**[A vitamin-C-derived DNA modification catalysed by an algal TET homologue]**

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**Key Words:**

TET， methylation, vitamin C, 2-oxoglutarate

**[Abstract ]Sequential oxidation of 5mC by ten-eleven translocation (TET) dioxygenases results in a cascade of additional epigenetic marks and promotes demethylation of DNA in mammals. However, the function of TET homologues still remains much to explore. The scientists found that the green alga,which contains the 5mC-modifying enzyme (CMD1), a kind of TET homologues use l-ascorbic acid (vitamin C) as an essential co-substrate whereas others usually use 2-oxoglutarate as a co-substrate.and then propose a completely new mechanism of glycerol modification of 5 mC methyl with vitamin C as substrate catalyzed by TET homologous protein CMD1 .**

**Introduction**

[ DNA methylation refers to the chemical modification of a methyl group by covalent bonding of a specific base in DNA sequence. It is a ubiquitous way of DNA modification in organisms. DNA methylation is one of the core research fields of epigenetics, which can alter genetic performance without altering DNA sequence. Current studies have shown that DNA methylation is closely related to genomic imprinting, X chromosome inactivation, transposon inhibition, aging and cancer occurrence, so it is one of the focuses and hotspots of epigenetics research.

TET (ten-eleven translocation) protein is a kind of alpha-ketoglutarate (alpha-KG) and Fe2+ dependent dioxygenase existing in organisms. It has a catalytic domain near C. Pyrimidine (5-mC) is converted to 5-hydroxymethyl cytosine (5-hmC), which is an important enzyme in DNA demethylation and plays an important role in maintaining the pluripotency of stem cells. The mutation of TET gene can cause many kinds of tumors, especially hematopoietic tumors.

 The scientists found that the green alga,which contains the CMD1, use vitamin-c as an essential substrate whereas others usually use 2-oxoglutarate as a substrate.

**Recent Progress**

[the international authoritative academic journal Nature published on-line the research achievement "A vitamin-C-derived DNA modification catalyzed by an algal TET homologue" which was completed by several Chinese scientists. In this study, a novel TET homologous protein was identified for the first time in Chlamydomonas reinhardtii, a single-cell eukaryotic organism, and it was found that the protein could transfer the carbon skeleton of vitamin C to DNA and produce a new DNA modification. The mechanism of vitamin C directly participating in the DNA modification was elaborated, and the important role of this protein and its DNA modification in regulating the photosynthesis of Chlamydomonas reinhardtii was revealed.

Here are how they determine TET homologous gene CMD1 performs its modification of methyl groups in 5mC. Firstly, eight TET homologous genes, such as CMD1, were identified in Chlamydomonas reinhardtii. The common feature of the homologous genes is that they have a conserved iron-binding HxD motif in dioxygenase, but do not have the binding site of ketoglutarate (2-OG). As ketoglutarate is the common substrate of dioxygenase, it is suggested that TET homologous gene in Chlamydomonas reinhardtii may involve a novel DNA methylation modification mechanism. In vitro enzymatic activity assay, the researchers detected that methyl groups of 5mC were modified under the catalysis of CMD1 enzyme to produce two unknown substances. Using nuclear magnetic resonance (NMR), the researchers finally determined that the two unknown substances were 5gmC isomers, i.e. a glycerol group was added to the methyl of 5mC through the C-C bond. The 5mC modified substrates in mammals are derived from ketoglutarate, and the glycerol groups catalyzed by CMD1 enzyme were identified from the substrates by a series of isotope labeling experiments. Therefore, a novel mechanism of glycerol modification of 5mC methyl with vitamin C as substrate catalyzed by TET homologous protein CMD1 in Chlamydomonas reinhardtii

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**Discussion**

[To elucidate the role of this mechanism in the physiological process of Chlamydomonas reinhardtii, the CMD1 mutant of Chlamydomonas reinhardtii was obtained by CRISPR/Cas9 technology. The mutant showed a high light intolerance phenotype. The absence of light harvesting complex stress-related gene LHCSR3 in npq4 mutant inhibits non-photochemical quenching (NPQ), an important mechanism for resisting light damage in high light. Further studies showed that the expression level of LHCSR3 was down-regulated in the CMD1 mutant, which was consistent with the hypermethylation of the 5'end of the LHCSR3 sequence compared with the wild type. These results indicate that CMD1 gene-mediated 5gmC modification mechanism can regulate the expression of LHCSR3 gene through demethylation, thus affecting the adaptability of Chlamydomonas reinhardtii to high light intensity. However, the sample selection of this experiment is not large enough, and the universality of the experimental results needs further confirmation.

In this study, Chlamydomonas reinhardtii, a single-celled green algae, was used as experimental material to reveal that TET homologous proteins in eukaryotes have a novel DNA methylation modification mechanism, which can directly regulate gene expression, thus affecting vital physiological functions such as photosynthesis. This study has important reference value for elucidating the mechanism of TET protein in Chlamydomonas reinhardtii in the study of DNA methylation in eukaryotes.

Futhermore, Are there similar mechanisms in other organisms, and how do they affect organisms? This is just the beginning. ]

**References**

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