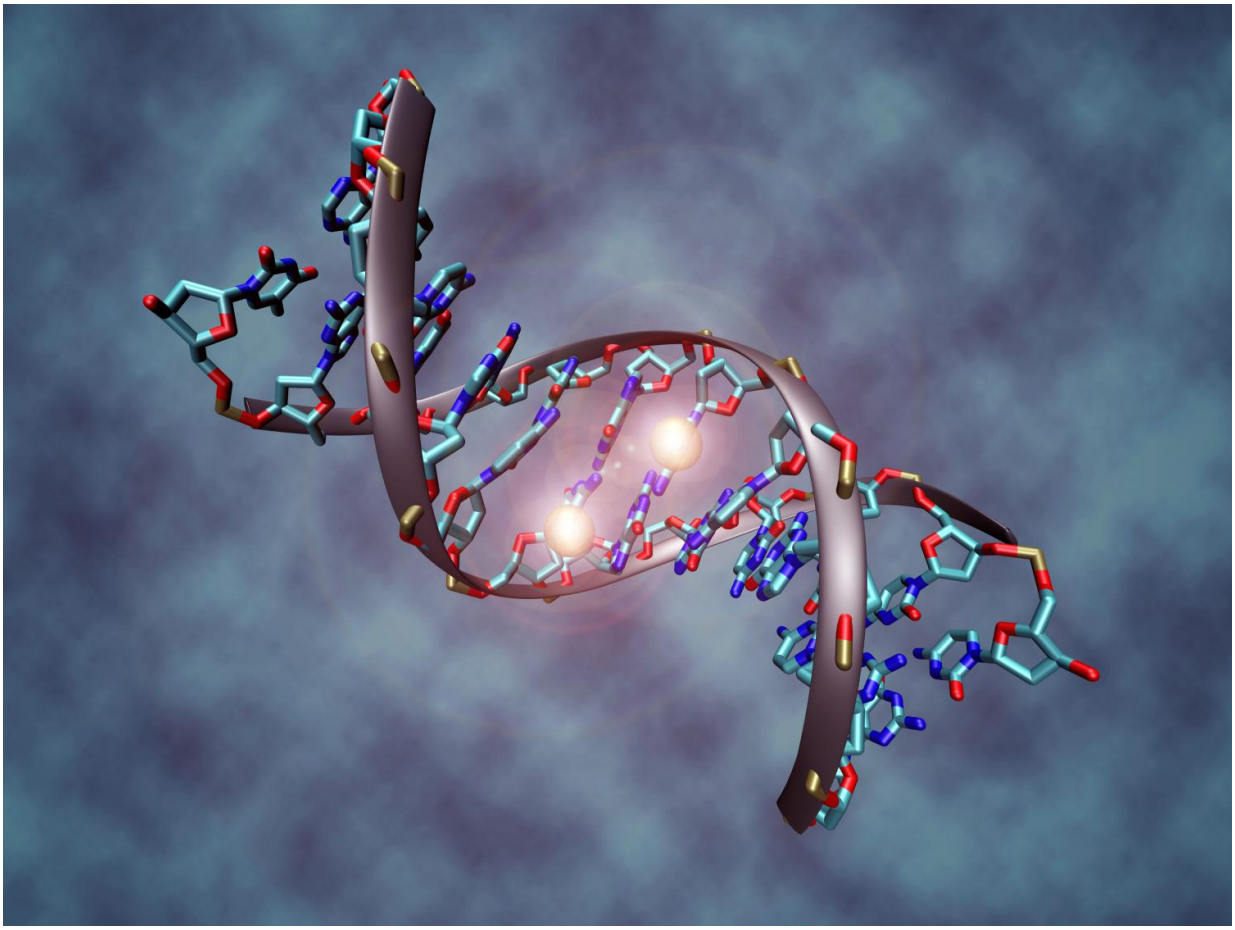
Epigenetic diversity in childhood cancer

January 30 2017



Artistic rendering of a methylated DNA molecule. Credit: Christoph Bock/CeMM

Tumors of the elderly, such as breast cancer and colon cancer, accumulate thousands of DNA mutations. These genetic defects

contribute to cancer-specific properties including uncontrolled growth, invasion in neighboring tissues, and evasion from the immune system. Similar properties are also found in childhood cancers, although those tumors carry much fewer genetic defects, making it difficult to explain their clinical heterogeneity.

This is particularly true for Ewing sarcoma, an aggressive bone cancer in children and adolescents. A single genetic defect - the EWS-ETS fusion - is present in all tumors, initiating cancer development and defining Ewing sarcoma as a disease. But the tumors carry very few DNA mutations that could explain the observed differences in the disease course of Ewing sarcoma patients. Tackling this question, a team of scientists from Austria, France, Germany and Spain led by Eleni Tomazou from the St. Anna Children's Cancer Research Institute in Vienna profiled many Ewing tumors. They found that the disease's clinical diversity is reflected by widespread epigenetic heterogeneity.

Using novel bioinformatic methods developed by Nathan Sheffield at CeMM, the team studied the tumors' DNA methylation patterns - one of the most important facets of the human epigenome. Ewing sarcoma showed unique characteristics that differ markedly from others cancers, and the DNA methylation patterns also varied between patients. Moreover, the researchers found that Ewing sarcoma tumors appear to retain part of the characteristic DNA methylation patterns of their cell-of-origin.

Thus, the diverse clinical courses observed among Ewing sarcoma patients may be explained epigenetically: As DNA methylation influences gene activity, the combination of Ewing sarcoma specific and cell-of-origin specific patterns can lead to different outcomes. The epigenetic diversity also appears to correlate with the tumors' aggressiveness and metastatic state.

Scientists at the laboratory of Heinrich Kovar. Credit: CCRI

Regarding the future of Ewing sarcoma treatment, Heinrich Kovar, Scientific Director of St. Anna Children's Cancer Research Institute, optimistically stated: "These new insights into the biology of Ewing sarcoma provide the basis for developing epigenetic biomarkers that can reliably predict disease course and therapy response. After two decades of stagnation in the therapy for patients with Ewing sarcoma, we expect new impulses for personalized therapy of this aggressive cancer".

"Our findings in Ewing sarcoma also provide an interesting concept for other cancer with low genetic complexity", Christoph Bock, Principal Investigator at CeMM, adds. "In the era of precision medicine,

understanding the causes and consequences of tumor heterogeneity will be crucial to develop personalized therapies. Only with precise knowledge of the molecular mechanisms underlying each tumor, we can hope to treat in a targeted way and with far fewer side effects."

More information: Nathan C Sheffield et al, DNA methylation heterogeneity defines a disease spectrum in Ewing sarcoma, *Nature Medicine* (2017). DOI: 10.1038/nm.4273

Provided by CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences