch; by 1910, hundreds of reproductively isolated colonies were created. Dr. Ober studied more than 1,000 people, all descendants of 62 of the 90 founders.

The Hutterite population has been shown to be a good model for outbred populations: allele frequency and the commonality of specific diseases are very similar. Because heterogeneity is so limited, the effects of genes are much more easily examined. To determine the roles of specific genes, quantitative traits are often studied instead of an entire disease. These traits are characteristic of and often lead to specific diseases, allowing the genes for complex diseases to be more easily located. Dr. Ober analyzed eight quantitative traits of asthma and found that only three were significantly represented. When the quantitative traits were examined specifically for each sex, however, the results were more significant: a sex-specific genetic architecture was discovered. Sexual dimorphism, differences in prevalence and age of onset are all believed to play a role in creating this variation. Seventeen quantitative traits were studied for sex-specific differences in heritability and linkage; almost all showed a difference.

Overall, susceptibility to disease is incredibly complex, more so than is often thought. Genes interact with other genes, the environment, sex of the individual,

and other factors creating a web of possibilities for the pathway from gene to disease or even to a certain trait.

Using Mouse Models to Understand the Primary Features of Parkinson's Disease

Dr. Gloria Meredith, Professor and Chair, Department of Cellular and Molecular Pharmacology, Rosalind Franklin University School of Medicine & Science

Parkinson's disease (PD), a debilitating disease which damages motor functions, affects 1.5 million Americans. To better understand the disease, animal models need to be developed. Dr. Gloria Meredith presented the possibility of using mice as effective models for understanding the mechanisms of this disease. When cross-sections of both mice and human brains were examined, clear similarities in structure were seen. PD patients suffer a 60% loss of dopamine nerve cells in the substantia nigra region of the brain. Symptoms include many motor deficits, such as rigidity, bradykinesia, and tremors. In order for mice to be a good model for this disease, the mice models should also show these symptoms.

A drug called MPTP was used to create irreversible signs of the disease within the mice. MPTP is a toxic metabolite similar to the herbicides and fungicides commonly believed to lead to Parkinson's disease in humans. C57 black mice were used due to their particular vulnerability to the drug. Three different drug administration schedules were tested. The chronic schedule was deemed most effective: mice were administered the drug two times a week for 5 weeks. In this schedule, neurons die progressively, as in PD cases seen in humans. All mice were then evaluated using several techniques: HPLC to measure dopamine levels, Nissel staining, confocal and electron microscopy to look for alpha synuclein, and behavioral tests.

Dr. Meredith believes that the results of these tests suggest that mice models would be effective. The motor tests showed an increased number of foot faults. The tests also showed decreased mRNA levels for alpha synuclein. Because decreasing the levels of mRNA would limit the amount of alpha synuclein that could be made, the lower levels may be a sign that too much alpha synuclein was present in the cells of the mice, a common characteristic of Parkinson's disease.

Dr. Meredith's research also evaluated the effects of three different drugs used to recover lost dopamine neurons. Sodium salicylate was able to restore behavior and the use of minocycline was able rescue dopamine neurons and decrease inflammation. While each medication helped the cells in different ways, the drugs were unable to solve all of the problems associated with the disease. Cystamine was also tested; it had no beneficial behavior to the cells.

Although there is currently no cure for Parkinson's disease, mice can be used to understand the mechanisms of PD and how progression of the disease can be stopped. Research with mouse models can also aid in developing symptom therapy. This work could also help to identify those who are susceptible to the disease.