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P^{53} and GADD45A: a new mechanism regulating TET-mediated epigenetic modulation

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Abstract

Epigenetic changes, including DNA methylation and histone modifications, play a profound role in cellular differentiation and cancer cells. Recently a new modified DNA base, 5-hydroxymethylcytosine (5hmC), was found in mammalian DNA, raising questions as to its role in mediating epigenetic control of gene expression. 5hmC constitutes a significant portion of nucleotides in brain cells (~0.6% of total nucleotides in Purkinje cells and ~0.2% in granule cells) and embryonic stem cells (~0.032%). 5hmC can be derived from the oxidation of 5-methylcytosine (5-mC) in a reaction catalyzed by one of three TET family members, TET1, TET2, and TET3. The TET protein-mediated cytosine modifications are involved in regulating embryonic stem (ES) cell pluripotency, tissue homeostasis, and disease pathogenesis. Here we show that the zebrafish ortholog of Tet3 plays an essential role in early development, and the loss of Tet3 leads to significant developmental arrest. We find that GADD45A biochemically and genetically interacts with TET proteins in both zebrafish and mammalian cells, functioning as a cofactor of TET proteins to regulate TET enzymatic activity for DNA demethylation via 5hmC modification. Furthermore, we show that p53 is involved in the regulation of TET-mediated epigenetic modifications, likely by controlling GADD45A expression. These findings together reveal a new mechanism involving p53 and GADD45A that regulates TET-mediated epigenetic modulation.

Biography

Yujing Li received his Ph.D Institute of Genetics, Chinese Academy of Sciences Beijing. He is a senior scientist at the Department of Human Genetics, Emory University School of Medicine. He has published more than 35 papers in reputed journals and is serving as editor-in-chief of Human Genetics and Embryology: Current Research and editorial board members of Cloning and Transgenesis and journal of Gene Therapy.