Undergraduate Research Symposium May 19, 2017 Mary Gates Hall

Online Proceedings

POSTER SESSION 2

MGH 241, Easel 160

1:00 PM to 2:30 PM

Analysis of Cyclic Force for Underbite Correction

Benjamin W (Ben) La Course, Senior, Integrated Sciences
Mentor: Susan Herring, Orthodontics
Mentor: Katherine Rafferty, Orthodontics

Underbites are when the lower jaw protrudes further than the upper jaw and can lead to respiratory and feeding complications. One method currently used to correct underbites is the reverse pull facemask which puts tensile strain on the nasofrontal suture to promote growth of the upper jaw. The reverse pull facemask has major shortcomings such as a long duration of the treatment (12-18 months 16-18 hours a day), and is aesthetically unappealing. An alternative treatment that may produce faster results is to use an oscillatory cyclic load on the nasofrontal suture to increase the growth rate of the upper jaw to correct the underbite in less time than the reverse pull facemask. However to know how effective this method is for underbite correction it is vital to understand how the cyclic treatment changes the nasofrontal suture. My question is how the cyclic load changes the suture gap and growth rate (Mineral Apposition Rate MAR) of the nasofrontal suture in farm pigs. To measure the effectiveness of this treatment, the nasofrontal suture was extracted from farm pigs after they had been treated with the cyclic load for 30 minutes for 5 days. The sutures were then embedded, sectioned and examined under a fluorescent microscope to measure the MAR and suture gap for the control, and cyclic treated pigs. The control pigs had a suture gap range of 157-179 μm (n=5) and a MAR range of 7.75-15.25 μm/day (n=4). The cyclic loaded pigs had a suture gap range of 326-383 μm (n=2) and a MAR range of 29.9-33.2 μm/day (n=2). These data suggest that our cyclic treatment increases the suture gap and MAR of the nasofrontal suture. However, more data will need to be collected to validate our preliminary findings.

POSTER SESSION 2

MGH 241, Easel 127

1:00 PM to 2:30 PM

Antimutator Screening: ***Identifying Genetic Pathways Involved in the Suppression of Elevated Mutation Rates***

Thao Thanh Tang, Junior, Biochemistry
Mary Gates Scholar
Ngoc Tran, Sophomore, Pharmacy, Biological Science, South Seattle College
Thu Tran, Sophomore, Pre Pharmacy, South Seattle College
Mentor: Alan Herr, Pathology
Mentor: Mitchell Lee, Pathology
Mentor: Matt Kaeberlein, Pathology

DNA replication is the process by which genetic information is duplicated and passed from cell to cell. The process of DNA replication occurs with the assistance of various enzymes, including DNA polymerases, which synthesize new DNA molecules using template DNA and deoxyribonucleotides (dNTPs). Faithful DNA replication is vital for population survival and protected by exonuclease domains on the major DNA polymerases, which proofread replication errors. A secondary error-correction pathway known as mismatch repair (MMR) also scans the genome for replication errors. Defects in proofreading and MMR lead to ”mutator phenotypes” marked by elevated mutation rates and increased cellular mutation burden. In microbial populations, mutators spontaneously emerge and can increase adaptation to new environments by fueling genetic diversity. However, at extreme mutation rates, the accumulation of harmful mutations can also drive extinction of mutators. Some mutator cells survive this ”error-induced extinction” (EEX) by acquiring antimutator mutations that suppress the mutator phenotype. We have identified *Saccharomyces cerevisiae* strains that suppress elevated mutation rates through a screen for mutants that survive EEX. Using these eex mutant strains, we are currently mapping the genetic changes responsible for the antimutator phenotypes. Changes in mutation rates in haploid spores derived from these eex suppressor strains are being tracked to identify antimutator segregants, which are then being subjected to whole genome sequencing. As mutator phenotypes are important drivers in cancer, our analyses may reveal novel pathways that influence cancer evolution.

SESSION 2M

FUNDAMENTAL IMMUNE MECHANISMS

Session Moderator: Alanna Ruddell, Comparative Medicine
MGH 287
3:30 PM to 5:15 PM
* Note: Titles in order of presentation.

A Novel Protein Regulates Lymph Node Lymphangiogenesis
Aubrey D (Aubrey) Brown, Senior, Biology (Molecular, Cellular & Developmental)
Mary Gates Scholar
Mentor: Alanna Ruddell, Comparative Medicine

This abstract is no longer available.

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Identification of Tumor-Draining Lymph Node Immunosuppressive Signaling Pathways
Ernie Tao, Senior, Political Science, Biochemistry
Mary Gates Scholar, UW Honors Program
Mentor: Alanna Ruddell, Comparative Medicine

This abstract is no longer available.

POSTER SESSION 3

Commons West, Easel 33
2:30 PM to 4:00 PM

Impact of Cognitive Training on Verbal Memory in Gynecologic Cancer Survivors
Rddhi Moodliar, Senior, Psychology
Mentor: Monique Cherrier, Psychiatry

Cancer survivors often experience memory and thinking problems after treatment. Cognitive rehabilitation has been shown to improve function in head injury patients. This study examined behavioral and neural responses to a group-based cognitive training intervention in cancer survivors with cognitive symptoms. Gynecologic cancer survivors (n=23) were randomized to treatment group (15) or attention control (8). A subset of participants were eligible for scanning from the treatment (6) and control (5) groups. Both groups attended a 7-session, weekly group-based workshop. The treatment group received education and practice in skills (e.g. method of loci), and the attention control group received only education on cognition and information processing. Prior to and following the 7-session group-based workshops, participants were evaluated with a comprehensive cognitive battery along with an in-scanner verbal memory task where they studied word-pairs (e.g. star–couch) for later recall. During the test phase of the word-pairs task, participants were shown original word-pairs, novel word-pairs, shuffled (old and new) word-pairs, or recombined (two old words not previously paired) word-pairs. Recall during the test phase was assessed at an item level, where responses were yes/no to the query "both old?" or at the relational level, where responses were yes/no to the query "together previously?" Participants in the treatment group showed significant improvement for in-scanner responses in accuracy in the Relational condition, $p < .04$. Image analysis of group comparison at second level revealed decreased activation in one region in anterior cingulate for the treatment group for item recall. Cognitive training in cancer survivors can improve both attention and verbal memory. Pre to post change in the anterior cingulate for the treatment group suggests additional attention recruitment, consistent with improvements in attention observed with out-of-scanner tasks (e.g. digit span). Overall, cognitive training may be a useful treatment for cancer patients suffering from cognitive symptoms.

POSTER SESSION 4

MGH 241, Easel 132
4:00 PM to 6:00 PM

Identifying Antimutators in *Saccharomyces cerevisae*
Julia Ho Young Joo, Senior, Biochemistry, Biology (Molecular, Cellular & Developmental)
UW Honors Program
Rebekah (Bekah) Ashpole, Senior, Neurobiology
Stuart Hamilton Macgeorge, Senior, Biochemistry
Mentor: Alan Herr, Pathology

Mutator phenotypes due to mutations in genes encoding DNA polymerases or mismatch repair proteins lead to increased error rates during DNA replication that accelerate the evolution of cancer cells and contribute to chemotherapy resistance. Work in the yeast *Saccharomyces cerevisae* indicates that excessive DNA replication errors can lead to error-induced extinction *(EEX)*, where every cell within the population dies due to a random lethal mutation. Thus, a possible direction for cancer therapy may be to modulate mutation rates of mutator cells – to either increase mutation rates to a lethal level or suppress mutation rates to their baseline levels in order to slow the rate of tumor evolution. Genetic pathways that

may be targeted to modulate mutator phenotypes have yet to be fully elucidated. To identify such pathways, we isolated spontaneous haploid yeast *eex* mutants that escaped from error-induced extinction caused by combining a mismatch repair defect *(msh2Δ)* with the *pol2-L439V* allele, which models a human cancer mutation affecting DNA polymerase epsilon. We crossed the *eex* mutants to wild type yeast, generating diploid strains that were heterozygous for *msh2Δ, pol2-L439V*, and the *eex* mutation. Following sporulation, we measured the mutation rates of haploid MMR-proficient *pol2-L439V* progeny in order to assess the presence or absence of the antimutator mutation. For each mapping experiment, cells showing evidence of suppressed mutation rates were pooled separately from those exhibiting the normal *pol2-L439V* mutator phenotype. Unique mutations present only in the antimutator pool were identified by Illumina Next Generation Sequencing. Candidate *eex* mutations were engineered into fresh strains to assess the antimutator phenotype. Our compiled list of antimutator mutations and their functions in yeast may allow us to identify analogous mutations in the human genome and explore new methods of cancer therapy by which specific genes can be targeted to lower mutation rates to normal levels.

POSTER SESSION 4

MGH 241, Easel 133

4:00 PM to 6:00 PM

Spontaneous Polyploidization Rescues Mutator Yeast from DNA Replication Error-Induced Extinction

Max Akio Tracy, Sophomore, Pre Engineering
Luke Thurber, Sophomore, Pre Engineering
Mentor: Alan Herr, Pathology

DNA polymerase (Pol) proofreading and mismatch repair (MMR) cooperatively guard against DNA replication errors and cancer. Defects in these activities produce "mutator" phenotypes characterized by elevated levels of base-substitutions and frameshifts. Haploid yeast with combined defects in these activities rapidly go extinct, with some strains failing to even form visible colonies - a process termed error-induced extinction (*EEX*). Haploid *eex* mutants escape extinction by acquiring antimutator mutations that suppress the mutator phenotype; however, sixty percent of *eex* mutants escape extinction through spontaneous polyploidization, which insulates them from mutation accumulation by doubling their number of chromosomes. In evolution experiments with *pol2-4 msh2Δ* strains, which display a synthetic-sick phenotype due to Pol ϵ proofreading and MMR defects, polyploids routinely beat out antimutator mutants, which maintain haploidy. Whether strong diploid mutators also escape *EEX* by polyploidization is unknown. To investigate whether polyploids arise during the evolution of mutator diploid strains, we propagated *pol3-01/pol3-01 msh6Δ/msh6Δ* diploids (Pol δ proofreading and base-base MMR defective) with a mutation rate an order of magnitude below the diploid error threshold. Mathematical modeling suggests that although these diploid mutators are not immediately inviable, they should be overtaken by an antimutator or tetraploid after 200 generations. We found a single tetraploid culture in 89 independent cultures propagated for 300 generations. We measured mutation rates of isolates from cultures that remained diploid and repeatedly found antimutator phenotypes. Thus, spontaneous antimutator alleles and polyploidization rescues haploid and diploid cells from *EEX* with markedly different efficiencies. Differences in the relative frequency of each escape mechanism may reflect the nature of the mutator alleles, the starting ploidy of the cells, or the magnitude of the initial mutation rate. Our findings in diploids suggest that mutator cancer cells near the edge of error-induced extinction may similarly be under selection for spontaneous antimutator mutations and polyploidization.