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Editorial

DNA Methylation and Its Application in IBD

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DNA methylation is an important process where small chemical groups called methyl groups are added to the DNA. This change can affect how certain parts of DNA work without changing the DNA sequence. When DNA methylation happens in a gene promoter, it usually stops the gene from being expressed. In mammals, this process is very important for normal growth. It is involved in several key functions in the body, such as controlling genes from both parents (genomic imprinting), shutting down one X chromosome in females (X-chromosome inactivation), preventing certain genes from moving around (suppressing transposable elements), aging, and the development of cancer (1).

DNA methylation is an important regulatory mechanism for suppressing transcription, especially in regions with high concentrations of CpG dinucleotides. This mechanism mainly affects protein-coding genes that require long-term and extensive silencing (2, 3). DNA methylation is not essential for repressing transcription, but it is believed to create a "locked" state that effectively stops transcriptional activity (4). Since 2016, adenine and cytosine have been identified as the primary nucleobases undergoing natural enzymatic DNA methylation (5) The conventional use of thymine solely in DNA and uracil exclusively in RNA can also have advanced as an error-control mechanism, to facilitate the elimination of uracils generated with the aid of the spontaneous deamination of cytosine. The methylation of cytosine to provide 5-methylcytosine happens at the equal site on the pyrimidine ring-the 5 positions-in which the methyl group of thymine is determined. This unique position serves to distinguish thymine from uracil, the corresponding RNA base, which no longer possesses a methyl group. Upon spontaneous deamination, five-methylcytosine is converted into thymine, main to a T:G mismatch. Ultimately, repair mechanisms are brought on to rectify this mismatch, both by way of reinstating the unique C:G pairing or through changing G with A, thereby changing the original C:G pair into a T: A couple and resulting in a mutation. If this faulty base incorporation stays uncorrected and the cell progresses into the cellular cycle, the strand containing T may be paired with an A in one of the daughter cells, thereby solidifying the mutation as an everlasting alteration (6, 7). The high ranges of CpG methylation inside the genome deliver an evolutionary burden, as they in-

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crease the chance of spontaneous mutations. Cytosines often go through the loss of amino groups, with various implications based totally on their methylation status. Over the years, methylated cytosine residues tend to deaminate, converting into thymine residues, which results in a slow transformation of CpG dinucleotides into TpG dinucleotides, a phenomenon pondered in the decreased incidence of CpG dinucleotides in the human genome (8). Conversely, the spontaneous deamination of unmethylated cytosine residues outcomes in the formation of uracil residues, a change that is directly detected and repaired via cell mechanisms **(Figure 1)**. In mammals, the only exception to the significant depletion of CpG sites takes place within a distinct class of sequences known as CpG islands, which can be characterized by their richness in GC and CpG content (9). Within somatic tissues, a trifling 10% of these CpG islands showcase methylation, with the majority located in both intergenic and intragenic regions (10, 11). This change is facilitated through a collection of enzymes called DNA methyltransferases (DNMTs) (12). The effect of DNA methylation on gene expression takes place via primary mechanisms: maintenance methylation and de novo methylation. Maintenance methylation performs an essential role in ensuring the continuity of DNA methylation throughout successive rounds of cellular DNA replication. In the absence of DNMT, the replication system would yield daughter strands that lack methylation, leading to a gradual process of passive demethylation (13-15). In mammals, the patterns of DNA methylation go through considerable changes throughout generations, characterized by means of a significant erasure accompanied by re-establishment. The majority of parental methylation marks are eliminated throughout gametogenesis and again inside the early stages of embryogenesis, with processes of demethylation and the next remethylation happening at each phase. During early embryogenesis, demethylation transpires in distinct stages all through the preimplantation duration: first in the zygote and subsequently throughout the preliminary embryonic divisions of the morula and blastula. Following this, a wave of methylation happens in the course of the implantation phase, in which certain CpG islands are safeguarded against methylation, main to a worldwide repression that helps the expression of housekeeping genes across all cells. Inside the post-implantation phase, the methylation patterns come to be specific to each developmental

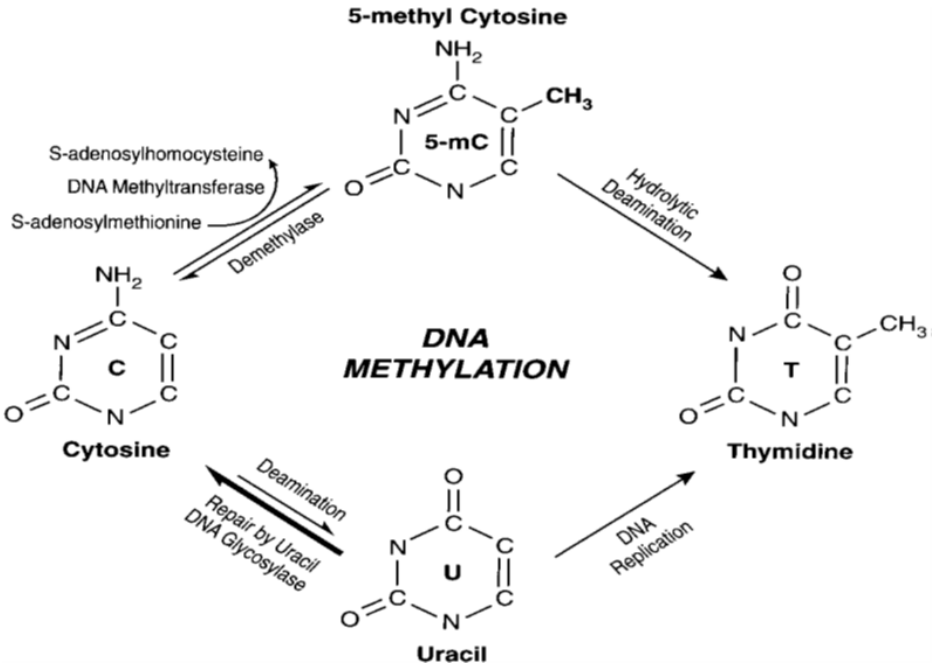

Figure 1. Schematic representation of the biochemical pathways for cytosine methylation, demethylation, and mutagenesis of cytosine and 5-mC.

level and tissue type, with enduring modifications that define the characteristics of each cell type over a prolonged period (16, 17).

Inflammatory bowel disease (IBD) represents a chronic and recurring inflammatory disorder of the gastrointestinal tract, that's connected to a heightened probability of colon cancer improvement. This situation encompasses Crohn's disease (CD) and ulcerative colitis (UC) and is characterized by its problematic nature, with the underlying mechanisms nevertheless not completely elucidated. Studies carried out on populations have found that IBD is formed through a mixture of environmental, genetic, immune, and gut microbiome factors. Further to improve the information on the disorder's pathophysiology, numerous tasks have been released to discover the molecular mechanisms related to diverse advanced treatment options for IBD and to pinpoint predictive biomarkers for remedy. Epigenetics has emerged as a considerable attention in the realm of molecular mechanisms, highlighting its significance in contemporary studies (18).

The changes related to epigenetics are identified for their important functions, probably establishing a connection among environmental elements, known as the exposome, and the biological underpinnings of diseases, thereby presenting insights into the elusive factors of heritability in IBD genetics. Among these changes, DNA methylation has garnered extensive interest in current research. Some of the genes that undergo methylation are implicated in the endurance of IBD, prompting investigations into their viability as diagnostic, prognostic, and therapeutic indicators for the circumstance. This exploration can also enhance scientific decision-making strategies and present direct options for remedy. The expression stages of genes related to IBD can be notably motivated by using alterations in methylation status, which in turn might also affect the ailment's development and progression. Studies into multigene DNA methylation in IBD have discovered significant variability among the recognized genes. Considerably, numerous pathways, such as IL 12/IL 23, Wnt, IL 6-associated STAT3/SOCS3, and apoptosis signaling pathways, were identified as interconnected. At the same time as the proper function of DNA methylation in IBD stays inadequately characterized, it is acknowledged as a measurable, dynamic, and usually strong epigenetic mechanism, making it a promising candidate for the development of diagnostic and prognostic biomarkers. Therefore, the states of DNA methylation have been related to diagnostic and prognostic applications that maintain therapeutic importance, mainly in advancing the field of precision medicine (19).

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