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From octopus to elephant: a molecular zoo of epigenetics

Christoph Bock's team at the CeMM Research Center for Molecular Medicine at the Austrian Academy of Sciences established a catalog of DNA methylation across 580 animal species. These data enabled a detailed dissection of the evolution of epigenetic regulation and the epigenome. The new study, published in Nature Communications, shows that the characteristic DNA methylation signatures of animal genomes are evolutionarily very old, having emerged long before the first mammals. Surprisingly, DNA methylation in starfish and sharks follows a very similar "code" as in orangutans or humans. This epigenetic code may even help protect against cancer – as indicated by DNA methylation patterns in birds, which rarely develop cancer.

(Vienna, 16 January 2023) Our genes are encoded in the DNA sequence of the genome, which is highly similar across the diverse cell types of our body. Yet, each cell can only access those genes that are in an epigenetically permissive state. The epigenome thus provides a form of molecular access control to the genes – an epigenetic "software" that protects our genetic "hardware" from activation in the wrong cells. This layer of regulatory control has been essential for the development of complex organisms comprising of many hundred different cell types. Moreover, epigenetic regulation helps reduce our risk of cancer by protecting critical areas of the genome from accidental activation.

DNA methylation is the best known and arguably the most important epigenetic mechanism. Methyl groups (CH_3) mark those parts of the DNA that are to be tightly packaged and protected from faulty activation. DNA methylation has many roles throughout our lives – ranging from the fertilized egg to the adult organism, in diseases such as cancer and in the biological aging of our bodies. Christoph Bock, a bioinformatician and genome researcher who is a principal investigator at CeMM and professor at the Medical University of Vienna, explains: "DNA methylation provides the cells with epigenetic memory, ensuring that a liver cell always remains a liver cell and a heart cell always remains a heart cell – even though all cells in our body are equipped with the same genes."

Over 500 animal species epigenetically mapped for the first time

DNA methylation is well-studied only in mammals, most notably in mice and humans. In a decade-long effort to fill critical gaps in our understanding of epigenetics, scientists from Bock's research group at CeMM have now mapped and analyzed DNA methylation profiles across 580 different animal species.

The study's lead authors, Johanna Klughammer and Daria Romanovskaia, together with Amelie Nemc, processed and analyzed a total of 2,443 animal tissue samples. Many of these samples came from the Wildlife Pathology Unit at the University of Veterinary Medicine in Vienna, and from the Ocean Genome

Legacy Center in Boston. In addition, seafood specimens were purchased at Vienna's *Naschmarkt*, and several collaborators provided samples from further animal species including camels and axolotls. "We made sure to get hearts and livers from as many species as possible to facilitate the cross-species comparison. Also lungs, gills, kidneys, brain and more," the authors explained.

DNA methylation more deeply rooted than previously thought

These data show that DNA methylation in animals followed very similar principles 500 million years ago as it does today. Daria Romanovskaia explains: "We looked at the relationship between DNA methylation and the underlying genetic DNA sequence in mammals, birds, reptiles, amphibians, fish and invertebrates. The patterns are very similar. For example, we were able to predict the distribution of DNA methylation in elephants genome using a model we had created for the octopus. These epigenetic patterns therefore very likely existed in the last common ancestor of these animals, a very long time ago."

The fundamental principles of DNA methylation thus appear highly conserved, enabling a deep look at the evolutionary history of vertebrates. However, this does not mean that DNA methylation remained unchanged over millions of years. Christoph Bock explains: "The genetic code of epigenetics looks clearer and more prescriptive in vertebrates than in invertebrates, even though the underlying patterns are similar. And with the emergence of reptiles, birds, and mammals, the genetic determinants of DNA methylation become even more pronounced. It seems that complex animals including humans particularly depend on epigenetic protection of the genome through DNA methylation."

Evolutionary adaptation to complex bodies and environmental conditions?

Large animals with a long lifespan should in theory have a higher risk of cancer, because their bodies consist of many more cells, and these cells have more time to develop into cancer cells. Yet elephants are no more likely to develop cancer than mice or trout. Scientists refer to this as Peto's paradox. The most plausible explanation is that large animals with a long lifespan have evolved special mechanisms that substantially reduce their cancer risk.

Results from the current study indicate that DNA methylation constitutes such a cancer-protective mechanism. Higher theoretical risk of cancer was generally associated with higher DNA methylation levels. This correlation was particularly evident in birds. Most birds have a low risk of cancer, even big birds with a long lifespan such as eagles and penguins. The higher DNA methylation levels in large and long-lived birds may thus help protect them against cancer.

New methods for the analysis of DNA methylation in evolution

Overall, this study provides the most comprehensive analysis of epigenetics in its evolutionary context to date. It also establishes new methods for studying DNA methylation in diverse animal species. For many species, no high-quality

genomes are yet available, which is why the team developed and optimized a method to analyze DNA methylation independently of any reference genomes.

Johanna Klughammer, who is now a professor at the Gene Center of the Ludwig Maximilian University of Munich, explains: “Our new method allows us to explore the interplay of genetics and epigenetics in all those animal species that were hardly accessible for epigenetic analyses. Hopefully, such evolutionary and comparative analyses will lead to a better understanding of epigenetics in humans, in diseases such as cancer, and in healthy aging.”

Photos attached:
Photo 1: A methylated DNA molecule. DNA methylation is a key component of epigenetics and controls which genes of a cell can be activated (© Christoph Bock, CeMM).
Photo 2: The study was based on tissue samples from animals examined at the University of Veterinary Medicine Vienna (© Johanna Klughammer, CeMM).
Photo 3: The study was also based on tissue samples of marine organisms collected by the Ocean Genome Legacy Center in Boston (© Johanna Klughammer, CeMM).
Photo 4: Mapping DNA methylation across 580 animal species at the CeMM Research Center for Molecular Medicine (© Klaus Pichler, CeMM).
Photo 5: Bioinformatic analysis of DNA methylation in its evolutionary context (© Laura Alvarez, CeMM).

The study “Comparative analysis of genome-scale, base-resolution DNA methylation profiles across 580 animal species“ was published on 16 January 2023 in the scientific journal *Nature Communications*, DOI: 10.1038/s41467-022-34828-y.

Authors: Johanna Klughammer*, Daria Romanovskaia*, Amelie Nemc, Annika Posautz, Charlotte Seid, Linda C Schuster, Melissa C. Keinath, Juan Sebastian Lugo Ramos, Lindsay Kasack, Annie Evankow, Dieter Prinz, Stefanie Kirchberger, Bekir Ergüner, Paul Datlinger, Nikolaus Fortelny, Christian Schmidl, Matthias Farlik, Kaja Skjærven, Andreas Bergthaler, Miriam Liedvogel, Denise Thaller, Pamela A. Burger, Marcela Hermann, Martin Distel, Daniel L. Distel, Anna Kübber-Heiss, Christoph Bock
*shared first authorship

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Christoph Bock is a Principal Investigator at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences and Professor of Medical Informatics at the Medical University of Vienna. His research combines experimental biology (high-throughput sequencing, epigenetics, CRISPR screening, synthetic biology) with computational methods (bioinformatics, machine learning, artificial intelligence) – for cancer, immunology, and precision medicine. Before coming to Vienna, he was a postdoc at the Broad Institute of MIT and Harvard (2008-2011) and a PhD student at the Max Planck Institute for Informatics (2004-2008). Christoph Bock is also scientific coordinator of the Biomedical Sequencing Facility of CeMM and MedUni Vienna, co-lead of the “Organoid Cell Atlas” network within the Human Cell Atlas, fellow of the European Lab for Learning and Intelligent Systems (ELLIS), and elected board member of the Young Academy in the Austrian Academy of Sciences. He has received important research awards, including an ERC Starting Grant (2016-2021), an ERC Consolidator Grant (2021-2026), the Otto Hahn Medal of the Max Planck Society (2009), the Overton Prize of the International Society for Computational Biology (2017), and the Erwin Schrödinger Prize of the Austrian

Academy of Sciences (2022). He has been included in the global list of “Highly Cited Researchers” by Clarivate Analytics (ISI Web of Science) in each year since 2019.

The **CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences** is an international, independent and interdisciplinary research institution for molecular medicine under the scientific direction of Giulio Superti-Furga. CeMM is oriented towards medical needs and integrates basic research and clinical expertise to develop innovative diagnostic and therapeutic approaches for precision medicine. Research focuses on cancer, inflammation, metabolic and immune disorders, and rare diseases. The Institute's research building is located on the campus of the Medical University and the Vienna General Hospital.
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Medical University of Vienna (MedUni Vienna) is one of the most traditional medical education and research facilities in Europe. With almost 8,000 students, it is currently the largest medical training centre in the German-speaking countries. With 6,000 employees, 30 departments and two clinical institutes, 13 medical theory centres and numerous highly specialised laboratories, it is one of Europe's leading research establishments in the biomedical sector. MedUni Vienna also has a medical history museum, the Josephinum.. www.meduniwien.ac.at

For further inquiries, please contact:
Anna Schwendinger
Head of PR & Communications

CeMM
Research Center for Molecular Medicine
of the Austrian Academy of Sciences
Lazarettgasse 14, AKH BT 25.3
1090 Vienna, Austria
Phone +43-1/40160-70 092
Fax +43-1/40160-970 000
aschwendinger@cemm.oeaw.ac.at
www.cemm.at