Functional characterization of a “plant-like” HYL1 homolog in the cnidarian *Nematostella vectensis* indicates a conserved involvement in microRNA biogenesis

Y. Admoni[1]*, A. M. Tripathi[1], , A. Fridrich[1], M. Lewandowska[1], J. M. Surm[1], R. Aharoni[1], Y. Moran[1]

[1]The Hebrew University of Jerusalem, Department of Ecology Evolution and Behavior, Alexander Silberman Institute of Life Sciences, Faculty of Science, The Hebrew University of Jerusalem, 9190401 Jerusalem, Israel.

* Corresponding Author: yael.admoni@mail.huji.ac.il

Abstract

The microRNA (miRNA) system directs post-transcriptional regulation in various eukaryotic lineages and is crucial for many physiological and developmental processes. The evolutionary history of this system in animals and plants is debated as the competing scenarios are: (i) the system convergently evolved in each kingdom from an ancient RNA interference system against genomic parasites or (ii) it emerged as a gene regulatory system before the two kingdoms separated. In both plants and animals, the miRNA biogenesis pathway depends on the RNase III Dicer, however, its helping partner proteins are considered distinct for each kingdom. Nevertheless, it was recently discovered that homologs of Hyponastic Leaves 1 (HYL1), a component of the plant miRNA biogenesis complex, are present in Cnidaria, the sister phylum to all other animals. In this study, we show that the HYL1 homolog HYL1-like a (HYL1La) is crucial for the biogenesis of miRNAs in the sea anemone *Nematostella vectensis*. We show that HYL1La knockdown leads to a metamorphosis arrest in developing animals and to a significant decrease in levels of most mature miRNAs. Furthermore, we show by immunoprecipitation followed by quantitative PCR that HYL1La interacts with the miRNA precursor and not with the primary miRNA as HYL1 does in plants. These results suggest an important role for HYL1La in the metazoan *N. vectensis* and support the hypothesis of early emergence of the miRNA system as the common ancestor of animals and plants most likely carried a HYL1 homolog that took part in the biogenesis of miRNAs.

A central human antiviral immune pathway evolved from a bacterial anti-phage defense system

G. Amitai[1]*, D. Cohen[1], S. Melamed[1], A. Millman[1], G. Shulman[1], Y. Oppenheimer-Shaanan[1], A. Kacen[1], S. Doron[1], R. Sorek[1]
[1]Weizmann Institute of Science, Molecular Genetics, gil.amitai@weizmann.ac.il
* Corresponding Author

Abstract

The cell-autonomous antiviral innate immune system allows individual cells to resist viral infection. The repertoire of immune sensors and antiviral effectors has long been considered to be derived from extensive evolutionary innovation, but our recent studies now change that dogma. We found that the human cGAS-STING antiviral pathway evolved from an ancient anti-phage defense system that is common in bacteria and archaea.

The cGAS-STING pathway has a central antiviral role in humans. cGAS (cyclic GMP-AMP synthase) is a sensor for cytosolic dsDNA, which is naturally perceived as a signature of viral infection in eukaryotes. Once activated by dsDNA, cGAS produces the unique signaling molecule cyclic GMP-AMP (cGAMP), which binds and activates the STING protein. STING, in turn, drives a signal transduction cascade that results in activation of the interferon response.

We discovered a bacterial defense system comprised of cGAS-STING gene pairs, which, similar to its human counterpart, produces cGAMP molecules once phage infection has been sensed. These molecules bind the bacterial STING protein and executes the immune response against phages. Although there is no sequence homology between the bacterial and human cGAS or STING proteins, comparisons of crystal structures show clear structural homologies and support an evolutionary scenario in which primitive cGAS and STING were acquired into the eukaryotes innate immune system early in evolution, and then underwent metazoan-specific modifications.

References:

Cohen D, Melamed S, Millman A, Shulman G, Oppenheimer-Shaanan Y, Kacen A, Doron S, Amitai G*, Sorek R*. Cyclic GMP-AMP signaling protects bacteria against viral infection. ***Nature***, 574(7780):691-695 (2019).
* co-corresponding author

Millman A, Melamed S, Amitai G, Sorek R. Diversity and classification of cyclic-oligonucleotide-based anti-phage signalling systems. ***Nature Microbiology***, 5(12):1608-1615 (2020).

Open issues in the evolution of vision and eye movements in primates and humans, emphasizing night vision

S. Barash[1]*
[1]Weizmann Institute of Science, Department of Brain Sciences,
shabtai.barash@weizmann.ac.il
* Corresponding Author

Abstract

The visual system takes up much of the primate brain and has likely contributed to primate cognition. Much is known about day vision but much less about night vision. A tenet of day vision is that high-acuity (sharp) vision is concentrated in a small region of the retina, the fovea. Seeing an entire scene is possible only by moving the eye so that, one after another, scene locations fall on the fovea. This involves specialized eye movements: "fixations" fixate the eyes on a location, and "saccades" shift the fovea to other image bits. It is not perfectly clear how these movements have evolved. Some ongoing debates regard the residual movements that occur during fixations. Thinking about the evolution of these fixation movements might lead to the resolution of some of these debates.

Although night vision lacks the acuity of day vision, discerning details at night is evidently vital for survival. It has not been clear at all whether there is a nighttime high-acuity preferred-processing pathway like that of the fovea and saccades in daytime. At nighttime, the daytime pathway will not work: the fovea is near-blind at nighttime. I will describe a possible solution to this question. Once this solution is known, it might be likely that the evolution of fixations and saccades was influenced by both the daytime and the nighttime pathways. This leads to unified view of daytime and nighttime primate eye movements, and of their evolution. It also raises the question of the fate of the monkey-based solution in humans. Current evidence tentatively suggests the possibility that the nighttime high-acuity pathway was lost very recently in human evolution.

Conservation genomics in species reintroductions: the Asiatic wild ass *Equus hemionus* in Israel

L. Zecherle [1,2,3], Hazel J. Nichols [4], Alan.R. Templeton [5], Helen Hipperson [3,] Gavin. J. Horsburgh [3], Richard.P. Brown [1], Shirli Bar-David [2*]

[1] School of Biological and Environmental Sciences, Liverpool John Moores University, Byrom Street, Liverpool L3 3AF, UK

[2] Mitrani Department of Desert Ecology, Jacob Blaustein Institutes for Desert Research, Ben-Gurion University of the Negev, Sede Boqer Campus, Midreshet Ben-Gurion, 84990, Israel

[3] NERC Biomolecular Analysis Facility, Department of Animal and Plant Sciences, University of Sheffield, Western Bank, Sheffield S10 2TN, UK

[4] Department of Bioscience, Swansea University, Singleton Park, Swansea SA2 8PP, UK

[5] Department of Biology, Washington University, St. Louis, MO 63110-1093, USA

* Corresponding Author: shirlibd@bgu.ac.il

Abstract

Conservation reintroductions are a frequently used management tool for the recovery of endangered species. However, many reintroductions fail to establish viable, self-sustaining populations. There are a multitude of factors that can impact the success of a reintroduction program and population genetic aspects have been identified as an essential factor in the long-term persistence of reintroduced populations. However, due to a general lack of detailed long-term data sets, little is known about how different reintroduction strategies affect the genetic viability of a population and the long-term reintroduction success. We applied high-resolution genomic tools to investigate the reintroduction of the Asiatic wild ass *Equus hemionus* in Israel. This case study provides an opportunity to investigate genetic impacts of conservation reintroductions, as it offers a long-term data set and a rare reintroduction protocol: founder individuals of the population were sourced from two different subspecies. We established a set of genetic markers for the species using high-throughput sequencing techniques. Analyses based on this data set show that the populations display high levels of subspecies admixture and that population genetic parameters indicate a relatively high genetic variability compared with other reintroduced *E. hemionus* populations. These findings suggest that the highly controversial practice of subspecies admixture may be beneficial to reintroduction success in certain scenarios. Furthermore, we applied tools and methods from landscape ecology to uncover that habitat characteristics impact individual habitat selection but not genetic relatedness across the landscape. These findings suggest that current landscape configurations pose no barrier to gene flow in the reintroduced population and that the observed genetic structure of the population may be a result of behavioral effects. Our study demonstrates the importance of understanding species genetic makeup to be applied for the long-term success of conservation reintroductions.

The evolution of biomineralization gene regulatory networks through the co-option of organic scaffold forming networks

Smadar Ben-Tabou de-Leon
The University of Haifa, the Marine Biology Department, Charney School of Marine Sciences, Haifa 31905, Israel. **sben-tab@univ.haifa.ac.il**

Abstract

Biomineralization is the process in which organisms use minerals to generate hard structures like teeth, skeletons and shells. Biomineralization is proposed to have evolved independently in different phyla through the co-option of pre-existing developmental programs. Comparing the structure of gene regulatory networks (GRNs) that drive biomineralization in different species could illuminate the molecular evolution of biomineralization. Here I compare the mesodermal GRNs that drive biomineralization in echinoderms and in vertebrates. The GRN that drives skeletogenesis in the sea urchin embryo was extensively studied and shows high conservation within echinoderms, larval and adult skeletogenesis. The organic scaffold in which the calcite skeletal elements form in echinoderms is a tubular compartment generated by the syncytial skeletogenic cells. This is strictly different than the organic cartilaginous scaffold that vertebrates mineralize to make their bones. Relatedly, the GRN that drives skeletogenesis in the sea urchin embryo shows little similarity to the GRN that drives bone formation and high resemblance to the GRN that drive vertebrates' vascular tubulogenesis. On the other hand, vertebrates' bone-GRNs show high similarity to the GRNs that operate in the cells that generate the cartilage-like tissues of amphioxus, a basal chordate that does not produced mineralized tissue. These comparisons suggest that biomineralization in deuterostomes evolved through the phylum specific co-option of GRNs that control distinct organic scaffolds for mineralization.

Aneuploidy as a rapid mechanism of adaptation to antifungal drugs

Judith Berman*, Feng Yang[1,2], Vladimir Gritsenko[1]
[1]Tel Aviv University, Shmunis School of Biomed, & Cancer Res., Britannia 418, Ramat Aviv
[2]Tonji University, Dept. of Pharmacy, Shanghai Tenth People's Hospital,
Shanghai, China

jberman@umn.edu
* Corresponding Author

Abstract

We study the evolution of drug tolerance and drug resistance in important fungal pathogens (*Candida albicans* and *Candida glabrata*) motivated by the desire to understand how eukaryotic cells respond rapidly to severe stresses and by the goal of devising better antifungal therapy strategies. Clinical studies of antifungal drug responses measure primarily the minimum inhibitory concentration (MIC): the concentration of drug at which 50% or more of the pathogen cells exposed to the drug do not grow (are susceptible to the drug). However, the majority of problematic (persistent or recurrent) fungal infections are caused by *susceptible* isolates despite treatment with drug concentrations above the MIC for the infecting organisms. Tolerance and hetero-resistance are responses in which *some* of the cells in an isogenic population grow slowly in the presence of supra-MIC drug concentrations. These tolerant subpopulations, together with the selective pressure of drug treatment acting upon them, have the potential to drive the evolution of new mechanisms for survival of the pathogen. One of the mechanisms that enables this transient survival despite drug concentrations that should be inhibitory, involves changes in chromosome stoichiometry, usually via aneuploidy, and its effects on the expression of specific genes. Indeed aneuploidy is a common, rapid and transiently stable mechanisms by which *C. albicans* cells respond to many different stress conditions. In addition, *C. glabrata,* a close relative of baker's yeast, develops respiratory deficiencies and/ or specific aneuploidies in response to antifungal drug stress. These and other mechanisms of drug adaptation that are being explored, will be discussed.

Inferring viral mutation rates & fitness effects using simulation-based inference and neural networks

I. Caspi[1], M. Meir[1], Y. Ram[2], A. Stern[1]*

[1]Tel Aviv University, The Shmunis School of Biomedicine and Cancer Research, Tel Aviv 69978, sternadi@tauex.tau.ac.il
[2]Tel Aviv University, School of Zoology, Tel Aviv 69978, yoavram@tauex.tau.ac.il

* Corresponding Author

Abstract

Motivation

The mutation rate of a virus defines the ability of viruses to generate genetic heterogeneity, and as such is a defining feature of viral evolution, yet inference of mutation rates is complicated by the interaction of mutation with fitness effects. In our lab, we now have available unique long read sequencing data for the virus MS2, which was serially passaged under a highly controlled setting. Our aim is to use this dataset to develop a method for simultaneously inferring mutation rates and distribution of fitness effects (DFE).

Methods

Our framework is based on Neural Density Estimation and Simulation Based Inference. Our key challenges are (1) simulating haplotypes and (2) using an appropriate summary statistic to compare between the simulated and empirical data.
We solve (1) by dividing mutations into 3 types (deleterious, neutral & adaptive), which enables us to model the entire viral population using less than 10 parameters and solve (2) by observing that even with a very high mutation rate and very strong selection, the number of mutations per genome can still be well approximated by a Poisson distribution, which allows us to use the average number of mutations per genome as the summary statistic.

Results

We show high accuracy of mutation rate and DFE inference for synthetic data across a wide range of parameter values. We explore reasons for a tendency to slightly under-estimate certain parameters. Finally, we present preliminary results from empirical data of an experimentally evolved population of phages.

Looking Forward

We aim to use this model to infer the mutation rate and DFEs of phages under different evolutionary pressures to obtain a complex view of the dynamics of viral evolution.
Moreover, we plan to adapt our method to allow for inference of DFEs and mutation rates under dynamic selective pressures in clinical setups.

Fitness landscape analysis reveals that the wild type allele is sub-optimal and mutationally robust

T. Gabzi[1], Y. Pilpel[1]*, T. Friedlander[2]*
[1]Weizmann Institute of Science, Department of Molecular Genetics, Rehovot 7610001
zahigabzi3@gmail.com , pilpel@weizmann.ac.il
[2]Hebrew University of Jerusalem, Faculty of Agriculture, Food and Environment, P.O. Box 12 Rehovot 7610001, tamar.friedlander@mail.huji.ac.il
* Corresponding Author

Abstract

Fitness landscape mapping and the prediction of evolutionary trajectories on these landscapes are major tasks in evolutionary biology research. Evolutionary dynamics is tightly linked to the landscape topography, but this relation is not straightforward. Models predict different evolutionary outcomes depending on mutation rates: high-fitness genotypes should dominate the population under low mutation rates and lower-fitness, mutationally robust (also called 'flat') genotypes - at higher mutation rates.

Yet, so far, flat genotypes have been demonstrated in very few cases, particularly in viruses. The quantitative conditions for their emergence were studied only in simplified single-locus, two-peak landscapes. In particular, it is unclear whether within the same genome some genes can be flat while the remaining ones are fit.

Here, we analyze a previously measured fitness landscape of a yeast tRNA gene. We found that the wild type allele is sub-optimal, but is mutationally robust ('flat').

Using computer simulations, we estimated the critical mutation rate in which transition from fit to flat allele should occur for a gene with such characteristics.

We propose that while the majority of genes are still selected to be fittest, there are a few mutation hot-spots like the tRNA, for which the mutationally robust flat allele is favored by selection.

Disorder Propensity of Proteins is a Continuum and is Under Negative Selection

N. Granik[1+], O. Willinger[2+], G. Hannuna[2], A. Kahan[2], Y. E. Maruvka*[2]
[1]Technion, Department of Applied Mathematics
[2]Technion, Department of Biotechnology and Food Engineering
yosi.maruvka@bfe.technion.ac.il
+ Equal contributor | * Corresponding Author

Abstract

The relationship between protein structure and function is a well-studied field. However, it was found that some proteins do not have a fixed structure, and they transition between different conformations. These intrinsically disordered proteins were found to be essential in biological processes and implicated in various diseases. The disorder propensity of a protein is determined by its amino acid sequence and composition, and multiple methods binarily classify proteins as ordered or disordered.

However, this classification is likely a simplification of more complex behavior. Here, we analyzed whether continuum analysis of protein disorder could better capture the features of protein evolution.

We used multiple algorithms that assign a continuous disorder propensity at the single residue resolution (IUPred, ESpritz, Metapredict), and correlated it with 2.4M cancer somatic mutations, 7.6M germline variants, and 73K de-novo mutations.

The mutation rates of both cancerous and de-novo mutations negatively correlate with the disorder propensity, while germline variants frequency correlate positively. These changes were observed at both the single-gene level and in the aggregated human proteome.

Additionally, we analyzed how mutations influence disorder propensity. We found a bias towards decreasing the cumulative disorder propensity of proteins in cancer somatic mutations, the majority of which are passenger mutations. This bias was smaller in germline variants, suggesting a negative selection against disorder reduction. Per our theme, this behaviour supports a continuum feature, as even ordered regions showed a selection against disorder reduction.

Preliminary analysis performed on viral evolution found a gradual decrease in protein disorder for the SARS-CoV2 and alternating periods of disorder increase and decrease in major influenza strains, supporting the continuum disorder behavior of proteins as a general phenomenon.

We propose that protein disorder content is under negative selection, with germline mutations showing the eventual outcome of all contemporary somatic mutations.

Alternative mating tactics in a moth.

Ally Harari[1], Ariel Glazer[2]

1. Department of Entomology, The Volcani Center, Israel. aharari@agri.gov.il
2. Koret School of Veterinary Medicine, The Hebrew University of Jerusalem. arielglezer@gmail.com

Female moths release a species-specific sex pheromone that attracts conspecific males. While natural selection acts to reduce variance in the sex pheromone to limit possible mistakes in species recognition, sexual selection acts in favor of discrimination among females that vary in their reproductive potential. Studies on the mating behavior of the pink bollworm, *Pectinophora gossypiella*, revealed (1) differences in female pheromone characteristics in relation to their reproductive potential, (2) males discriminate among females, preferring large females as mates, (3) large female reject males, and (4) males reject small females. To overcome repeated rejections males and females adopted alternative mating strategies: Large males copy the choice of successful males, approaching mating couples and interfering with their mating in the attempt to disengage the couple and replace the smaller male in copulating the female. Small females are also attracted to the mating couple lurking males that failed in their interference attempts.

Title: Concerted evolution reveals the exact substitutions that allowed *Leptodactylus* frogs to prey on toxic toads

Presenter: Arbel Harpak, PhD, University of Texas at Austin, arbelharpak@utexas.edu

Abstract:

Gene duplication is an important source of evolutionary innovation, but the divergence of duplicates in function can be opposed by a mechanism that copies the sequence of one paralog onto the other---gene conversion. This gloomy fate of "concerted evolution" was evaded by ATPase gene duplicates shared by *Leptodactylus* frogs---a group of species that feeds on toxic toads. Within each species, one paralog of the gene evolved novel resistance to the prey toad toxins while the other retained ancestral susceptibility. Frequent gene conversion homogenized most of the sequence between the two paralogs, but was counteracted by natural selection on 12 amino acid substitutions that distinguish the two paralogs across *Leptodactylus* species. Our protein-engineering experiments show that 2 of these substitutions substantially increase toxin resistance, whereas the additional 10 mitigate deleterious pleiotropic effects on ATPase activity. Our results reveal how examination of the evolution of neo-functionalized genes can help pinpoint key functional substitutions and interactions with the genetic backgrounds on which they arise.

Gene swamping as a fail-safe strategy in gene drive deployment

K. D. Harris[1], G. Greenbaum[1]*
[1]The Hebrew University of Jerusalem, Department of Ecology, Evolution and Behavior, Givat Ram, Jerusalem 9190401, gil.g@mail.huji.ac.il
* Corresponding Author

Abstract

Gene drives are genetic constructs that can spread deleterious alleles in wild populations by generating non-Mendelian inheritance patterns. Lab experiments of CRISPR-Cas9-based gene drives have been shown to drive populations to extinction within a few generations, paving the way for deployment of gene drives to control disease vectors and invasive species. However, given that a gene drive can potentially spill over to, and modify other populations or even other species, they must be designed in a way that allows this process to be controlled. Due to the ecological risks involved in deployment, studying behaviors of gene drive spread in wild populations currently relies on mathematical and computational models. We developed a model of gene drive spillover that combines evolutionary and demographic dynamics, in a two-population setting. Gene drive spread presents a unique case where an allele with a high fitness cost spreads rapidly in a population; due to the effect on population fitness, evolutionary and demographic changes will occur within a similar time-frame. The model demonstrates how feedback between these dynamics produces additional outcomes to those demonstrated by the evolutionary dynamics alone. We identify an outcome where the short-term suppression of the target population is followed by gene swamping and loss of the gene drive. Using our model, we demonstrate the robustness of this outcome to spillover and the evolution of resistance, and suggest it as a fail-safe strategy for gene drive deployment.

Protein innovation through template switching in the *Saccharomyces cerevisiae* lineage

May Abraham[1] and Einat Hazkani-Covo[1]*

[1] Department of Natural and Life Sciences, The Open University of Israel, Ra'anana, Israel

* einatco@openu.ac.il

Abstract

DNA polymerase template switching between short, non-identical inverted repeats (IRs) is a genetic mechanism that leads to the homogenization of IR arms and to IR spacer inversion, which cause multinucleotide mutations (MNMs). It is unknown if and how template switching affects gene evolution. In this study, we performed a phylogenetic analysis to determine the effect of template switching between IR arms on coding DNA of *Saccharomyces cerevisiae*. To achieve this, perfect IRs that co-occurred with MNMs between a strain and its parental node were identified in *S. cerevisiae* strains. We determined that template switching introduced MNMs into 39 protein-coding genes through *S. cerevisiae* evolution, resulting in both arm homogenization and inversion of the IR spacer. These events in turn resulted in nonsynonymous substitutions and up to five neighboring amino acid replacements in a single gene. The study demonstrates that template switching is a powerful generator of multiple substitutions within codons. Additionally, some template switching events occurred more than once during *S. cerevisiae* evolution. Our findings suggest that template switching constitutes a general mutagenic mechanism that results in both nonsynonymous substitutions and parallel evolution, which are traditionally considered as evidence for positive selection, without the need for adaptive explanations.

Serine substitutions are linked to codon usage and differ for variable and conserved protein regions

U. Hershberg*, T. Shauli[1], M. Linial[2], G.W.. Schwartz[3]
[*]Department of Human Biology, Faculty of Science, University of Haifa, Haifa, Israel
[1]School of Computer Science and Engineering, The Hebrew University of Jerusalem, Jerusalem, Israel
[2]Department of Biological Chemistry, Institute of Life Sciences, The Hebrew University of Jerusalem, Jerusalem, Israel
[3]Department of Medical Biophysics Faculty of Medicine, University of Toronto
* Corresponding Author – uri@sci.haifa.ac.il

Abstract

Serine is the only amino acid that is encoded by two disjoint codon sets (TCN & AGY) so that a tandem substitution of two nucleotides is required to switch between the two sets. We show that these codon sets underlie distinct substitution patterns at positions subject to purifying and diversifying selections. We found that in humans, positions that are conserved among ~100 vertebrates, and thus subjected to purifying selection, are enriched for substitutions involving serine (TCN, denoted S′), proline, and alanine, (S′PA). In contrast, the less conserved positions are enriched for serine encoded with AGY codons (denoted S″), glycine and asparagine, (GS″N). We tested this phenomenon in the HIV envelope glycoprotein (gp120), and the V-gene that encodes B-cell receptors/antibodies. These fast evolving proteins both have hypervariable positions, which are under diversifying selection, closely adjacent to highly conserved structural regions. In both instances, we identified an opposite abundance of two groups of serine substitutions, with enrichment of S′PA in the conserved positions, and GS″N in the hypervariable regions. Finally, we analyzed the substitutions across 60,000 individual human exomes to show that, when serine has a specific functional constraint of phosphorylation capability, S′ codons are 32-folds less prone than S″ to substitutions to Threonine or Tyrosine that could potentially retain the phosphorylation site capacity. Combined, our results, that cover evolutionary signals at different temporal scales, demonstrate that through its encoding by two codon sets, serine allows for the existence of alternating substitution patterns within positions of functional maintenance versus sites of rapid diversification.

The first evolving entities may have been nanoscopic lipid micelles

D. Lancet[1]*, A. Kahana[1]
[1]The Weizmann Institute of Science, Dept of Molecular Genetics, Rehovot 7610001, Israel
doron.lancet@wizmann.ac.il
* Corresponding Author

Abstract

A most important open question in evolutionary biology is how evolution emerged. The key question is what might be the earliest chemical entities capable of reproduction, selection and Darwinian evolution. Protocells are often conceived as bilayer-enclosed vesicles, whose self-reproduction rests on replicating catalytic biopolymers. We have been exploring an alternative scenario, wherein reproducing nanoscopic lipid micelles with catalytic capabilities ("lipozymes") were forerunners of biopolymer-containing protocells. This postulate gains considerable support from decades of research describing micellar lipid catalysis and autocatalytic proliferation. More recent studies report on cross-catalysis in mixed micelles, leading to life-like steady-state dynamics (Kahana and Lancet, Nature Reviews Chemistry 2021). Such results synergize with predictions of our rigorous chemical kinetics computer-simulated Graded Autocatalysis Replication Domain (GARD) model. GARD illustrates how mutually catalytic lipid networks may enable micellar compositional reproduction that could underlie primal selection and evolution. Compositional information transfer across micellar growth-fission generations bears profound analogy to epigenetic inheritance in contemporary life. A beginning with simple nanoscopic assemblages bears significant points of realism, including ready formation under harsh, heterogeneous conditions. Further, the small assembly size and the high external molecular repertoire begets a huge variety of micelles with different compositions, a planet-wide "random library" capable of pre-evolutionary selection. Such characteristics lends support to the micellar model, as matched to the improbability of emergence under harsh conditions of utterly complex entities such as self-replicating RNA. In our recent analyses, we highlight how evolving micelles could have guided further protocellular complexification, including micelle to vesicle transition and monomer to biopolymer progression. We reckon that this would constitute very early steps in an extremely long path to the Last Universal Common Ancestor (LUCA), possibly over a half a billion years, longer than the track from nematodes to man.

Evolutionary conservation of cnidarian cell type programs revealed by single-cell genomics

S. Levy[1]*, A. Elek[2,3], X. Grau-Bove[2,3] S. Menendez-Bravo[2,3], M. Iglesias[2,3], A. Tanay[4], T. Mass[1], and A. Sebe-Pedros[2,3]

[1] University of Haifa, The Leon H. Charney School of Marine Sciences, Marine Biology Department. mailto:levyshani78@gmail.com

* Corresponding Author

[2]Centre for Genomic Regulation (CRG), Barcelona Institute of Science and Technology.

[3]Universitat Pompeu Fabra (UPF), Barcelona, Spain.

[4]Weizmann Institute of Science, Rehovot, Department of Computer Science and Applied Mathematics and Department of Biological Regulation.

Abstract

Corals belong to the eumetazoan ancestor phylum Cnidaria that includes anemones, jellyfish, and hydras. Cnidarians are the earliest metazoan that display most of the characters considered as milestones of metazoan evolution. Hence, they hold an interesting and important key position for understanding evolutionary origin. In addition to their evolutionary position corals, and specifically stony corals, hold a great ecological importance as they build and sustain the most biodiverse marine ecosystems on Earth: coral reefs. Despite their ecological importance, little is known about the cell types and molecular pathways that underpin the biology of reef-building corals. In this study we used single-cell RNA sequencing to create the first stony coral single-cell atlas. We identified and characterized gene expression profile of over 40 cell types across the life cycle of the stony coral *Stylophora pistillata*. From this reference atlas, we analyzed the molecular basis of mineral skeleton formation by the calicoblastic cells. We described the metabolic program involved in the symbiosis between the coral host and its algal photosynthetic partner. We identified specialized immune cells, that haven't been reported before in corals or any other cnidarians. Finally, we compared our *S. pistillata* cell atlas with available single-cell data from three other cnidarian species: the solitary sea anemone *Nematostella vectensis*, the soft coral *Xenia* sp., and the fresh-water polyp *Hydra vulgaris*. This comparative analysis offers the opportunity to study the evolution of cell type programs across three major cnidarian lineages that diverged from a common ancestor 500 million years ago. This multi-species single-cell comparison revealed strong transcriptional similarities at the broad cell type level, with specific co-expression of orthologous genes. Overall, this study reveals the molecular and cellular basis of stony coral biology and provides systematic evidence of the evolutionary conservation of major cnidarian cell type programs (e.g., cnidocytes, neurons, gland cells, and gastrodermal cells).

De novo mutation rates at the single-mutation resolution in a human HBB gene-region associated with adaptation and genetic disease

Daniel Melamed[1;2] Yuval Nov,[3] Assaf Malik,[4] Michael B. Yakass,[5;6] Evgeni Bolotin[1;2], Revital Shemer[7], Edem K. Hiadzi,[6] Karl L. Skorecki,[8] Adi Livnat*[1;2]

1 Department of Evolutionary and Environmental Biology, University of Haifa, 3498838, Israel,

2 Institute of Evolution, University of Haifa, 3498838, Israel

3 Department of Statistics, University of Haifa, 31905, Israel

4 Bioinformatics Unit, Faculty of Natural Sciences, University of Haifa, 3498838 Israel

5 West African Centre for Cell Biology of Infectious Pathogens (WACCBIP),

Department of Biochemistry, Cell & Molecular Biology, University of Ghana,

Legon P.O. Box LG 54, Ghana

6 Assisted Conception Unit, Lister Hospital & Fertility Centre,

Accra P.O. Box CT 966, Ghana

7 The Ruth and Bruce Rappaport Faculty of Medicine & Research Institute,

Technion - Israel Institute of Technology, Haifa, 3525433, Israel

8 The Azrieli Faculty of Medicine, Bar-Ilan University, Safed, 1311502 Israel

* To whom correspondence should be addressed; E-mail: alivnat@univ.haifa.ac.il

Abstract

While it is known that the mutation rate varies across the genome, previous estimates were based on averaging across various numbers of positions. Here we describe a method to measure the origination rates of target mutations at target base positions and apply it to a 6-bp region in the human hemoglobin subunit beta (HBB) gene and to the identical, paralogous hemoglobin subunit delta (HBD) region in sperm cells from both African and European donors. The HBB region of interest (ROI) includes the site of the hemoglobin S (HbS) mutation, which protects against malaria, is common in Africa and has served as a classic example of adaptation by random mutation and natural selection. We found a significant correspondence between de novo mutation rates and past observations of alleles in carriers, showing that mutation rates vary substantially in a mutation-specific manner that contributes to the site frequency spectrum. We also found that the overall point mutation rate is significantly higher in Africans than Europeans in the HBB region studied. Finally, the rate of the 20A>T mutation, called the "HbS mutation" when it appears in HBB, is significantly higher than expected from the genome-wide average for this mutation type. Nine instances were observed in the African HBB ROI, where it is of adaptive significance, representing at least three independent originations, and no instances were observed elsewhere. Further studies will be needed to examine mutation rates at the single-mutation resolution across these and other loci and organisms and to uncover the molecular mechanisms responsible.

Should we worry about the "evolutionary safety" of anti-COVID-19 mutagenic drugs?

Gabriela Lobinska[1], Yitzhak Pilpel[1*], Martin A Nowak[2*]

1 Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel,

gabriela.lobinska@weizmann.ac.il pilpel@weizmann.ac.il

2 Department of Mathematics, Department of Organismic and Evolutionary Biology, Harvard University, Cambridge MA 02138, USA martin_nowak@harvard.edu

*corresponding authors

Abstract

Recently, Merck applied for authorization for a new oral treatment against COVID-19, molnupiravir. Molnupiravir gives rise to many G->A mutations in the viral genome. The majority of these mutations are deleterious. The fitness of newly synthetized virions is thus severely impaired, leading to a decrease in the patient's viral load.

However, in the context of the COVID-19 pandemic, the mutagenic potential of molnupiravir is concerning. After all, molnupiravir could also cause mutations that are beneficial to the virus. This led us to the question: could widespread treatment of COVID-19 patients with molnupiravir accelerate the rate of emergence of new variants of concern?

To answer this question, we built a mathematical framework to model the evolution of the viral load within a patient, with and without treatment with a mutagenic drug. Our model included parameters such as the clearance rate of the virus, the viral mutation rate before and after treatment, and the number of positions in the viral genome that have a beneficial or deleterious effect to the viral fitness when mutated. All of these parameters were fitted from the vast existing literature about SARS-COV2.

We used our model to quantify the total amount of mutant produced by an infected individual with and without treatment with a mutagenic drug, and estimate the increase in risk of emergence of a variant of concern.

We made several counterintuitive observations which might inform treatment policy, in particular that the increase in risk of producing undesirable mutants under treatment is highest in immunocompetent individuals. This is because the treatment reduces the total viral load, which in turn reduces the probability of generating an undesirable variant. Yet, given our current estimates of the model's parameters, we find that molnupiravir is relatively evolutionarily safe.

A role for ecologically-tuned chunking in the evolution of advanced cognition demonstrated by modelling the cleaner fish market problem

Yosef Prat[1], Redouan Bshary[1], Arnon Lotem[2*]
[1] Institute of Biology, University of Neuchâtel, Neuchâtel, Switzerland.
[2] School of Zoology, Faculty of Life Sciences, Tel Aviv University, Tel Aviv, Israel.
* Corresponding Author: lotem@tauex.tau.ac.il

Abstract

What makes cognition 'advanced', and how it can evolve, is an open and not precisely defined question. One perspective involves increasing the complexity of associative learning, from conditioning to learning sequences of events ('chaining') to representing various cue combinations as 'chunks'. Here we develop a weighted-graph model to study the mechanism enabling chunking ability and the conditions for its evolution and success, based on the ecology of the cleaner fish *Labroides dimidiatus*. In some environments, cleaners must learn to serve visitor clients before resident clients, because a visitor leaves if not attended while a resident waits for service. This challenge has been captured in various versions of the ephemeral-reward task, which has been proven difficult for a range of cognitively capable species. We show that chaining is the minimal requirement for solving this task in its common simplified laboratory format that involves repeated simultaneous exposure to an ephemeral and permanent food source. Adding ephemeral-ephemeral and permanent-permanent combinations, as cleaners face in the wild, requires individuals to have chunking abilities to solve the task. Importantly, chunking parameters need to be calibrated to ecological conditions in order to produce adaptive decisions. Thus, it is the fine tuning of this ability which may be the major target of selection during the evolution of advanced associative learning.

Community composition of microbial microcosms follows simple assembly rules at evolutionary timescales

Nittay Meroz[1*], Nesli Tovi[1], Yael Sorokin[1], and Jonathan Friedman[1]
[1]Department of Plant Pathology and Microbiology, The Hebrew University of Jerusalem, Rehovot, Israel. *Nittay.meroz@mail.huji.ac.il

Managing and engineering microbial communities relies on the ability to predict their composition. While progress has been made on predicting compositions on short, ecological timescales, there is still little work aimed at predicting compositions on evolutionary timescales. Therefore, it is still unknown for how long communities typically remain stable after reaching ecological equilibrium, and how repeatable and predictable are changes when they occur. Here, we address this knowledge gap by tracking the composition of 87 two- and three-species bacterial communities, with 3-18 replicates each, for ~400 generations. We find that community composition typically changed during evolution, but that the composition of replicate communities remained similar. Furthermore, these changes were predictable in a bottom-up approach - changes in the composition of trios were consistent with those that occurred in pairs during coevolution. Our results demonstrate that simple assembly rules can hold even on evolutionary timescales, suggesting it may be possible to forecast the evolution of microbial communities.

Bacterial retrons function in anti-phage defense and show conceptual similarities to plant immunity

A. Millman[1]*, A. Bernheim[1], A. Stokar-Avihail[1], T. Fedorenko, M. Voichek, A. Leavitt, Y. Oppenheimer-Shaanan, R. Sorek
Weizmann Institute, Department of Molecular Genetics, adi.millman@weizmann.ac.il
[1] Equal contribution
* Corresponding Author

Abstract

Retrons are bacterial retroelements that generate chimeric RNA/DNA molecules in which the RNA and DNA components are covalently linked. Although retrons were discovered three decades ago, their function remained unknown. We report that retrons function in bacterial anti-phage immunity, and show that various retron systems confer defense against a broad range of phages via abortive infection. Focusing on retron Ec48, we show evidence that it "guards" RecBCD, a complex with central anti-phage functions in bacteria. Inhibition of RecBCD by phage proteins activates the retron, leading to abortive infection and cell death. Thus, the Ec48 retron forms a second line of defense that is triggered if the first lines of defense have collapsed. Such a defensive strategy has been documented as a central aspect of the immune system of plants, where it was termed "the guard hypothesis". Our discovery therefore shows that similar immunological principles govern the design of immune systems across bacteria and plants.

Demographic separation in populations of Desert Chameleons that live in spatial overlap

Liran Sagi*, Amos Bouskila

The Department of Life Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Liransag@post.bgu.ac.il

Almost all individuals of the desert subspecies of the common chameleon in Israel, *Chamaeleo chamaeleon musae*, do not survive after their first reproductive season, about a year from birth. Annual life spans are not very exceptional among desert lizards, but when combined with semelparity (death following reproduction) and the long incubation period (11 months) this may lead to sub-population separation in *C. c. musae*: The first sub-population hatches in odd years and reproduces in even years, while the second – hatches in even years. As a consequence of this temporal separation, the populations rarely mix. There are not many cases of sympatric speciation, and temporal separation is seen only in insect and Pink Salmons. In this case we have the opportunity to understand a rare mechanism that may explain sympatric speciation and apply to other species with a similar life-history. Our field records include 1081 individuals in 1551 observations during the last 12 years in Holot Mash'abim, Negev, Israel. We checked the survival rate of the chameleons using the program MARK under the 'robust design'. The survival decreases rapidly in the first months after hatching in all years. The survival up to the end of the first year, after egg laying, is 1.8%. Reaching a second reproduction season is even more rare – only 0.1% survive. This confirms that there is almost a full separation between the two sub-populations. Yearly survival depends on rain and evaporation, leading to variations in the number of offspring in the next generation. There variations seem to persist throughout the years, further suggesting of the separation. These results show that the unique biennial life cycle in *C. c musae* can result in demographic separation into two distinct sub-populations and may lead to sympatric speciation.

Horizontal pathway transfer facilitates an unexpected re-acquisition of sterol synthesis during the evolution of insects

Amir Sapir

Faculty of Natural Sciences, University of Haifa and Oranim Collage of Education, Tivon, 36006

Israel

E-mail: amirsapir1@gmail.com

Summary

Cholesterol is one of the hallmarks of animals. Studying the evolution of the cholesterol-synthesis pathway (CSP) in metazoans, we found this pathway to be conserved from unicellular Holozoa to vertebrates. Intriguingly, we discovered that the first three CSP enzymes that mediate the synthesis of the sterol backbone were lost in major taxa of invertebrates including nematodes and insects. Addressing the question of how these sterol auxotrophs acquired cholesterol that is essential for their development, we discovered a biochemical pathway that facilitates the conversion of dietary plant and fungal sterols to cholesterol in *Caenorhabditis elegans*. We propose that interkingdom interactions between sterol-auxotrophic animals and sterol-producing fungi and plants enabled widespread sterol auxotrophy in the animal kingdom. While searching the genomes of insects, we unexpectedly identified a few species of insects with a full set of enzymes supporting sterol synthesis. This is in sharp contrast to the auxotrophy of most insects including basal species. Phylogenetic analysis suggests that the acquisition of a functional CSP took place independently in several sterol-producing insects. Moreover, our analysis predicts that each autotropic insect uses enzymes from different donor species acquired through multiple steps of horizontal transfer. Our future plans are to investigate how this multistep process could be positively selected before the CSP was fully functional. In summary, we propose that the beneficial potential of sterol autotrophy was the driving force for the transfer of the CSP pathway to auxotrophic insects. Our findings demonstrate how the horizontal transfer of an entire pathway rather than a single gene is a mechanism of metabolic innovation during the evolution of animals.

Determine the constraints on the evolution of replicative aging

E. Havkin[1], Y. Savir[1,*]

[1]Technion, Faculty of Medicine, Dept. of Physiology, Biophysics & System Biology

*Corresponding Author, yoni.savir@technion.ac.il

Abstract

Many fundamental questions regarding the nature of aging and its underlying mechanisms remain elusive. In particular, the answer to the most basic question – why do we age at all? – is still not fully understood. Some theories suggest that aging is the result of natural selection getting constrained as the biological systems age. These include mutations with late-age deleterious (mutation accumulation), selection of genes that are beneficial early in life but are deleterious at late-age (antagonistic pleiotropy) and the existence of a tradeoff between damage repair and reproduction (disposable soma). On the other hand, some theories advocate the notion of aging as a selected trait. These include the selection of a shorter lifespan since it accelerates the removal of old cells that can compete with young cells with beneficial mutations. This debate is not only a theoretical question as these two opposing views suggest different experimental strategies toward understanding and modulating the aging process. One of the main limitations of current models that try to explain the selection of aging is that they assume an unrealistically fast-changing environment or rely on complex spatial, social interactions that lead to the co-existence of aging throughout kin selection. In this work, we develop a stochastic model for the evolution of replicative aging, the phenomenon where an organism dies after a certain number of replications, in a changing environment. By combing analytic analysis with stochastic simulations, we determine fixation probabilities of replicative aging in well-mixed and 2D environments, as a function of the population size and beneficial mutation rates. We show that even slow environmental changes can facilitate the fixation of replicative aging in 2D. Our results suggest that the evolution of replicative aging in organisms living on surfaces does not require fast environmental changes or complex social interactions.

Two-state sleep and its modulation by temperature in the lizard Stellagama stellio

D. Udi[1,†], N. Albeck[1,2,,†], M. Shein-Idelson[1,2,*]
[1]Tel Aviv University, School of Neurobiology, Biochemistry, and Biophysics
[2]Sagol School of Neuroscience, Tel Aviv University, Israel
* Corresponding Author - sheinmark@tauex.tau.ac.il
† equal contribution

Abstract

During sleep our brain switches between two dramatically different brain states - slow wave sleep and rapid eye movement sleep. The normal manifestation of such two-state sleep is vital to our survival. While two-state sleep is abundant across birds and mammals, its homology in other vertebrates is controversial and its evolutionary emergence is unclear. Correspondingly, it is undetermined whether the manifestation of two-state sleep is a fundamental property of vertebrate brains or an adaptation that is specific to homeotherms. To address these questions, we conducted electrophysiological recordings to measure brain states in the Agamid lizard, Stellagama stellio. We found clear signatures of two-state sleep that resemble the mammalian and avian sleep patterns. These two states switch periodically throughout the night with a cycle of ~90 seconds. Interestingly, the oscillatory nature of state switches is conserved across a wide range of temperatures and scaled with a Q10 value of 2.3, despite marked changes in neuronal excitability across temperatures. These results suggest the existence of special mechanisms in poikilotherms that ensure the robustness of sleep states transitions, hinting on their importance. Finally, these sleep patterns are remarkably similar to previous data collected from the agamid lizard Pogona Vitticeps, despite the fact that these two species are located on different branches that split more than 100MYA. Collectively, these findings suggest that two-state sleep is strongly conserved across the agamid family, increasing the probability that they existed already in the ancestor of stem amniotes.

Emergent Adaptation by Natural Improvisation

Yoav Soen,
Weizmann Institute of Science

Abstract

Traditional view of adaptation cannot explain how every individual cope with the unimaginably large number of newly-forming variations in its epigenome, microbiome and even in the somatic genome. Notably, **many** of these variations are generated in **novel combinations** that are **unique to the individual**. Since natural selection only accounts for adaptation of the population as a whole, it is incapable of accounting for sufficient coping with individual-specific variations. Put differently, we understand how selection of variation in a population supports adaptation to changing environments, but not how these variations emerge in the first place and how every individual adapts to novel internal variations that emerge during its lifetime.

To address this fundamental gap, we proposed a non-traditional principle of dynamic, individual-specific adaptation within a lifetime, extending the good old (population-based) adaptation by natural selection to newly-forming adaptation within every individual cell, animal and plant. Some of these newly-forming adaptations can also be inherited, thus demonstrating Lamarckian capabilities.

Experimental work-in-progress in both flies and cell culture models provide substantial evidence in support of the hypothesized emergent adaptation by exploratory dynamics within the individual's lifetime. Confirming the characteristics of this individual-specific adaptation will close the unrealized gap in the traditional theory of evolution by accounting for emergent adaptation on all time scales and levels of organization.

Co-evolution based machine-learning for predicting functional interactions between human genes

Doron Stupp [1], Elad Sharon[1], Idit Bloch[1], Marinka Zitnik [2], Or Zuk [3] & Yuval Tabach [1]

[1] Department of Developmental Biology and Cancer Research, The Institute for Medical Research Israel-Canada, The Hebrew University of Jerusalem, 9112001 Jerusalem, Israel.
[2] Department of Biomedical Informatics, Harvard University, Boston, MA 02115, USA.
[3] Department of Statistics and Data Science, The Hebrew University of Jerusalem, Jerusalem 9190501, Israel.

Over the next decade, more than a million eukaryotic species are expected to be fully sequenced. This has the potential to improve our understanding of genotype and phenotype crosstalk, gene function and interactions, and answer evolutionary questions. Here, we develop a machine-learning approach for utilizing phylogenetic profiles across 1154 eukaryotic species. This method integrates co-evolution across eukaryotic clades to predict functional interactions between human genes and the context for these interactions. We benchmark our approach showing a 14% performance increase (auROC) compared to previous methods. Using this approach, we predict functional annotations for less studied genes. We focus on DNA repair and verify that 9 of the top 50 predicted genes have been identified elsewhere, with others previously prioritized by high-throughput screens. Overall, our approach enables better annotation of function and functional interactions and facilitates the understanding of evolutionary processes underlying co-evolution. A webserver available at: https://mlpp.cs.huji.ac.il.

Genomic analysis of wild populations of *Drosophila* reveals adaptive polymorphism in circadian clock genes

E. Tauber*, L. Khatib , B. Fishman
University of Haifa, Department of Evolutionary and Environmental Biology, 199 Aba Khoushy Ave, Haifa, eran.tauber@gmail.com
* Corresponding Author

Abstract

From its early days, Drosophila has been an instrumental model system in the field of population genetics. Later, the fly become a major model system in chronobiology, allowing the first identification of circadian clock genes. Over the last decades there was a growing interest in studying genetic variation in clock genes to identify local adaptations of the clock. This molecular analysis was limited to individual polymorphisms in clock genes. The recent development of high throughput sequencing provides an opportunity to analyse evolutionary processes at the genome level (population genomics). The European Drosophila Population Genomics Consortium (DrosEU) was founded in 2014 and was aimed at extensive sampling and sequencing natural populations on a continent-wide scale and across distinct timescales. The first DrosEU pool-sequencing dataset, consisting of 48 population samples collected across the European continent has been recently published. The analysis of this dataset has revealed patterns of variation at multiple levels: genome-wide neutral SNPs, mtDNA haplotypes, inversions and TEs that exhibit longitudinal population structure across the European continent. Many populations shared signatures of selective sweeps and exhibit adaptive geographical clines in chromosomal inversions. We have also surveyed geographic variation in transposable elements and gut microbiota composition. Analysis of 11 genes that represent the core members of the circadian clock circuit reveals a large number of SNP whose distribution follows a latitudinal cline and presumably is driven by natural selection. The functional role of these SNP is currently being tested and will reveal the molecular adaptations of the clock.

High-throughput functional analysis of natural genetic variation in yeast

C. Yeh[1], M. Dunham[1]*
[1]University of Washington, Genome Sciences, 3720 15th Ave NE, Seattle, WA 98195 USA, ccyeh@uw.edu
* Corresponding Author

Abstract

Deducing phenotype based on natural genetic variation is difficult to determine given our incomplete ability to predict the functional impact of mutations. Current computational and experimental tools may predict and measure allele function, but to date there has been no assay that does so in a high-throughput manner while also representing haplotypes derived from wild populations. Here, I present such an assay that measures the functional impact of polymorphisms in hundreds of natural alleles of a given gene without site-directed mutagenesis or DNA synthesis. We first piloted this technique with a large collection of diverse *Saccharomyces cerevisiae* natural isolates using the gene *SUL1*, which encodes a high-affinity sulfate permease that, at increased copy number, can improve the fitness of cells growing under sulfate limitation. We cloned all alleles from 1011 natural isolates on low-copy plasmids *en masse* and transformed the reference S288C strain with this library. These plasmids were also barcoded, and each allele was matched with its respective allele using PacBio long-read sequencing. Using barcode sequencing, we tracked the growth ability of cells in sulfate limitation and measured the fitness effects of polymorphisms in this population. We show that this approach is effective in measuring the fitness changes conferred by each allele and stratify functional, intermediate, and nonfunctional alleles. Additionally, we can pinpoint which polymorphisms in both coding and noncoding regions are detrimental to fitness or are of small effect and result in intermediate phenotypes. Using a phylogenetic tree, we are further able to determine how often loss-of-function occurs and whether there is an evolutionary pattern to phenotypic results. This approach is broadly applicable to other genes and complement current genotype-phenotype mapping strategies to help us better understand how much one gene on a species-wide scale can contribute to a population's phenotypic variation.

Rapid evolution of de novo oxalate metabolism in human gut *E. coli* isolates

Avihu Yona, The Hebrew University of Jerusalem

How new functions arise denovo is a fundamental question in evolution.
We previously demonstrated in *E. coli* that a metabolic gene with a deleted promoter typically requires only a single mutation to evolve a new promoter from random sequences. In the presented work we demonstrate that metabolic functions themselves can also rapidly evolve. We focus on oxalate ($C_2O_4^{2-}$) as a target molecule as it causes stones. Gut microbes that can degrade oxalate in the gut are therefore a potential treatment for kidney stone disease.
We evolved three *E. coli* directly isolated from human volunteers and the probiotic *E. coli* Nissle 1917 under anaerobic conditions that mimic the gut. While no wild *E. coli* is known to utilize oxalate, our isolates evolved robust growth on oxalate as a sole source of carbon and energy. We performed whole-genome sequencing and revealed that denovo oxalate metabolism was obtained by evolving a missing reaction needed for oxalate metabolism. Interestingly, the missing reaction evolved in two paralogous enzymes from different pathways that have long diverged in terms of function and cellular localization.
Our work shows that laboratory evolution can uncover efficient mechanisms for de novo metabolism of target molecules that could not have been predicted based on existing knowledge.

The tradeoff between resistance to phages and nitrogen fixation in bloom-forming cyanobacteria

D. Kolan[1], E. Cattan-Tsaushu[1], M. Higaze[1], S. Avrani[1*]
[1]University of Haifa, Department of Evolutionary and Environmental Biology and Institute of Evolution, savrani@univ.haifa.ac.il
* Corresponding Author

Abstract

Cyanobacterial blooms negatively impact aquatic environments worldwide. Diazotrophic cyanobacteria, such as Cylindrospermopsis, can even form blooms under nitrogen starvation, due to their ability to fix N2. Phages could potentially control cyanobacterial growth; however, cyanobacteria are able to adapt to the presence of phages quite rapidly by acquiring resistance to the phage, thus, the role of phages in bloom dynamics is -as yet- unclear. We examined the resistance to phages of diazotrophic bloom-forming cyanobacteria. Our results demonstrate that this resistance, comes with reduced ability to induce heterocyst cells, in which N2 is fixed. This reduction causes reduced N2 fixation by the mutant strains, along with reduced growth or even death under nitrogen starvation. Such cost can prevent the survival of phage-resistant cyanobacteria under nitrogen starvation, and may suggest that spontaneous resistance to phages is a transient trait in diazotrophic bloom-forming cyanobacteria. Whole genome sequence analysis of the resistant strains sheds light on a possible explanation to this intriguing pleiotropy.

Transgenerational heat stress effects in dairy cattle associated with broad phenotypic impact and reduced selection efficiency: a study of four consecutive generations

Moran Gershoni[1*], Ephraim Ezra[2] & Joel Ira Weller[1,2]

1 The Volcani Institute, Department of Ruminant Science, Institute of Animal Sciences, Agricultural Research Organization, Rishon LeZion, Israel

2 Israeli Cattle Breeders Association, Caesarea, Israel

* Corresponding author: gmoran@volcani.agri.gov.il

Background

Global warming has increased the frequency of heat stress in livestock. Although heat stress directly leads to negative effects on production and reproduction traits in dairy cattle, the transgenerational transition of these changes is poorly understood. We hypothesized that heat stress in pregnant cows might induce epigenetic modifications in the developing embryo germ cells, which, in turn, might lead to phenotypic effects in the offspring. Here, we examined whether transgenerational effects of heat stress contribute to the phenotypic expression of economic traits in Israel dairy cattle. Since heat stress in Israel occurs specifically between June and October, first we examined the association of the month of birth of F1 cows (pregnancy of the F0 dam) with the performance of the F2 and F3 female offspring. Then, we calculated an annual heat stress index and examined the association of the heat stress index during the pregnancy of the F0 dam with the performance of her F2 and F3 offspring. Finally, we examined intergenerational interactions of heat stress by comparing the performance of F3 cows according to the pregnancy seasons of the F0 and F1 animals.

Results

We found a significant association of the month of birth, season of pregnancy, and heat stress index of F0 females, with the performance of their F2 and F3 progenies, which suggests a true transgenerational effect. The most significant transgenerational effects were on fat yield and concentration, dystocia, still-birth, and maturation.

Conclusions

These findings suggest that heat stress during pregnancy affects the performance of offspring, regardless of life circumstances in at least the last three generations. Therefore, heat stress can reduce selection efficiency in breeding programs and may have economic significance in livestock.

Population level genetic memory of prior metabolic adaptation in E. coli

Sophie Katz, Technion - Israel Institute of Technology

Bacteria must often survive following the exhaustion of their external growth resources. Fitting with this need, many bacterial species that cannot sporulate, can enter a state known as long term stationary phase (LTSP) in which they can persist for years within spent media1. Several recent studies have revealed the dynamics of genetic adaptation of *Escherichia coli* under LTSP. Yet, the metabolic consequences of such genetic adaptation were not addressed. Here, we characterized the metabolic changes LTSP populations experience and link them to their genetic adaptation. We observed that during growth within fresh resources *E. coli* produces the short chain fatty acid butyrate, which wildtype
E. coli cannot consume. Once resources are otherwise exhausted, *E. coli* adapts genetically to consume butyrate through the convergent, temporally precise acquisition of mutation combinations within genes that regulate fatty acid metabolism. These mutations appear to negatively affect bacterial fitness when butyrate is not available, and hence rapidly decrease in frequency, once all butyrate is consumed. Yet despite this, *E. coli* populations show a remarkable capability of maintaining a population-level genetic 'memory' of prior adaptation to consume butyrate. The maintenance of such a 'memory' allows bacteria to rapidly re-adapt, at an ecological, rather than an evolutionary timeframe, to re-consume previously encountered metabolites.