曹雪涛院士团队发现免疫炎症平衡调控新机制

Xuetao Cao’s team Revealed the Mechanism for Inflammatory Response in an Enzymatic Activity-independent Way

1 月 24 日，医学免疫学国家重点实验室主任曹雪涛院士团队在《Nature》期刊发表文章揭示，DNA 修饰酶 Tet2 分子通过调控 RNA 修饰的新方式。这一机制能够促进机体增加天然免疫细胞的数量和功能，以应对病原体感染及其炎症反应。

研究团队从表观转录组的角度研究了 RNA 修饰在天然免疫与炎症中的作用，发现 DNA 羟甲基化酶 Tet2 能够作为一种 RNA 结合蛋白作用于免疫分子 mRNA 水平，进而促进感染状态下机体外周血天然免疫细胞的数量增加，利于病原体的清除。

他们利用紫外交联免疫共沉淀结合高通量测序（CLIP-seq）和单个核苷酸分辨率的全转录组 RNA 甲基化测序等 RNA 相关组学技术，进一步在分子机制上揭示了 Tet2 能够直接结合免疫信号通路负调控分子 Socs3 的 mRNA 的 3`-UTR，并抑制该区域 RNA 胞嘧啶甲基化，促进了 Socs3 mRNA 的降解，达到了负负得正的效果，促进了机体在感染早期天然免疫细胞的发生及其功能。

这一最新发现不仅从免疫学角度为机体抵抗病原体感染的天然免疫机制提出了新观点，也在表观机制层面揭示了 Tet2 参与基因表达转录后调控的新模式，为有效防治感染性疾病和控制炎症性疾病提供了新思路和潜在药物研发靶标。

Tet2 promotes pathogen infection-induced myelopoiesis through mRNA oxidation

DNA 羟甲基化酶 Tet2 通过调控 RNA 修饰促进天然免疫细胞数量增加

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Varieties of RNA modification form the epitranscriptome for post-transcriptional regulation. 5-Methylcytosine (5-mC) is a sparse RNA modification in messenger RNA (mRNA) under physiological conditions. The function of RNA 5-hydroxymethylcytosine (5-hmC) oxidized by ten-eleven translocation (Tet) proteins in Drosophila has been revealed more recently. However, the turnover and function of 5-mC in mammalian mRNA have been largely unknown. Tet2 suppresses myeloid malignancies mostly in an enzymatic activity-dependent manner, and is important in resolving inflammatory response in an enzymatic activity-independent way. Myelopoiesis is a common host immune response in acute and chronic infections; however, its epigenetic mechanism needs to be identified. Here we demonstrate that Tet2 promotes infection-induced myelopoiesis in an mRNA oxidation-dependent manner through Adar1-mediated repression of Socs3 expression at the post-transcription level. Tet2 promotes both abdominal sepsis-induced emergency myelopoiesis and parasite-induced mast cell expansion through decreasing mRNA levels of Socs3, a key negative regulator of the JAK–STAT pathway that is critical for cytokine-induced myelopoiesis. Tet2 represses Socs3 expression through Adar1, which binds and destabilizes Socs3 mRNA in a RNA editing-independent manner. For the underlying mechanism of Tet2 regulation at the mRNA level, Tet2 mediates oxidation of 5-mC in mRNA. Tet2 deficiency leads to the transcriptome-wide appearance of methylated cytosines, including ones in the 3′ untranslated region of Socs3, which influences double-stranded RNA formation for Adar1 binding, probably through cytosine methylation-specific readers, such as RNA helicases. Our study reveals a previously unknown regulatory role of Tet2 at the epitranscriptomic level, promoting myelopoiesis during infection in the mammalian system by decreasing 5-mCs in mRNAs. Moreover, the inhibitory function of cytosine methylation on double-stranded RNA formation and Adar1 binding in mRNA reveals its new physiological role in the mammalian system.