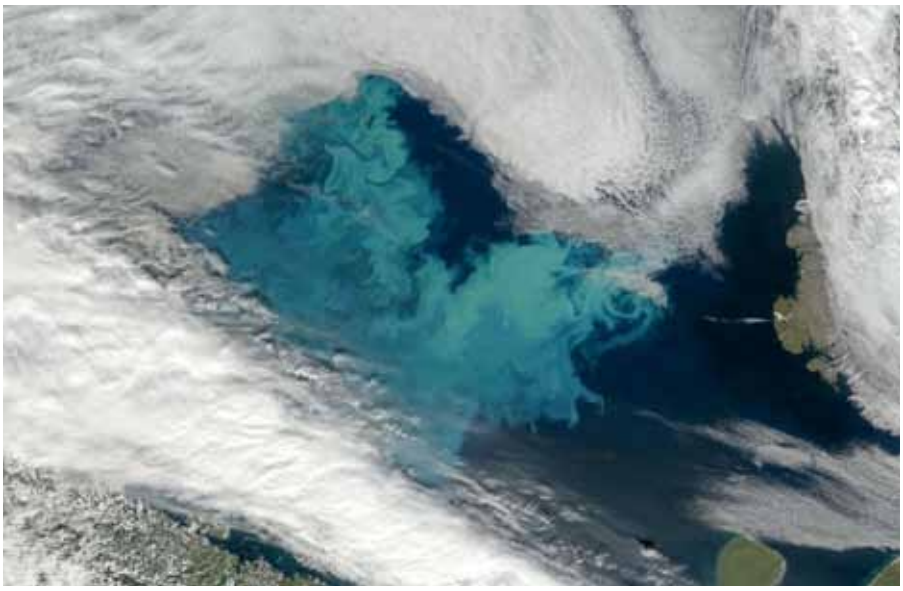
מכון ויצמן למדע
WEIZMANN INSTITUTE OF SCIENCE

Science Tips

Media Relations Department
Tel: 972-8-934-3852 / 56 Fax: 972-8-934-4132
http://wis-wander.weizmann.ac.il news@weizmann.ac.il
October 2014

The Ocean's Living Carbon Pumps



Satellite image showing a patch of bright waters associated with a bloom of phytoplankton in the Barents Sea off Norway. Image courtesy of Norman Kuring, Ocean Color Group at Goddard Space Flight Center, NASA

When we talk about global carbon fixation –"pumping" carbon out of the atmosphere and fixing it into organic molecules by photosynthesis – proper measurement is key to understanding this process. By some estimates, almost half of the world's organic carbon is fixed by marine organisms called phytoplankton – single-celled photosynthetic organisms that account for less than one percent of the total photosynthetic biomass on Earth.

Dr. Assaf Vardi, a marine microbiologist in the Weizmann Institute's Plant and Environmental Sciences Department, and Prof. Ilan Koren, a cloud physicist, and Dr. Yoav Lehahn an oceanographer, both from the Earth and Planetary Sciences Department, realized that by combining their interests, they might be able to start uncovering the role that these minuscule organisms play in regulating the carbon content of the atmosphere.

Tiny as they are, phytoplankton can be seen from space: They multiply in blooms that can reach thousands of kilometers in area, coloring patches of the ocean that can be tracked and measured by satellites. These blooms have a tendency to grow quickly and disappear suddenly. How much carbon does such a bloom fix, and what happens to that carbon when the bloom dies out? That depends, in part on what kills the bloom. If it is mostly eaten by other marine life, for example, its carbon will be passed up the food chain. If the phytoplankton are starved or infected with viruses, however, the process is more complicated. Dead organisms that sink may take their carbon to the ocean floor with them. But others may be scavenged by certain bacteria in the surface waters; these remove the organic carbon and release it back into the atmosphere through their respiration.

Phytoplankton multiply in blooms that can reach thousands of kilometers in area

Vardi, Koren and Lehahn asked whether one can use the satellite data to detect the signs of the demise of a bloom due to viral infection, an occurrence that Vardi has investigated in natural oceanic blooms and in the lab. During a recent research cruise near Iceland with colleagues from Rutgers University and Woods Hole Oceanographic Institute, the researchers were able to collect data on the algal-virus interactions and their effect on carbon cycles in the ocean.

By combining satellite data with their field measurements, they were able, for the first time, to measure the effect of viruses on phytoplankton blooms on large, open ocean areas. To do this, the scientists first had to identify a special subset of ocean patches in which such physical processes as currents did not affect

>>>

http://www.sciencedirect.com/science/article/pii/S0960982214009099

««« the blooms – so they could observe just the biological effects. Then, following a bloom in one of these patches, they managed to trace its whole life cycle. This enabled them to quantify the role of viruses in the demise of this particular bloom. Their conclusions were verified in data collected in a North-Atlantic research expedition.

The scientists estimated that an algal patch of around 1,000 sq km – which forms within a week or two – can fix around 24,000 tons of organic carbon – equivalent to a similar area of rain forest. Since a viral infection can rapidly wipe out an entire bloom, the ability to observe and measure this process from space may greatly contribute to understanding and quantifying the turnover of carbon cycle and its sensitivity to environmental stress conditions, including marine viruses.

Prof. Ilan Koren's research is supported by the J&R Center for Scientific Research; the Scholl Center for Water and Climate Research; and the estate of Raymond Lapon.

Dr. Assaf Vardi's research is supported by Roberto and Renata Ruhman, Brazil; Selmo Nussenbaum, Brazil; the Brazil-Israel Energy Fund; the Lord Sieff of Brimpton Memorial Fund; the European Research Council; and the estate of Samuel and Alwyn J. Weber. Dr. Vardi is the incumbent of the Edith and Nathan Goldenberg Career Development Chair.

Reading a Biological Clock in the Dark

Proper coordination between our gut bacteria and our biological clocks may be crucial for preventing obesity and glucose intolerance

Our species' waking and sleeping cycles – shaped in millions of years of evolution – have been turned upside down within a single century with the advent of electric lighting and airplanes. As a result, millions of people regularly disrupt their biological clocks – for example, shift workers and frequent flyers – and these have been known to be at high risk for such common metabolic diseases as obesity, diabetes and heart disease. A new study published in *Cell*, led by Weizmann Institute scientists, reveals for the first time that our biological clocks work in tandem with the populations of bacteria residing in our intestines, and that these microorganisms vary their activities over the course of the day. The findings show that mice and humans with disrupted daily wake-sleep patterns exhibit changes in the composition and function of their gut bacteria, thereby increasing their risk for obesity and glucose intolerance.

A consensus has been growing in recent years that the populations of microbes living in and on our bodies function as an extra "organ" that has wide-ranging impacts on our health. Christoph Thaiss, a research student in the lab of Dr. Eran Elinav of the Weizmann Institute's Immunology Department, led this research into the daily cycles of gut bacteria. Working together with David Zeevi in the lab of Prof. Eran Segal of the Computer Science and Applied Mathematics Department, and Maayan Levy of Elinav's lab, he found a regular day-night cycle in both the composition and the function of certain populations of gut bacteria in mice. Despite living in the total darkness of the digestive system, the gut microbes were able to time their activity to the mouse's feeding cycles, coordinating daily microbial activities to those of their host.

The jet-lagged mice stopped eating at regular times, and this interrupted the cyclic rhythms of their internal bacteria

Does this finding have any medical significance? To further investigate, the researchers looked at "jet-lagged" mice, whose day-night rhythms were altered by exposing them to light and dark at different intervals. The jet-lagged mice stopped eating at regular times, and this interrupted the cyclic rhythms of their internal bacteria, leading to weight gain and high blood sugar levels. To verify these results, the scientists transferred bacteria from the jet-lagged mice into sterile mice; those receiving the "jet-lagged microbes" also gained weight and developed high blood sugar levels.

The research group then turned to human gut bacteria, identifying a similar daily shift in their microbial populations and function. To conduct a jet-lag experiment in humans, the researchers collected bacterial samples from two people flying from the US to Israel – once before the flight, once a day after landing when jet lag was at its peak, and once two weeks later when the jet lag had worn off. The researchers then implanted these bacteria into sterile mice. Mice receiving the jet-lagged humans' bacteria exhibited significant weight gain and high blood sugar levels, while mice getting bacteria from either before or after the jet lag had worn off did not. These results suggest that the long-term disruption of the biological clock leads to a disturbance in their bacteria's function that may, in turn, increase the risk for such common conditions as obesity and imbalances in blood sugar levels.

Segal: "Our gut bacteria's ability to coordinate their functions with our biological clock demonstrates, once again, the ties that bind us to our bacterial population and the fact that disturbances in these ties can have consequences for our health."

Elinav: "Our inner microbial »»»

rhythm represents a new therapeutic target that may be exploited in future studies to normalize the microbiota in people whose life style involves frequent alterations in sleep patterns, hopefully to reduce or even prevent their risk of developing obesity and its complications."

Also participating in this research were Gili Zilberman-Schapira, Jotham Suez, Anouk Tengeler, Lior Abramson, Meirav Katz and Dr. Hagit Shapiro in Elinav's lab; Tal Korem in Segal's lab; Prof. Alon Harmelin, Dr. Yael Kuperman and Dr. Inbal Biton of the Veterinary Resources Department, Dr. Shlomit Gilad of the Nancy and Stephen Grand Israel National Center for Personalized Medicine; and Prof. Zamir Halpern and Dr. Niv Zmora of the Sourasky Medical Center and Tel Aviv University.

Dr. Eran Elinav's research is supported by the Abisch Frenkel Foundation for the Promotion of Life Sciences; the Benoziyo Endowment Fund for the Advancement of Science; the Gurwin Family Fund for Scientific Research; the Leona M. and Harry B. Helmsley Charitable Trust; the Adelis Foundation; Yael and Rami Ungar, Israel; the Crown Endowment Fund for Immunological Research; John L. and Vera Schwartz, Pacific Palisades, CA; the Rising Tide Foundation; Alan Markovitz, Canada; Cynthia Adelson, Canada; the estate of Jack Gitlitz; the estate of Lydia Hershkovich; the European Research Council; CNRS - Centre National de la Recherche Scientifique; the estate of Samuel and Alwyn J. Weber; and Mr. and Mrs. Donald L. Schwarz, Sherman Oaks, CA. Dr. Elinav is the Incumbent of the Rina Gudinski Career Development Chair.

Prof. Eran Segal's research is supported by the Kahn Family Research Center for Systems Biology of the Human Cell; the Cecil and Hilda Lewis Charitable Trust; the European Research Council; and Mr. and Mrs. Donald L. Schwarz, Sherman Oaks, CA.

YEDA-XL-Protein GmbH Agreement

YEDA Research and Development Company Ltd., the technology transfer arm of the Weizmann Institute of Science, Israel, and XL-protein GmbH, Germany, a privately owned biopharmaceutical company, have signed a business collaboration agreement to commercialize a PASylated interferon superagonist – PAS-YNSα8 – which has been jointly developed by scientists at the Weizmann Institute and XL-protein. Under this agreement, YEDA acquires the worldwide exclusive rights for marketing and out-licensing of this compound.

One of the potential uses of PAS-YNSα8 is for treating inflammatory diseases, in particular of the central nervous system. An example is multiple sclerosis (MS), a devastating chronic, progressive immune disease of the central nervous system that can eventually lead to paralysis. Among the drugs today used to treat MS are those based on interferon-beta (IFN-beta). Weizmann Institute scientists developed a novel, highly active interferon variant, YNSα8. This modified IFN was engineered to bind much more tightly to the interferon receptors. The result is a very potent molecule, which shows a gene activation profile and biological activities that surpass any naturally existing interferon.

Together with scientists at XL-protein, the activity of PAS-YNSα8 was boosted by extending its half-life in the body using PASylation® technology. PASylation involves the genetic fusion of the therapeutic protein or peptide with a non-structured, expanded polypeptide made of the small amino acids Pro, Ala and Ser (PAS).

Weizmann Institute scientists developed a novel, highly active interferon variant

In a study that appeared in the *Journal of Biological Chemistry* and was led by Dr. Daniel Harari and Prof. Gideon Schreiber at the Weizmann Institute, it was found that the *in vivo* half-life of PAS-YNSα8 was increased 10-fold in comparison to standard interferon. Most importantly, the PASylation did not interfere with the biological activity of this potent IFN; this has been a common technical problem for other methods of extending drug circulation. In a head-to-head comparison with conventional IFN-beta, this long-living superagonist conferred highly improved protection from disease progression in a mouse model of human multiple sclerosis, despite being injected four times less often than IFN-beta and at one-sixteenth of the dosage.

"We are excited by the pronounced therapeutic effect of our PASylated IFN superagonist, which was not accompanied by any observable immunogenic side effects in mice," said Prof. Schreiber. "Our studies suggest that this potential drug could be safe and might provide clinical benefit surpassing that of IFN-beta, all this with a significantly reduced number of injections and lower dosage. We hope it will soon be possible to check the effectiveness of our molecule in clinical trials in humans."

"The biological potency and bioavailability of this novel IFN-based molecule is remarkable. Improved receptor binding, achieved by advanced protein engineering, in synergy with the half-life extension provided by our PASylation technology, will result in more effective and less frequent dosing for the benefit of patients," said Prof. Arne Skerra, CSO of XL-protein and co-author of the study. "We are pleased to forge this business alliance with a renowned partner such as YEDA to commercialize this potent biological drug candidate," added Claus Schalper, CEO of XL-protein.

Prof. Gideon Schreiber and Dr. Daniel Harari acknowledge the generous financial support of Merck Serono for the study in mice with EAE. Prof. Gideon Schreiber's research is supported by the Dana and Yossie Hollander Center for Structural Proteomics, which he heads; and the R Baby Foundation.