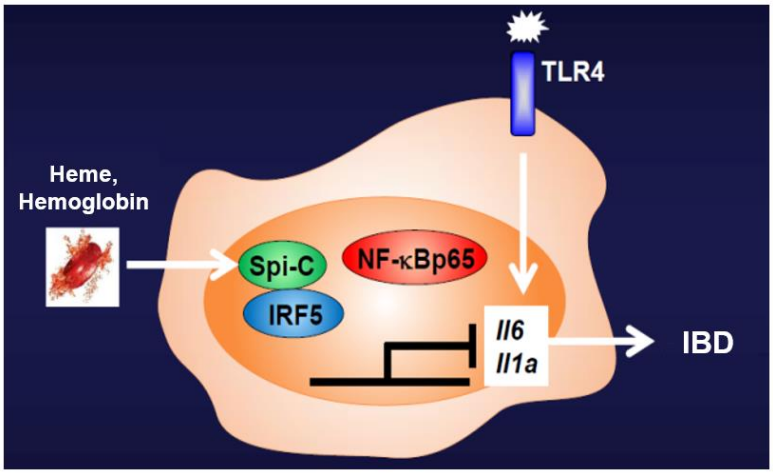
Heme ameliorates the colitis through providing intestinal macrophages with non-inflammatory profiles

Abstract

The local environment is crucial for shaping the identities of tissue-resident Mϕs. When hemorrhage occurs in damaged tissues, hemoglobin induces differentiation of anti-inflammatory Mϕs with reparative function. Mucosal bleeding is one of the pathological features of inflammatory bowel diseases. However, the heme-mediated mechanism modulating activation of intestinal innate immune cells remains poorly understood. Hisakao Kayama, Masako Kohyama, and Kiyoshi Takeda group show that heme regulates gut homeostasis through induction of Spi-C in intestinal CX_3CR1^{high} Mϕs. Intestinal CX_3CR1^{high} Mϕs highly expressed Spi-C in a heme-dependent manner, and myeloid lineage-specific *Spic* deficient (*Lyz2-cre; Spic*$^{flox/flox}$) mice showed severe intestinal inflammation with increased number of Th17 cells during dextran sodium sulfate-induced colitis. Spi-C downregulated the expression of a subset of TLR-inducible genes in intestinal CX_3CR1^{high} Mϕs to prevent colitis. LPS-induced production of IL-6 and IL-1α, but not IL-10 and TNF-α, by large intestinal Mϕs from *Lyz2-cre; Spic*$^{flox/flox}$ mice was markedly enhanced. The interaction of Spi-C with IRF5 was linked to disruption of IRF5-NF-κB p65 complex formation, thereby abrogating recruitment of IRF5 and NF-κB p65 to the *Il6* and *Il1a* promoters. Collectively, these results demonstrate that heme-mediated Spi-C is a key molecule for the non-inflammatory signature of intestinal Mϕs by suppressing the induction of a subset of TLR-inducible genes through binding to IRF5.



Mechanism of the regulation for the intestinal macrophages.
The heme-induced transcription factor Spi-C inhibits the dimer formation of transcription factors IRF5 and NF-κB p65. As a result, the expression of some TLR4-dependent genes is suppressed.

➢ Significance

Following hemorrhage in damaged tissues, hemoglobin induces Mϕs possessing the ability to protect against tissue inflammation. Hemorrhage-appearing mucosa is observed in patients with IBD. However, heme-mediated modulation of intestinal Mϕ activity remains poorly understood. Here, we provide evidence that Spi-C induced by heme is a key molecule for providing non-inflammatory gene expression patterns of intestinal CX_3CR1^{high} Mϕs. We found that the *Spic* deficiency in intestinal Mϕs resulted in increased sensitivity to DSS-induced colitis. Heme-mediated Spi-C inhibited a subset of LPS-induced gene such as *Il6* and *Il1a* by intestinal CX_3CR1^{high} Mϕs through inhibition of IRF5-NF-κB p65 complex formation. These results reveal a novel mechanism modulating non-inflammatory phenotype of intestinal Mϕs and may help identify new targets for therapy of intestinal inflammation.

➢ Article

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