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Epigenesis, methylation and single strand breaks

In vivo enzymatic methylation of cytosine in DNA is one molecular mechanism of epigenetic modification of gene expression. Epigenetic imprinting refers to the silencing of the genes from one parent, accomplished by DNA inactivation. The pathway following chemical methylation is: methylation of a purine → apurinic sites → single strand breaks → double strand breaks (scission). Our studies of *in vitro* methylation of DNA isolated from the bacterium *Bacillus subtilis* indicate that single strand breaks account for all the inactivation of methylated purines. The methylating agent was the chemical mutagen Methyl Methane Sulfonate (MMS). Biological inactivation was detected by decrease in transforming activity at the indole locus. Single strand breaks were detected by sedimentation velocity analysis of denatured DNA. DNA methylated to 1, 3 and 5 inactivating hits/locus and denatured, gave S_{20} values of 17.8, 11.2 and 6.8, respectively, compared to 33 for denatured untreated control DNA. The S_{20} value and molecular weight of native double stranded DNA that had been alkylated to the same level showed no such decrease, indicating that the double stranded DNA molecule remained intact, despite the single strand breaks. Control studies with the enzyme DNase, known to cause single strand breaks exclusively, produced the same S_{20} value fragments after denaturation, when treated to the same level of inactivation. Since single strand breaks appear to account for all inactivation by MMS, it follows that alkylated purines or apurinic sites cannot account for any inactivation. This supports the methylation of cytosine at CpG sites as the epigenetic inactivating event.

Biography

Rosemarie Wahl has earned her BS degree in Quantitative Biology from MIT, MS degree in Biochemistry and a PhD in Microbiology from the University of Chicago. She has been a Faculty Member at the University of Illinois at Chicago Circle, Texas Christian University, the University of Texas at Austin and St Mary's University. She was Chair of the Department of Biological Sciences at St Mary's University for 25 years (1979-2004) and is currently Professor of Biology. Her research contributions are in the molecular structure of bacterial viruses, the chemical basis of genetic mutation and the mechanism of DNA replication.

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