The image depicts LUCA as a glowing, complex microbe surrounded by a vibrant microbial community, set against a fiery, primordial Earth transitioning from dark hydrothermal depths to a lighter ocean surface, with subtle DNA-like strands symbolizing its sophisticated genome. See the writeup by Swarnendu Saha for more details.

Insight Digest

In Insight Digest, we showcase simplified summaries of recent research articles in science, to give a feel for what's happening at the frontiers.

Leishmania major-induced alteration of host cellular and systemic copper homeostasis drives the fate of infection

Paul, R., Chakrabarty, A., Samanta, S. et al. Commun Biol 7, 1226 (2024)

Contributed by **Shruti Santosh Sail (DBS, IISER Kolkata)**

Keywords: *Copper, ATP7A, Leishmaniasis, Host-Pathogen Interplay*

Copper plays an intriguing dual role in biology despite being a trace element - a nutrient and a toxin. Copper Metabolism Group from IISER Kolkata explores this duality using the protozoan parasite Leishmania major and how it hijacks host copper pathways to evade immune defenses. The work provides interesting perspectives on potential therapeutic interventions for the tropical disease of Leishmaniasis. Copper toxicity is a powerful weapon that host macrophages use to counteract invading pathogens. They accumulate copper in the phagolysosomal compartments leading to the macrophages generating Reactive Oxygen Species (ROS) that can damage or kill intracellular parasites. However, L. major has managed to evade this threat using interesting tactics revealing that the parasite manipulates two key copper-regulating proteins in host macrophages: ATP7A, which transports copper to pathogen-containing compartments, and CTR1, the primary copper importer. The parasite then induces ATP7A degradation through proteasomal and lysosomal pathways. Simultaneously, CTR1 is downregulated at the transcriptional level and endocytosed, leading to limited copper supply to the macrophage. These multiple strategies ensure its survival within the host.

The researchers observed a remarkable systemic redistribution of copper during the infection, suggesting a reverse strategy by the host to protect itself. The heart, which forms a major copper reservoir, shows downregulation of CTR1, leading to the release of stored copper into systemic circulation. This copper is directed to the infection site, enabling the host to combat the pathogen. It has been observed in mice models that copper supplementation slows down lesion development and reduces parasite load, whereas copper chelation triggers the infection further, highlighting the role of copper as not only a metabolic cofactor but also an active participant in immune defense. So far, new avenues for the treatment of Leishmaniasis have opened up that could target the copper pathways. Modulating copper levels can be done in several ways like by supplementation or selective chelation, and could complement current treatment methods. The idea of combining systemic copper mobilization or developing drugs that mimic this redistribution is another avenue. Such approaches could also help battle the existing problems with drug resistance and toxicity.

Reversion of colorectal cancer cell, a new approach towards anti-cancer therapeutics

J.-R. Gong, C.-K. Lee, H.-M. Kim, J. Kim, J. Jeon, S. Park, K.-H. Cho. Adv. Sci., 12, 2402132 (2025)

Contributed by **Monjuri Hembram (Phd Scholar, IISER Kolkata)**

Keywords: *colorectal cancer, cancer reversion, BENEIN, anti-cancer therapy*

A new approach towards anti-cancer therapy has emerged. Kwang-Hyun Cho and group from Korea Advanced Institute of Science and Technology has found cancer reversion to be effective in treating colorectal cancer. The team has found a trio of master regulators which can transform back colorectal cancer cells into typical healthy enterocytes. Inhibition of the maestro regulators trio consisting MYB, HDAC2, and FOXA2 has been found to collectively induce differentiation while suppressing malignancy. Current research on reversing cancer cells lacks the expertise to understand the mechanism of cellular differentiation and has a restricted systemic approach to discover the key regulators. A computational scheme for single-cell Boolean network inference and control entitled BENEIN was established by Cho and colleagues. It can restore Boolean models of gene regulatory networks (GRNs) and pinpoint a group of master regulators in charge of desired cellular differentiation. The possibility of blocking the master regulators in cancer cells' reversion was validated by in silico study. Based on the in-silico analysis, three different cancer cell lines namely HT-29, HCT-116, and CACO-2 were evaluated in-vitro and in-vivo for cancer reversion upon inhibition of the master regulators. In-vitro analysis showcased decrease in proliferation rate for simultaneous inhibition as compared to the single gene knockouts. In-vivo experiments in knocked down colorectal cancer cell engrafted nude mice model, suggests simultaneous knock down of the master regulators to be successful in reverting colorectal cancer cells. Western blot analysis of healthy enterocyte protein in reverted cancer cells further confirms the successful conversion. Thereby, this study shows a promising approach to colorectal cancer therapy by just converting the cancer cells into healthy ones.

The First Ancestor: How LUCA Shaped Life on Earth

Moody, E.R.R., Álvarez-Carretero, S., Mahendrarajah, T.A. et al. Nat Ecol Evol 8, 1654–1666 (2024)

Contributed by **Swarnendu Saha (Department of Physical Sciences, IISER Kolkata)**

Keywords: *LUCA, evolution, ancient microbes, common ancestor, molecular clock, genetic heritage*

Imagine when Earth was just a young, boiling mass of rock and water, with no plants, animals, or even bacteria as we know them today. Now, picture a tiny, ancient life form—the Last Universal Common Ancestor (LUCA)—swimming in that primordial world, setting the stage for all life on our planet. This new research takes us back 4.2 billion years to uncover LUCA's nature, its environment, and how it kick-started life's evolution.

The study uses cutting-edge molecular clock techniques and phylogenetics (a genetic family tree) to pinpoint LUCA's age to about 4.2 billion years ago—right after Earth became stable enough to support life. LUCA wasn't just a simple blob of organic material. It had a complex genome, roughly 2.5 megabases, coding for around 2,600 proteins—comparable to modern prokaryotes. This means LUCA had a working metabolism, an early immune system, and interactions with other microbes in its environment.

One of the most exciting aspects of this study is how it places LUCA within a broader ecological system. Rather than existing in isolation, LUCA likely lived in a bustling microbial community, shaping the chemistry of early Earth. It thrived as an anaerobic acetogen, producing energy by converting carbon dioxide and hydrogen into acetate, much like some modern bacteria. This metabolic process was crucial because it created a niche for other microbes, including early methanogens, which produced methane, feeding into Earth's early atmospheric and climate systems.

The study also challenges the long-held idea that LUCA lived exclusively in extreme environments like hydrothermal vents. While that remains a possibility, researchers suggest that LUCA might have also existed near the ocean's surface, benefiting from atmospheric hydrogen. This new perspective opens doors to reconsidering how and where life first took hold on our planet.

LUCA represents our shared ancestry with every living thing on Earth—from bacteria to blue whales, fungi to humans. Understanding LUCA helps scientists piece together the grand puzzle of evolution, shedding light on how life emerged and adapted to a changing planet.
This paper goes beyond history—it reveals the intricate connections between life and planetary systems. LUCA's legacy is still alive in every cell today, making this research essential for anyone curious about the origins of life.

Persistent currents in 1-dimensional spin-orbit coupled rings under influence of Zeeman field

Bijay Kumar Sahoo, Subroto Mukerjee, and Abhiram Soori. Phys. Rev. B 110, 195426 (2024)

Contributed by **Bijay Kumar Sahoo (University of Hyderabad)**

Keywords: *Persistent current, spin-orbit coupling, Persistent spin current, mesoscopic ring*

Persistent currents (PCs) can be induced in rings with circumferences smaller than the electron's phase-coherence length by threading magnetic flux through the center of the ring. PCs in mesoscopic rings have been the subject of intense investigation since their proposal by Buttiker, Landauer, and Imry in 1983. In this work, we investigate PC's behavior in spin-orbit coupled rings under the influence of a Zeeman field (without a need for a flux threading the ring), which contrasts with traditional PC observed in rings threaded by magnetic flux. We find that non-zero values of the Zeeman field and spin-orbit coupling are necessary for the emergence of PC in our setup.

Mainly, in ballistic rings, we observe that PC varies inversely with system size, along with PC being zero at half-filling for an even number of sites. At half-filling PC becomes zero, because the current carried by m^{th} electron from the bottom of the bands is the same as the current carried by mth electron from the top of the band, which makes the currents at filling N_e (number of electrons) and $2N\text{-}N_e$ (N being the number of sites in the ring) equal in magnitude and opposite in sign. Moreover, introducing on-site disorder to our setup results in a suppression of PC, with exponential decay observed for large disorder strengths and quadratic decay for smaller disorder strengths. Notably, we find that at half-filling disorder can enhance the PC in individual samples, though the configuration-averaged PC is zero.

Furthermore, we find that the standard deviation of PC increases with disorder strength, reaching a maximum before decreasing to zero at high disorder strengths. We also find that with disorder the PC varies exponentially with system size. We also investigate persistent spin current, which behaves similar to PC except that it is not zero at half-filling. Our findings shed light on the intricate interplay between spin-orbit coupling, Zeeman fields, and disorder in mesoscopic quantum systems, offering new avenues for theoretical exploration and experimental verification.