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Methyl group, hyperconjugation and human diseases

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Abstract

Methylations are widespread in the biological kingdom. However, their chemical and biochemical roles have not been fully dissected. A hypothesis was put forward previously in which methylation is proposed to lead to hyperconjugation, whose electron donating feature weakens the chemical bonds and increases the bond lengths of C-N, therefore resulting in stronger secondary bonding between nitrogen atoms and cations or protonation of nitrogen atoms. Consequently ion homeostasis of the cells is compromised giving rise to certain diseases. Protonation of nitrogen atoms in 5-methyl cytosine enhances interaction with negatively charged phosphate groups and contributes to the formation of heterochromatin.

Keywords

methylation; hyperconjugation; electron delocalization, human diseases

DNA methylation has been linked to cancer, atherosclerosis and aging.[1-3] Histone methylation is also related to aging, neurodegenerative illnesses, and intellectual debility such as Rubinstein–Taybi Syndrome and X-linked mental retardation. [4-8]

DNA methylation mostly arises at the carbon-5 position of a cytosine base. It underlies transcriptional repression, and is a fundamental feature of heterochromatin [9]. CpG islands typically appear in gene promoters. They are often devoid of methylation allowing gene activation [10-13]. Methylation enables hyperconjugation with adjacent carbon atoms, and the higher electron density in C⁴ indicated by NMR data in comparison to cytosine extends C⁴-N bond length [14-16], allowing easier protonation in the nitrogen atom and generation of a positive charge.[16-18] The electrostatic interactions between charged amino groups and negatively charged phosphate groups generate compact DNA and contribute to the formation of heterochromatin, consequently repressing gene expression. The protonation in the amino nitrogen of 5-methyl cytosine can hasten C to T transition mutations, accelerating evolution and speciation.

Methylation of lysine 9 of histone H3 has been associated with constitutively transcriptionally silent chromatin. Yet, tri-methylation of histone H3 at lysine 4 is strongly linked with transcriptional activation. Tri-methylation here would bring about a positive charge on the tail. However, the electron delocalization of 3 electron-donating methyl groups can effectively reduce the positive charge and stabilize lysine 4 of histone H3.

Conflict of interest

None declared.

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Fig 1. Chemical perspective of cytosine methylation.