REVIEW

许多研究人员试图找到IBD的其他遗传风险因素。基于许多研究人员的努力，已发现许多遗传风险因素，包括溶质载体家族22，成员4 (SLC22A4)，SLC22A5，前列腺素E受体4 (PTGER4)，白细胞介素23受体 (IL23R)，自噬相关16-like 1 (ATG16L1)，与免疫相关的GTP酶家族M (IRGM)，discs，大型同源5 (DLG5)，和X-box结合蛋白1 (XBP1) 与IBD的发展有关，除了NOD2。

3-5 其中，XBP1基因多态性与IBD的遗传关联，被提出是由于IBD患者中存在低功能单核苷酸多态性，和内质网（ER）压力与肠炎的诱导有关。4

有趣的是，许多IBD的遗传风险因素与潘氏细胞的成熟和功能有关。

6,7 潘氏细胞是存在于小肠的隐窝中，产生抗微生物的专门化上皮细胞。8

INTRODUCTION

炎症性肠病（IBD）是一种慢性炎症性疾病，存在于小肠和大肠中，包括两种主要临床形式，克罗恩病（CD）和溃疡性结肠炎（UC）。1 尽管引起IBD的确切原因尚未被广泛了解，但早期研究旨在识别与IBD相关的与人类IBD相关的核酸结合寡聚化域相关蛋白2 (NOD2) 作为CD的易感基因。2 自NOD2被引入以来，

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Myeloid-Derived Suppressor Cells in Inflammatory Bowel Disease

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未成熟的髓系细胞，也称为髓系衍生抑制细胞（MDSCs），包括中性粒细胞和单核细胞性髓系细胞，并存在于炎症部位和次级淋巴器官中，在小鼠中引起肠道炎症，IBD患者，和肿瘤组织中。然而，MDSCs在IBD中的作用尚未完全了解，并且有争议的关于它们在IBD患者中的免疫抑制功能。此外，最近的研究表明，内质网（ER）压力在肠上皮细胞，尤其是在潘氏细胞中，与IBD的发展有关。然而，ER压力在MDSCs积累在IBD患者的炎症组织中，尚未完全了解。在当前的综述中，我们将讨论在IBD患者的肠隐窝中积聚的MDSCs的生理功能，包括促进和抑制Th17细胞的分化。在特定情况下，我们将讨论在ER压力肠上皮环境下的MDSCs的炎症或免疫抑制作用的差异功能，根据内质网（ER）压力引起的未折叠蛋白反应在肠上皮细胞中引起。

Key Words: 炎症性肠病；髓系衍生抑制细胞；内质网压力；肠； interleukin-17
MDSCs IN IMMUNE SYSTEMS

MDSCs are a heterogeneous cell population consisting of macrophage precursors, dendritic cells, granulocytes, and early myeloid progenitors. The definition of this cell population is based on its origin, myeloid lineage, and its immunosuppressive function. Since the term "MDSC" does not directly reflect the immaturity of this population, they are also called immature myeloid cells. They expand during pathological conditions, including infections, inflammations, and cancers in experimental animal models, as well as in human patients. There are two main subsets of MDSCs: polymorphonuclear MDSCs (PMN-MDSCs) and monocytic MDSCs (Mo-MDSCs), especially in murine models of tumor transplantation. In mice, PMN-MDSCs are CD11b^+Ly-6G^+Ly-6C^lo^ cells, while Mo-MDSCs are CD11b^+Ly-6G^+Ly-6C^hi^ cells. There are some differences in suppressive capacity and functional mechanism between the two subsets and both PMN-MDSCs and Mo-MDSCs can be found in humans.

In the immune system, it is known that the major role of MDSCs is immune suppression, and this seems to be especially true in tumor tissues. The accumulation of MDSCs in tumor-bearing mice and cancer patients is correlated with poor prognoses. MDSCs can inhibit the proliferation and cytokine production of CD4^+ and CD8^+ T cells through amino acid deprivation and the release of oxidizing molecules. They also induce regulatory T cells to suppress immune responses against tumor cells. Besides, they can modulate the function of T cells as well as their migration and viability. In addition to T cell inhibition, MDSCs suppressed natural killer (NK) cell cytotoxicity and cytokine production, and suppress the antigen presenting functions of dendritic cells.

Despite their inherent suppressive functions, MDSCs can be converted into immunostimulatory myeloid cells in specific circumstances. In acute inflammation, such as trauma and sepsis, MDSCs are the sentinel cells for immune-surveillance and act as immune effectors. Even in the ovarian cancer model, MDSCs in ascites play a role as immunostimulatory antigen presenting cells (APCs). Furthermore, there is plasticity in the suppressive function of MDSCs. Our recent study also showed that intra-tumoral injection of attenuated Salmonella induced tumor necrosis factor α (TNF-α)-producing PMN-MDSCs, which can function as immune effectors. With the help of NKT cells, MDSCs became immunogenic APCs and stimulated antigen specific T cells. Hence, the divergent roles and the functional plasticity of MDSCs are now interesting subjects in MDSC studies.

MDSCs IN IBD

IBD is an autoimmune-associated disease characterized by small and large intestinal inflammation. There are two major forms of IBD, CD and UC. In the chronic inflammatory condition of IBD, there are complex interactions between several immune cells infiltrating into the intestinal mucosa, with epithelial cells even ignoring the effects of microbiota. Among them, myeloid cells, including neutrophils, macrophages, and MDSCs, have been a focus of study due to their divergent role in inflammation. In particular, the immunosuppressive function of MDSCs was suggested in several mouse models of IBD (Table 1). It was reported that CD11b^Gr-1^ MDSCs were accumulated in a murine colitis model, and they expressed nitric oxide synthase 2 and arginase, which are known to be critical functional mediators of MDSCs. As well as in a model of IBD, CD14^HLA-DR^ hi^ MDSCs with suppressive functions were reported to be increased in the peripheral blood of IBD patients.

Besides MDSCs in IBD models being initially reported as immunosuppressive, as shown in tumor-bearing hosts, the roles of MDSCs during intestinal inflammation have become controversial since recent studies suggested that they functioned as pro-inflammatory myeloid cells. Colonic Mac-1^Ly6C^hi^Gr-1^ cells, similar to PMN-MDSCs, acquired...
Table 1. Pros and Cons of Myeloid-Derived Suppressor Cells (MDSCs) in IBS

| Function of MDSC | Model | Role | Reference |
|------------------|-------|------|-----------|
| Immunosuppression | 2,4,6-TNBS-induced murine colitis | Adoptive transfer of CD11b<sup>+</sup>Gr-1<sup>+</sup> MDSCs decreased intestinal inflammation, levels of IFN-γ, IL-17, and TNF-α | 39 |
| DSS-induced murine colitis | Anti-Gr-1 antibody treatment exacerbated the DSS-induced colitis | | 64 |
| CD4<sup>+</sup>CD45RB<sup>hi</sup> T cell transfer-induced chronic colitis in RAG-1<sup>−/−</sup> mice | Ly6C<sup>int</sup> monocyte-derived cells restrained Th1 cell responses and promote generation of Foxp3<sup>+</sup> Tregs and Th17 cells | | 38 |
| HA-specific CD8<sup>+</sup> T cell transfer-developed colitis in VILLIN-HA mice | Transfer of CD11b<sup>+</sup>Gr-1<sup>+</sup> MDSCs ameliorated intestinal inflammation | | 32 |
| Spontaneous developed chronic colitis in IL-10<sup>−/−</sup> mice | Resveratrol-induced CD11b<sup>+</sup>Gr-1<sup>+</sup> cells attenuated T cell proliferation, and reduced IFN-γ and GM-CSF production by lamina propria derived T cells | | 65 |
| Pro-inflammation | DSS-induced murine colitis | CD11b<sup>+</sup>CD14<sup>+</sup>CX3CR1<sup>+</sup> lamina propria DCs were derived from transferred Ly6C<sup>hi</sup> monocytes contributed to severe intestinal inflammation in TNF-α-dependent manner | 12 |
| CD4<sup>+</sup>CD45RB<sup>hi</sup> T cell transfer-induced chronic colitis in RAG-1<sup>−/−</sup> mice | Colonic Mac-1<sup>+</sup>Ly6C<sup>int</sup>Gr-1<sup>−/−</sup> cells induced T cell activation/proliferation and pro-inflammatory cytokines, including IFN-γ, IL-17, TNF-α, and IL-1β production in vitro | | 33 |
| CD4<sup>+</sup>CD45RB<sup>hi</sup> T cell transfer-induced chronic colitis in RAG-2<sup>−/−</sup> mice | Ly6C<sup>hi</sup> monocytes differentiated into CD103<sup>+</sup>CX3CR1<sup>+</sup>CD11b<sup>+</sup> DCs, and produced high levels of pro-inflammatory cytokines, including IL-12, IL-23, iNOS, and TNF, in the colon | | 34 |

TNBS, trinitrobenzene sulfonic acid; IFN-γ, interferon γ; IL-17, interleukin 17; TNF-α, tumor necrosis factor α; DSS, dextran sulfate sodium; GM-CSF, granulocyte-macrophage colony-stimulating factor; DCs, dendritic cells; RAG-1, recombination activation gene-1; iNOS, inducible nitric oxide synthase.

stimulatory APC functions and induced T cell activation and pro-inflammatory cytokine production. In addition, adoptive transferred Ly6C<sup>hi</sup> monocytes were converted into pro-inflammatory cells. They then contributed to intestinal inflammation, and produced pro-inflammatory cytokines in a murine model of IBD.

These controversial roles of MDSCs in IBD might be partially due to interleukin 17 (IL-17) cytokine production, which could be at least partially ascribed to increased differentiation of Th17 cells. Th17 cells are known to act as pathogenic effector cells in various immune-related diseases, including experimental autoimmune encephalomyelitis, arthritis, and IBD. In the case of IL-17, one study showed that this cytokine had a pathogenic role in severe intestinal inflammation, but another study demonstrated IL-17-mediated protection in murine colitis.

Interestingly, it was recently reported that CD11b<sup>+</sup>Gr-1<sup>+</sup> MDSCs enhanced Th17 cell differentiation and contributed to the pathogenesis of experimental autoimmune encephalomyelitis. Likewise, a recent study showed that immunosuppressive MDSCs inhibited Th1 responses while they enhanced Th17 generation. In a chronic colitis model, pro-inflammatory colonic Mac-1<sup>+</sup>Ly6C<sup>int</sup>Gr-1<sup>+</sup> cells induced IL-17 production by T cells. Collectively, this series of studies suggest that MDSCs induced by intestinal inflammation conditions might be involved in Th17 generation and IL-17 production. As described, Th17 cells can contribute to establishing the pro-inflammatory environment and pathogenesis of IBD. On the contrary, MDSCs were initially reported to inhibit the production of several pro-inflammatory cytokines including IL-17, and functioned as immune regulators in several other inflammatory conditions including cancer and chronic infections. Thus, the role of MDSCs in IBD is still controversial, and might be closely associated with the production of IL-17 or the induction of IL-17-producing T cells.

**ER STRESS AND IBD**

ER is a type of organelle in eukaryotic cells responsible for the folding, modification, maturation, and trafficking of newly synthesized proteins, and only properly folded proteins are transported from the rough ER to the Golgi apparatus for secretion. Thus, the precise regulation of ER function is critical for the maintenance of cellular homeostasis. The condition in which unfolded or misfolded proteins accumulated in the ER is known as ER stress, and can be caused by...
several factors including disturbances in redox regulation, calcium regulation, glucose deprivation, and viral infection.\(^4\) Experimentally, several conditions including ER Ca\(^{2+}\) depletion, defective glycosylation, viral infection, and inflammatory conditions are also known to induce ER stress.\(^4\)

ER stress activates multiple cellular processes known as unfolded protein responses (UPRs), and three branches of UPRs have been discussed extensively in previous reviews.\(^42,43\) Under ER stress conditions, misfolded or unfolded protein are accumulated in the ER lumen, and trigger UPRs to restore normal ER function. UPR signaling results in the adaptation of cells to ER stress by increasing activation of ER chaperon function, ER trafficking, degradation of ER-resident protein, as well as by inhibiting CAP-dependent translation through phosphorylation of the \(\alpha\)-subunit of eukaryotic initiation factor 2 (eIF2\(\alpha\)).\(^45\) Otherwise, excessive ER stress induces apoptosis via C/EBP-homologous protein (CHOP) and the inositol-requiring transmembrane kinase/endoribonuclease 1 \(\alpha\) (IRE1\(\alpha\))/TNF receptor-associated factor 2 (TRAF2)/TNF-\(\alpha\) pathway.\(^46\) In addition, sustained ER stress also induces cell death due to failure in UPR signaling to induce the homeostatic adaptation of cells.\(^47\)

In mammalian cells, ER stress evokes UPR to resolve constraint inside the ER.\(^44\) UPRs consist of three highly conserved pathways including PKR-like eukaryotic initiation factor 2\(\alpha\) kinase (PERK), IRE1, and activating transcription factor-6 (ATF6). Among them, the IRE1\(\alpha\) pathway includes splicing of a gene encoding XBP1.\(^4\) Spliced XBP1 (sXBP1) is critical for the functions of the ER such as expansion and secretion, especially in several highly secretory cells including plasma cells and pancreatic and salivary gland epithelial cells.\(^48,49\) The function of the unspliced form of XBP1 (uXPB1) is not well known, and uXBP1 is highly unstable.\(^4\) Instead, sXBP1 triggers the transcription of genes for the quality control and maintenance of ER functions. IRE1 is an ancestrally conserved pathway of UPR, and also possesses kinase activity to phosphorylate TRAF2 as well as endonuclease activity.\(^4\) Accordingly, intestinal epithelial cell-specific depletion of XBP1 is known to initiate spontaneous small intestinal inflammation in mice.

UPR is known to intersect with several inflammatory pathways including IκB kinase (IKK) and c-Jun N-terminal kinases (JNK),\(^50,51\) and is also associated with inflammation in obese and diabetic patients.\(^52\) In addition, ER stress has been associated with the development of IBD.\(^4\) In humans, several genes associated with ER stress including XBP1, anterior gradient 2 (AGR2), mucin 19 (MUC19), and ORMDL1 sphingolipid biosynthesis regulator 3 (ORMDL3) have been reported as genetic risk factors for IBD, and increased ER stress has been observed in patients with IBD.\(^5\) In several mouse models, ER stress induced by deletion of some ER chaperones such as ATF6 or p58\(^\text{IPK}\) led to the development of severe intestinal inflammation after dextran sulfate sodium (DSS) administration.\(^53\) and the administration of chemical chaperones including 4-phenylbutyrate and tauroursodeoxycholate ameliorated colitis in those mice.\(^53\) In addition, conditional knockout of XBP1 in intestinal epithelial cells causes small intestinal enteritis with crypt abscesses reminiscent of human IBD,\(^4\) and AGR2 knockout mice develop granulomatous ileocolitis.\(^54\) Interestingly, UPR signaling was found to be impaired in colonic epithelial cells of protein kinase RNA-activated (PKR)\(^-/-\) mice with a reduced level of phosphorylated eIF2\(\alpha\) and diminished ER chaperons, resulting in more severe DSS-induced colitis in these mice.\(^55\) In addition, glutamine treatment attenuates ER stress increased in a trinitrobenzene sulfonate (TNBS)-treated colitis model through modulation of UPR signaling, and diminishes the severity of macroscopic damage and apoptotic cell death.\(^56\)

**ER STRESS AND THE DIVERGENT FUNCTIONS OF MDSCs**

In tumor-bearing hosts, it has been reported that ER stress is transmitted from tumor cells to myeloid cells.\(^57\) In association with increased inflammation by ER stress, ER stress-conditioned medium obtained from tumor cells culture with ER stress inducers resulted in up-regulation of ER stress in myeloid cells. Similarly, infectious ER stress has also been reported in tumor cells, which was known to be mediated by Par-4 secreted by ER stressed cells.\(^58\) Hypoxic tumor microenvironments could induce an ER stress condition, as well as increased reactive oxygen species generated in MDSCs induced ER stress. Increased ER stress results in early apoptosis of MDSCs in a TNF-related apoptosis-inducing ligand-receptor (TRAIL-R)-dependent manner, which in turn accelerates the generation of MDSCs in bone marrow. Indeed, MDSCs found in tumor-bearing mice and cancer patients showed significantly higher levels of ER stress compared with healthy controls.\(^59\) However, it is not clear whether ER stress increased in IBD condition influences on intestinal MDSCs found in IBD patients as well as on their immunosuppressive or inflammatory functions.

Although aggravation of inflammation by ER stress seems to be certain in several disease conditions, the mechanism by which ER stress triggers inflammation remains largely unknown. IRE1/TRAF2-mediated JNK activation and the
nuclear factor-κB (NF-κB) pathway could explain the inflammatory responses observed in the ER stress condition. ER stress also activates cleavage of ATF6 to activate the expression of acute-phase protein genes in the liver, and mediates acute inflammatory responses. Recent studies have also suggested the role of the nucleotide-binding oligomerization domain, leucine rich repeat, and pyrin domain containing 3 (NALP3) inflammasome in chronic inflammatory disease with ER stress. Unregulated activation of caspase-1 and subsequent overproduction of IL-1β through inflammasome activation might be associated with the perpetuation of IBD. Indeed, there is an increased level of IL-1β in the intestinal specimens of IBD patients. On the contrary, loss of function in NOD2 or inflammasomes could result in dysbiosis by decreased IL-1β. Thus, the involvement of several genetic risk factors, including NOD2, ATG16L1, NALP3, and chemokine (C-C motif) receptor 6 in the inflammatory status of MDSCs need to be further elucidated.

CONCLUSIONS

ER stress responses in MDSCs as well as in intestinal epithelial cells might be critical for the homeostatic regulation of gut immunity. In this review, we focused on the roles of MDSCs on intestinal inflammation, especially in animal models of IBD and also in IBD patients. The recent advances in experimental techniques for intestinal tissues, wide availability of germ-free mice, genome-wide analysis of patients’ genetic information, and metagenomic analysis of commensals increase the understanding of the development and progress of IBD, and hence provide some clues for the development of therapeutic drugs for the treatment of IBD. In particular, some strategies to regulate ER stress responses in MDSCs as well as in the intestinal epithelium might be novel ways to prevent or treat intestinal inflammation in IBD patients.

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