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EDITORIAL

PD-L1 Shapes B Cells as Safeguards in Circadian Clock Disorder

Circadian homeostasis helps individuals adapt physiological state to daily changes of the environment. The homeostasis is maintained by circadian clock genes, such as Bmal1 and clock. Disruption of circadian clock gene contributes to various diseases, many of which are closely related to the immune system.[1] Circadian clock gene deficiency not only dampens immune cells to cope with and eliminate pathogens, but also leads to irregulated inflammation or even autoimmunity, suggesting a pathogenic role of regulatory immune cell dysfunction in the process of circadian clock disorder. Recent studies have indicated a link between altered circadian rhythms and inflammatory bowel disease. Inflammatory bowel disease happens once the exquisite adaption and tolerance between intestinal flora and the host's immune system is broken. B cell has been proved to support immunologic tolerance by releasing interleukin (IL)-10 in homeostasis and pathologic conditions, including intestinal inflammation.[2] However, whether Bmal1 can impact on B-cell biology and inflammation, such as that observed in colitis, has never previously been described. Furthermore, a related issue that must be addressed in this context is how B cells exert immune suppressive function in intestinal homeostasis and how this axis is disrupted by circadian clock disorder.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Liu et al[3] present a comprehensive study of how circadian clock disorder contributes to inflammatory bowel disease and colitis-associated colorectal cancer. Using social jet lag and circadian clock gene Bmal1 deficiency mice, they identify a unique regulatory B cell (Breg) subset that highly express PD-L1 as a protective factor for intestinal homeostasis. These PD-L1$^+$ B cells are specifically induced and maintained by intestinal microenvironment-derived IL33, which is transcriptionally regulated by circadian clock gene Bmal1 and is disrupted in Bmal1-defective mice. Dysregulation and decrease of PDL1$^+$ B cells led to cell death of activated CD4$^+$ T cells in DSS-treated Bmal1-defective mice, thus promoting colitis and colorectal cancer progression.

The pathogenic role of Breg cells in established tumors has been well appreciated in mouse and human tumor models.[4,5] These suppressive cells dampen antitumor effects of T cells by secreting IL10 or expressing coinhibitory molecules, therefore promoting immune privilege and progression of a tumor. Of note, in spite of the importance of immune suppression in facilitating tumor progression, uncontrollable inflammation is also considered as an aggressive hallmark. It is reasonable that individuals with chronic inflammation or some forms of autoimmunity (rheumatoid arthritis or systemic sclerosis) harbor an increased relative risk for cancer.[6,7] In this case, Bmal1 disruption-related colitis associates with colorectal cancer. Occurrence of Breg cells has also been indicated to clear excessive inflammation, which is crucial for tumor initiation. However, the role of Breg cells in inflammation-related precancerous lesions has not been so well studied. Liu et al[3] show that chronic inflammation during colitis may lead to the apoptosis of overactivated CD4$^+$ T cell, probably through an activation-induced cell death manner, which subsequently creates an immune desert favorable for tumor development. Local Breg cells are able to suppress the overactivation of T cells by PD-L1 signals and ensure their durable survival and proliferation. These results reveal a paradoxical role of Breg cells in inflammation-related precancerous lesions and in established tumor, and provide insights into how immunosuppression is converted into antitumor immune response. The coexistence and interconversion of immune inflammation and immunosuppression is an important prerequisite for maintaining homeostasis and prevention of tumor formation. At present, the mechanism of how irrepressible inflammation promotes tumor initiation is mainly focused on its role in facilitating gene instability and malignant transformation.[8] In fact, overintensive and extensive inflammation could cause secondary immune tolerance and anergy, which subsequently leads to tumor immune escape.[9,10] In this aspect, proper immune regulation is important for a compromise, but extensive and sustainable antitumor function. Thus, it is not Breg cells per se but rather the inflammatory "context" that determines the function and pathogenic role of the cells (Figure 1).

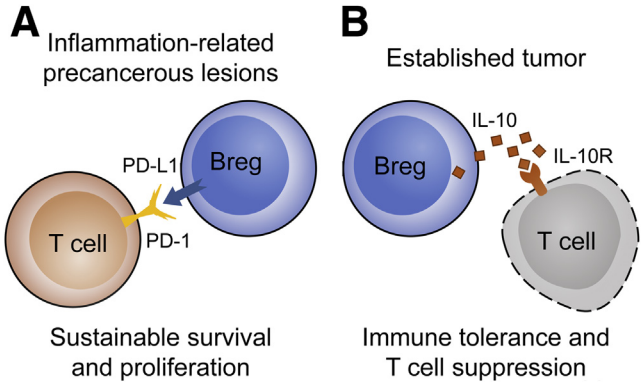

Figure 1. The role of the Breg cells in inflammation-related precancerous lesion and established tumor. (*A*) PD-L1$^+$ Breg cells prevent T-cell overactivation and apoptosis, which sustains T-cell survival and proliferation in inflammation-related precancerous lesion. (*B*) Breg cells induce T-cell tolerance by secreting IL10 in established tumor. The artwork is created by Microsoft Office PowerPoint.

Overall, this study has identified a unique role of Breg cell in maintaining intestinal homeostasis, which is under precise regulation of circadian clock gene Bmal1 and steady biologic rhythm. Dysfunction of this population contributes major pathogenies of Bmal1 deficiency–related colitis by conniving T-cell overactivation and apoptosis. It would be interesting to know whether functionally re-establishing Bmal1/IL-33/PD-L1^{+} Breg cells would benefit circadian clock disorder–related colitis in clinic.

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Conflicts of interest
The authors disclose no conflicts.

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