Clinical Immunology 171 (2016) 62–64

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Commentary

An altered gut microbiota may trigger autoimmune-mediated acquired bone marrow failure syndromes

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ARTICLE INFO

Article history:
Received 28 July 2016
Received in revised form 5 August 2016
accepted with revision 5 August 2016
Available online 6 August 2016

The human body is colonized by a number of different nonpathogenic microbes that, as a whole, play crucial roles in health and disease. These commensal microorganisms exert profound effects on the development and function of the immune system and therefore strongly influence immune-mediated diseases [1]. Acquired bone marrow (BM) failure syndromes encompass a group of disorders characterized by a reduction in the effective production of mature erythrocytes, granulocytes, and platelets by the bone marrow, which in most cases result from the immune-mediated inhibition of hematopoiesis at specific stages of differentiation. We hypothesize here that altered immune-commensal interactions induced by dysbiosis may contribute to triggering autoimmune-mediated acquired bone marrow syndromes.

Dysbiosis of the gut, which is characterized by the outgrowth of potential pathogenic bacteria or a decrease in the number of beneficial bacteria, has been implicated in various autoimmune disorders, including ulcerative colitis (UC), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) [1]. Dysbiosis may promote autoimmunity via molecular mimicry or by inducing post-translational modifications of host proteins, turning autologous peptides into immunogenic ones, suitable for recognition as exogenous by immune cells [2].

Experimental evidence indicates that intestinal microbiota play pivotal roles in the development of Th17 cells in the gut. In addition, several commensal microbes and their metabolites, such as butyrate, propionate, and acetate, induce the differentiation and proliferation of regulatory T cells (Treg) [1,2]. Recent evidence indicates that commensal microbes or their metabolites directly modulate hematopoiesis [3]. The complexity of the intestinal microbiota regulates the myeloid cell pool size in BM and thus actively shapes innate immune cell populations [4].

Aplastic anemia (AA), the paradigm of BM failure syndromes, is characterized by pancytopenia and hypoplastic BM in the absence of an abnormal infiltrate or marrow fibrosis. Although the pathophysiology of acquired AA is not completely understood, the fact that most patients with AA respond to immunosuppressive therapy (IST) with anti-thymocyte globulin (ATG) and cyclosporine (CsA) implies an underlying immune disorder. Aberrant immune response in patients with acquired AA involves the oligoclonal expansion of CD8 + T, CD4 + Th1, and Th17 cells, leading to hematopoietic stem/progenitor cell (HPSC) apoptosis [5]. The concomitant decrease in the population of Treg cells and abnormal production of myelosuppressive cytokines, including IFN-γ and TNF-α, aggravate this autoimmune response [5].

Treg cells are decreased in the majority of patients with acquired aplastic anemia [6], and as described above, metabolites produced by gut bacteria, especially butyrate produced by *Clostridia*, can promote the differentiation of Tregs in the colon, spleen, and lymph nodes to suppress inflammation.

Intriguingly, in some patients with acquired AA, this disease is preceded by the occurrence of other autoimmune diseases such as RA, SLE, or UC. However, AA may also be complicated with the onset of other autoimmune disorders. The pathogenetic events that link these diseases remain unknown. In some reports, mesalazine, which is an anti-inflammatory drug used to treat UC, has been implicated as a cause of AA. In these patients, marrow aplasia typically occurred several months to a year after exposure to mesalazine. In some UC patients, however, AA presented before any diagnosis of UC or treatment with these drugs [7].

We recently reported that simultaneous presentation of UC and acquired BM syndromes is relatively frequent (Nakagawa et al., ASH Abstract, 2015). The high prevalence of increased PNH-type cells in patients with concomitant AA and UC, together with the high rate of

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http://dx.doi.org/10.1016/j.clim.2016.08.008
1521-6616/