Methyl CpG binding domain protein 2 (MBD2) in inflammation

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To the Editor: Methyl CpG binding domain protein 2 (MBD2) belongs to the histone deacetylase family, which promotes multi-gene expression by inhibiting methylation and participates in the pathological process of various diseases. Apoptosis and inflammatory response are the main mechanisms leading to a variety of immune diseases. MBD2, as an important methylation protein reader, has in recent years been shown to be indispensable in the inflammatory response. This paper summarizes the current understanding of inflammatory MBD2 biology and provides additional direction for the study of inflammatory mechanisms by summarizing the current understanding of the regulatory mechanisms of MBD2 in inflammatory diseases and the inflammatory pathways that may regulate dysfunction. PubMed, Embase, and Wanfang Data were searched up to May 2022 with no language restriction for reports on MBD2 in inflammatory pathways, immune cell differentiation, and macrophage polarization, among others. The identified literature showed that MBD2 can produce changes in the inflammatory disease-related cells, and regulate the inflammatory process by affecting the classical inflammatory pathway mitogen-activated protein kinase, the immune cells T helper (Th) cell 17 (Th17), Th1, and Th2 cells, and the macrophage polarization. Therefore, we infer that MBD2 may be an effective therapeutic target for inflammatory diseases, which should aid future research.

In mammals, deoxyribonucleic acid (DNA) methylation is a common epigenetic modification that occurs at the carbon-5 position of cytosine residues at CpG nucleotides through the action of DNA methyltransferase (DNMT) enzymes, forming 5-methylcytosine (5-mC). Functional proteins involved in the regulation and interpretation of DNA methylation patterns have the roles of "author," "reader," and "editor." Here, we focus on one of these readers, MBD2 of the methyl-CpG-binding domain (MBD) family, which not only binds specifically to CpG dinucleotides, but also participates in the translation of DNA methylation and histone modifications, facilitating a multi-level regulatory program. As a key determinant of the transcriptional state of the epigenome, the MBD protein family has a separate MBD structural domain, which is responsible for specific binding to the methylated DNA binding domain, and a transcriptional repressor domain, which mediates interactions with protein chaperones. Unlike other MBD family members, these two structural domains overlap at the center of the MBD2 protein sequence, suggesting that the methylation binding and transcriptional repression functions of MBD2 are tightly coupled. The nucleosome ribosome remodeling and deacetylase (NuRD) complex mediates histone demethylation and deacetylation, such as Mi-2/NuRD, which has the ability to remodel ribosomes, and MBD2-NuRD/Mi-2 interaction thereby directs DNA methyltransferase 1 (DNMT1)/DNA methyltransferase 3B (DNMT3B) activity to sites of DNA methylation, giving MBD2 the ability to maintain and propagate methylation [Figure 1]. That is, the typical role of MBD2 is to recruit NuRD to the CpG islands of methylated DNA and exert its transcriptional repression through transcriptional regulation and chromatin modification by interacting with binding partners such as Mi-2/NuRD.[1]

Research has shown that the overexpression of MBD2 in Boston University mouse proximal tubule cells (BUMPT) and kidney tissues during acute kidney injury induced by lipopolysaccharide and cecal ligation and puncture induced the expression of B-cell lymphoma-2 (BCL2)-associated X protein and cleaved caspase-3, thereby increasing the apoptosis rate of BUMPT cells. This is achieved by demethylation of the promoter by MBD2 to promote the upregulation of protein kinase C-eta (PKCη), which is directly at the downstream of MBD2, followed by the induction of p38 mitogen-activated protein kinase phosphorylation. Subsequent findings in this model also suggested that extracellular signal-regulated kinase (ERK) phosphorylation was promoted through the increase in

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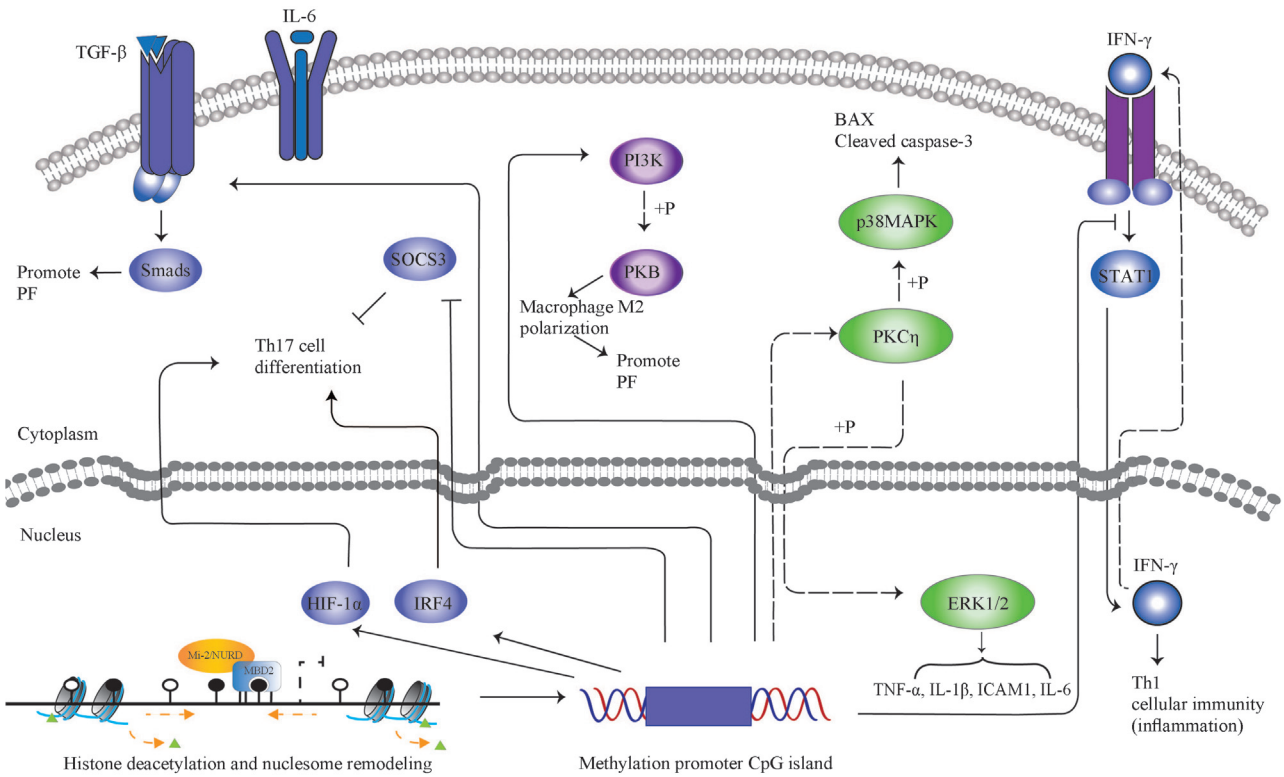

Figure 1: MBD2 in inflammatory signaling pathways. Through the NuRD/Mi-2 complex-binding partner, MBD2 directs transcriptional repression that enables histone deacetylation and nucleosome remodeling. MBD2 aggravates pulmonary fibrosis by enhancing TGF-β/Smad signaling. MBD2 promotes Th17 cell differentiation by downregulating SOCS3 expression. MBD2 inhibits the expression of Ship, enhances the PI3K/PKB signaling pathway, and then induces pulmonary fibrosis. MBD2 activates p38MAPK and ERK1/2 pathways by upregulating the expression of PKCη, and induces the release of proinflammatory factors. MBD2 acts as a suppressor to maintain the steady state of the Th1 program by regulating the STAT1–IFN-γ axis. IRF4 and HIF-1α promote Th17 cell differentiation, while MBD2 regulates their expression. BAX: B-cell lymphoma-2-associated X protein; BCL-2: B-cell lymphoma-2; ERK1/2: Extracellular signal-regulated kinase1/2; HIF-1α: Hypoxia-inducible factor-1α; ICAM1: Inter-cellular adhesion molecule 1; INF-γ: Interferon-γ; IL-1β: Interleukin 1β; IL-6: Interleukin 6; IRF4: Interferon regulatory factor 4; MBD2: Methyl CpG binding domain protein 2; Mi-2/NURD: Mi-2/nucleosome remodeling and deacetylase (NuRD) complex; P: Phosphorylation; PF: Pulmonary fibrosis; PI3K: Phosphatidylinositol 3-kinases; PKB: Protein kinase B; PKCη: Protein kinase C eta; p38MAPK: p38 mitogen-activated protein kinase; Ship: SH2-containing inositol 5′-phosphatase; Smad: Drosophila mothers against decapentaplegic protein; SOCS3: Suppressor of cytokine signaling 3; STAT1: Signal transducer and activator of transcription 1; TGF-α: Transforming growth factor-α; TGF-β: Transforming growth factor-β; Th1: T helper cell 1; Th17: T helper cell 17.

PKCη expression, resulting in positive regulation of inducible nitric oxide synthase and cyclooxygenase-2 expression, and ultimately increasing the expression of tumor necrosis factor (TNF)-α and interleukin (IL)-1β, and inter-cellular adhesion molecule 1 in BUMPT cells, thus inducing an inflammatory response [Figure 1].[2]

Cluster of differentiation 4-positive ($CD4^+$) T cells are cytotoxic and play an important role in inflammation. These cells undergo differentiation after stimulation by antigen-presenting cells, resulting in different types of effector T cells such as Th1, Th2, Th17, and regulatory T cell (Treg). TNF-β and IL-6 are important for Th17-induced differentiation. Zhilin *et al*[3] found that, in the airways of patients with chronic obstructive pulmonary disease, MBD2 promotes the secretion of IL-6 and IL-8 via the ERK1/2 pathway. In addition, in lung fibrosis, studies have shown that transforming growth factor (TGF)-β1 induced overall DNA hypermethylation, and MBD2 was overexpressed in fibroblasts in a TGF-β receptor I/drosophila mothers against decapentaplegic protein 3 (TβRI/Smad3)-dependent fashion. MBD2 selectively binds to hypermethylated CpG DNAs in the erythroid differentiation regulator 1 (Erdr1) promoter to inhibit its expression, enhance TGF-β/Smad signaling, and promote fibroblast differentiation to myofibroblasts, which aggravates lung fibrosis [Figure 1].[4]

In mice with Th17-mediated severe asthma, MBD2 overexpression significantly decreased suppressor of cytokine signaling 3 (SOCS3) expression, and Th17 cell differentiation was negatively correlated with this change in SOCS3. After establishing a severe asthma model, increased SOCS3 expression and decreased Th17 differentiation were observed in MBD2 knockout mice, and it was hypothesized that MBD2 may promote Th17 cell differentiation by downregulating SOCS3 expression in severe asthma patients [Figure 1].[5] Similarly, in a severe asthma model, MBD2 protein expression was increased in lung and spleen cells. The expression of IL-17 protein increased significantly with the overexpression of *MBD2* gene and decreased with the silence of *MBD2* gene. MBD2 ultimately regulates the differentiation of Th17 cells in asthma by promoting interferon regulatory factor 4 (IRF4) expression to influence inflammatory responses [Figure 1].[6]

Severe asthma causes hypoxia. Hypoxia-inducible factor-1 (HIF-1) modulates the effect of hypoxia. In a mouse model of neutrophilic inflammatory asthma characterized

by Th17 cell differentiation as well as activated and elevated IL-17, MBD2 and HIF-1α expression were markedly increased in lung and spleen cells. Studies of MBD2 and HIF-1α overexpression or silencing have shown that MBD2 is upstream and regulates HIF-1α expression, thereby regulating Th17 cell differentiation and IL-17 secretion in neutrophil-dominant asthma [Figure 1].[7]

In a study to model MBD2 knockout in the context of non-obese diabetes (NOD), it was confirmed that MBD2 deficiency aggravated type 1 diabetes progression in NOD mice. Combining this with the findings of subsequent experiments, MBD2 is considered to be a repressor that preserves Th1 cell homeostasis in patients with type 1 diabetes by regulating the signal transducer and activator of transcription 1-interferon-γ (STAT1–IFN-γ) axis [Figure 1].[8]

In bleomycin-induced pulmonary fibrosis, TGF-β1 caused DNA hypermethylation and MBD2 overexpression in fibroblasts. MBD2 binds to the Src homology 2 domain (SH2)-containing inositol 5′-phosphatase (Ship) promoters in macrophages and accelerates M2 polarization in macrophages by inhibiting Ship expression and enhancing the phosphatidylinositol 3-kinases/protein kinase B (PI3K/PKB) signaling pathway, which leads to pulmonary fibrosis [Figure 1].[9]

Inflammation underlies many pathological processes, and the understanding of the pathological and physiological aspects of inflammation has been refined and refreshed over the years. In recent years, genes and DNA methylation have been identified to be associated with cell death and inflammatory processes in a variety of disease pathologies. MBD2, a DNA methylation-associated readout of protein, is not only involved in the inflammatory process, but may also be an attractive therapeutic target. Research into upstream and downstream signaling components may provide unexpected insights into disease treatments and prevention. An in-depth analysis of MBD2 participation in both typical and atypical activation of inflammation may reveal the differences between these pathways and explain why DNA methylation is widely involved in acute and chronic inflammatory processes. This article focuses on MBD2 and inflammatory mechanisms to provide useful insights for future studies.

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Conflicts of interest

None.

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