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An appreciation of Sir Adrian Peter Bird: winner of the Charles Rodolphe Brupbacher Prize for Cancer Research 2017

Josef Jiricny

Institute of Molecular Life Sciences, University of Zurich, Switzerland, and Institute of Biochemistry, ETH, Zurich, Switzerland

The Watson-Crick model of DNA consists of two anti-parallel sugar-phosphate chains that are held together in the double helix by pairs of complementary bases: adenine/thymine and guanine/cytosine. But DNA of most organisms also contains a fifth base, 5-methylcytosine, first described in 1925 by Johnson and Coghill as a constituent of nucleic acid isolated from *Mycobacterium tuberculosis*. The biological roles of 5-methylcytosine remained enigmatic for many years until the demonstration that it is a key component of the bacterial restriction/modification system, which brought Werner Arber, Daniel Nathans and Hamilton Smith the 1978 Nobel Prize in Physiology or Medicine, and made restriction enzymes the primary tools of molecular biology. Four decades have passed since then, but the role of 5-methylcytosine in eukaryotic DNA metabolism is still shrouded in mystery. We know that the sperm methylation pattern is largely erased after fertilisation and that methylation is gradually reintroduced during embryogenesis and differentiation, but the processes that regulate the cell type- and tissue-specific methylation patterns remain to be elucidated. We have also learned that DNA can be not only methylated, but also demethylated, and that aberrant methylation can lead to disease – including cancer. Again, how these processes are regulated remains to be discovered. However, we have learnt a great deal about 5-methylcytosine metabolism during the past three decades, and much of our knowledge came from the laboratory of Adrian Bird.

Adrian spent his doctoral and postdoctoral time in Max Birnstiel's laboratory, first in Edinburgh and then in Zurich, studying the amplification of ribosomal DNA in *Xenopus laevis*. In this organism, genomic rDNA in somatic tissues is highly methylated, whereas the extrachromosomal amplicons are unmethylated. When he returned to Edinburgh to establish his own group, Adrian set out to study the methylation pattern of these loci using the newly available methylation-sensitive restriction enzymes. Moving from frogs to sea urchins to mice, he noted that, whereas genomic DNA was largely resistant to cleavage with *Hpa*II, a restriction enzyme inhibited by methylation, a small fraction was cut into very small fragments, which he called *Hpa*II tiny fragments, or HTF islands. These genomic features, later renamed CpG islands, were subsequently shown to be frequently associated with active housekeeping genes and to be generally unmethylated. Their aberrant methylation, for example in cancer cells, resulted in transcriptional silencing, and Adrian was able to show that the latter phenomenon was linked to the binding of factors displaying high affinity for densely methylated DNA. These polypeptides share a conserved "methylated-CpG binding domain", and have many interesting biological roles. Thus, MBD2 and MBD4 have been shown to suppress intestinal tumourigenesis. However, one member of this protein family, MeCP2, stands out from the rest. Adrian's laboratory established a knock-out mouse model and noted that its pathology was reminiscent of that seen in individuals affected with a severe neurological disorder, Rett syndrome (RTT), which affects around one person (predominantly female) in 10 000. Indeed, RTT patients could be shown to carry mutations in the *MeCP2* gene. Importantly, the Bird laboratory showed that the resulting severe neurological phenotype is reversible when the protein is re-expressed, which promises that the Rett syndrome might be curable in the future.

Adrian has unquestionably made a major contribution, not only to our understanding of DNA methylation, but also to the entire field of epigenetics, which plays a key role in development and in disease. But his influence is much broader than that. He is a role model for young scientists as a teacher, as a tutor and as a member of numerous advisory boards. He is also a member of key strategic bodies that decide on the future of scientific research. With people like Adrian at the helm, the ship of science need not fear even the stormiest seas.

The Charles Rodolphe Brupbacher Prize for Cancer Research

Biennially, the Charles Rodolphe Brupbacher Prize for Cancer Research is awarded to scientists who have made extraordinary contributions to basic oncological research. The Charles Rodolphe Brupbacher Prize for Cancer Research 2017 has been awarded to Sir Adrian Peter Bird, PhD for his contributions to our understanding of the role of DNA methylation in development and disease. A review article based on his award lecture has been published in

Correspondence:
Professor Josef Jiricny, Institute of Molecular Life Sciences, UZH, Institute of Biochemistry, ETHZ, Otto-Stern-Weg 3, CH-8093 Zürich, jjiricny@ethz.ch

Figure 1: The logo of the Brupbacher foundation.

Swiss Medical Weekly [1]. This viewpoint is based on the laudatio held in Zurich, Switzerland, during the CRB Symposium 2017.

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Reference

1 Bird A. Genetic determinants of the epigenome in development and cancer. Swiss Med Wkly. 2017;147:w14523. https://smw.ch/en/article/doi/smw.2017.14523