Foreword

The replacement of uracil with its methylated derivative, thymine, in relevant polynucleotides was a major step in the generation of a robust carrier of genetic information. However, substantial misincorporation of dUMP residues instead of TMP during DNA replication, as well as mutagenic hydrolytic deamination of cytosine to uracil in DNA, remains as threats to genetic stability and requires continuous correction by DNA editing and DNA repair by special mechanisms. In recent years, it has become clear that such DNA lability is not only a problem of genomic stability but can be of physiological advantage in targeted processing of immunoglobulin genes to provide expanded antibody diversity, and epigenetic oxidative processing of 5-methylcytosine residues during organ differentiation. This makes the study of uracil in DNA of topical interest.

DNA repair research has been a strong field in Norway for decades, thanks to the eminent research groups of Hans Krokan in Trondheim and the late Erling Seeberg in Oslo. An early key contribution from the Krokan group was the isolation from human tissues of large amounts of the low abundance repair enzyme that specifically excises uracil from DNA, the DNA glycosylase UNG. This heroic effort provided the key to the cloning and sequencing of the relevant gene, and subsequent studies of its physiological expression. Hans Krokan, Geir Slupphaug and their key collaborators in Trondheim have continued to make highly relevant contributions to the investigation of the roles of uracil residues in DNA and here provide a broad overview, including the presumed intriguing role of uracil in polynucleotides during the origin of life.

An important aspect of understanding the roles of uracil in DNA concerns the mode of action of the widely used anticancer drug 5-fluorouracil. In a classical achievement of translational research, Charles Heidelberger postulated that a compound such as 5-fluorouracil might interfere with the synthesis of DNA pyrimidine precursors and therefore act as an anticancer agent. When the compound was synthesised and tested, it was found to have profound activity as a useful drug, and it remains a mainstay of drug treatment of several forms of cancer. From this success, it was deduced that the proposed mode of action of 5-fluorouracil had been established, although subsequent studies have only provided controversial support for the model. Recently, Slupphaug and Krokan have obtained new data and propose that the main effect of the drug is due to an entirely different mechanism involving incorporation of 5-fluorouracil residues into DNA to generate toxic base pairs with guanine in the complementary DNA strand. This new approach may improve our understanding of the role of 5-fluorouracil in therapy. It is only one of several recent advances in this area. The present timely volume should be very helpful to understanding the broad implications, positive as well as negative, of the transient occurrence of uracil residues in DNA.

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