5-formyl deoxycytosine (5-f-dC) pairs with dG, but also is capable of mispairing with both dA anddT; in the latter case, at a level that is 3-4 times higher than either unmodified dC or 5-Me-dC (1). Consequently, 5-formyl-dC is highly mutagenic, capable of driving both C-to-T transitions and C-to-A transversions (1). However, current research interest in 5-formyl-dC is focused, not on its mutagenic properties, but rather on its potential role as an intermediate in a putative (active) oxidative demethylation pathway for conversion of 5-Me-dC to dC. Demethylation of 5-Me-dC is necessary for epigenetic control of gene expression in the cell, and plays a key role in cellular reprogramming, embryogenesis, establishment of maternal and paternal methylation patterns in the genome (2), and also in certain autoimmune disorders and cancer (3). Recent observations of the presence of 5-hydroxymethyl-dC (5hm-dC) in a variety of tissues, most notably neuronal cells (4,5), and the discovery of an enzymatic pathway for conversion of 5-Me-dC to 5hm-dC, mediated by the enzyme Tet1 (6), has spurred efforts to determine whether or not 5-hm-dC is then subsequently converted to dC through a 5-formyl-dC intermediate. In 2011, Ito and co-workers showed that Tet enzymes are able to convert 5hm-dC to 5-formyl-dC, and also observed the presence of 5-formyl-dC in mouse embryonic stem cells and various mouse organ tissues. Genomic content of both 5hm-dC and 5-formyl-dC can be modulated through overexpression or depletion of Tet proteins in these tissues (7). These experiments provide strong supporting evidence for DNA demethylation occurring via a Tet-mediated enzymatic pathway involving 5-formyl-dC as a key intermediate. 5-formyl-dC modified oligos can serve as important research tools for probing the DNA demethylation process.

References
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