Review Article

Relationship of gut microbiota and immunity

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Abstract

Microbiome that inhabits within the GIT tract contributes many health benefits to the host by regulating the immune homeostasis. Alterations of these gut microbial communities can cause immune dysregulation, resulting in autoimmune disorders. The mammalian intestine is colonized by trillions of microorganisms most of which are bacteria that have co-evolved with the host in a very symbiotic relationship. The gathering of microbial populations that resides on and within the host is commonly known as "microbiota". A principle function of the microbiota is to protect the intestine against colonization by exogenous pathogens and potentially harmful indigenous microorganisms via several mechanisms, which include direct competition for limited nutrients and therefore the modulation of host immune responses. Understanding the interaction of the microbiota with pathogens and therefore the host might provide new insights into the pathogenesis of disease for preventing and treating intestinal and systemic disorders.

Keywords: gut microbiota, autoimmunity, GIT, symbiosis, homeostasis

Introduction

The skin and mucosal surfaces of vertebrates are colonized by many microorganisms which include bacteria, fungi, parasites, and viruses which are commonly said as microbiota in humans, over100 trillion organisms mostly bacteria colonize the oral-GIT tract, and most of those microorganisms reside within the distal intestine. Millions of years of co-evolution between the host and microorganisms have led to a mutualistic relationship within which the microbiota contributes to several host physiological processes and therefore the host then provides niches and nutrients for microbial survival. The 2 main contributions of the microbiota to the host include the digestion and fermentation of carbohydrates [1-3]. The gut immune responses that are induced by the populations regulate the composition of microbiota. The complex process between the host immune system and microbiota is very much important for homeostasis. Hence, if the mutualistic relationship between the host and microbiota is disrupted the gut microbe can cause diseases [4-5].

Gut Microbiota and Immune Homeostasis

Many approaches have been made to demonstrate the signals derived from gut microbiota are critical for the developing of the system, in among them the germ-free models; the animals are reared in a sterile environment and have not were exposed to microorganisms, the powerful approach that reveals the importance of microbiota in shaping both innate and adaptive immunity. The manipulation of microbiota with antibiotic treatment or microbiota reconstitution provides a piece of evidence for the role of microbiota in immune homeostasis and autoimmunity [6-9].

Microbiota and innate immune homeostasis

The antigen presenting cells are co-evolved with microbiota

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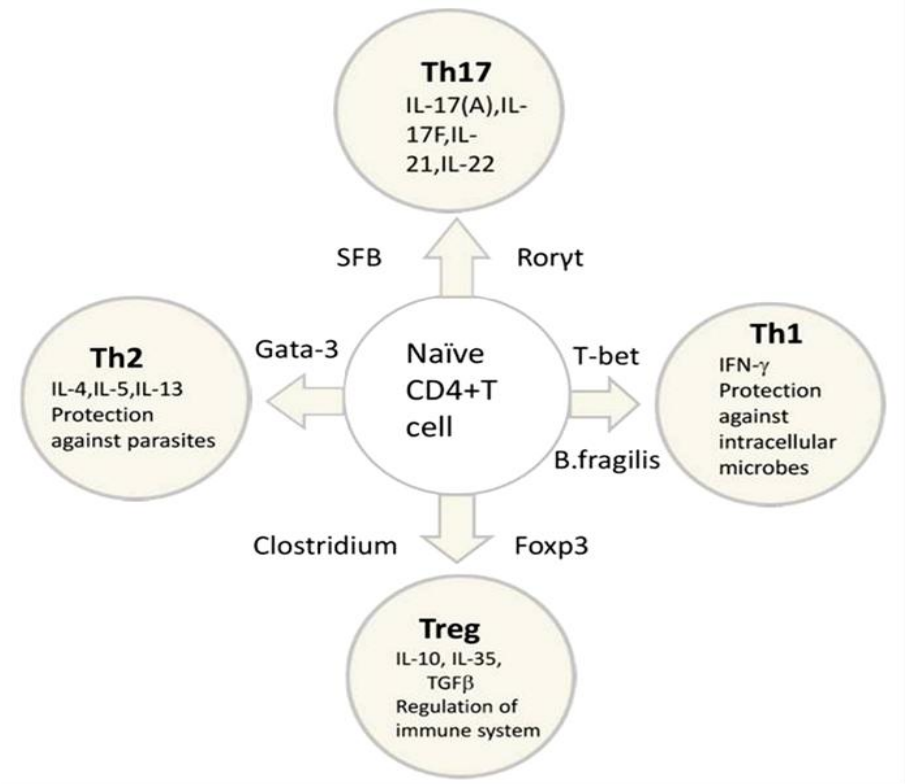

Fig1: Microbiota and adaptive immune homeostasis.

which may be key feature of intestinal APCs. Their ability is to guard the body from infection whereby still maintaining the immune tolerance to the gut microbiota. For example, the dendritic cells of Payer's patches (the lymphoid nodules are embedded within the gut wall), produce high levels of interleukin-10 (IL-10), compared with splenic DCs which are activated under similar conditions [10]. Almost like DCs the gut macrophages are located near the intestinal microbiota, and that they develop a singular phenotype called "inflammatory anergy," which refers to the non-inflammatory profile of intestinal macrophages once they encounter the microbial stimuli in homeostatic conditions [11]. As an example, the intestinal macrophages don't produce pro-inflammatory cytokines in response to microbial stimuli like Toll-like receptor (TLR) ligands which are a group of microbe associated molecular patterns [12].

Microbiota and adaptive immune homeostasis

The $CD4^+$ T cells are key component of the adaptive system. The intestinal CD4+ T cells are mostly located in the intestine. When stimulated CD4+ T cells is differentiated into four major subtypes: T helper 1 (Th1), Th2, Th17, or regulatory T cell (Treg). These various CD4+ T cell subtypes are distinguished by the expression of various transcription factors and cytokines. The right regulation and balance of T cell subtypes may be a crucial factor in determining the health status. Th1 cells are critical for the host's defense against intracellular microbial infections, while Th2 cells play a significant role within the elimination of parasitic infections. The responses maybe pathological, as the Th1 and Th17 responses are linked to autoimmune diseases while the Th2 response is related to allergic reactions. The T cell could be a key mediator of immune tolerance where the dysfunction can lead to autoimmune disorders. The gut microbiota plays a major role within the development of CD4+T cells, inside and outside the intestine [13]. The relationship has been schematically shown in Fig.1.

Microbiota-Independent Immune Disease

Many autoimmune diseases result from genetic and environmental factors. In some cases genetic factor contributes to the disease development. The severity of auto-immune disorders doesn't depend upon the presence or absence of the commensal bacteria like an auto immune regulator the (AIRE) deficient mice. The AIRE mouse may be animal models of autoimmune polyendocrinopathy candidiasis ectodermal dystrophy which is (APECED) a polyendocrine disease that happens from mutations within the AIRE protein which is a transcriptional regulator that plays an important role in T cell tolerance induction within the thymus [14]. Breaking of central tolerance within the thymus alone can lead to an autoimmunity that reverses the peripheral tolerance mechanism without the need or requirement for microbial stimulation [15]. The MRL/LPR mouse model of human SLE and activation induced cytidine deaminase deficient mice, an autoimmune model that exhibits comparable disease phenotypes with the GF state. The result demonstrates that live commensal organisms don't seem to be involved in pathology found in these models. In this the genetic factors play a major role in development of some autoimmune disorders or diseases [16-17].

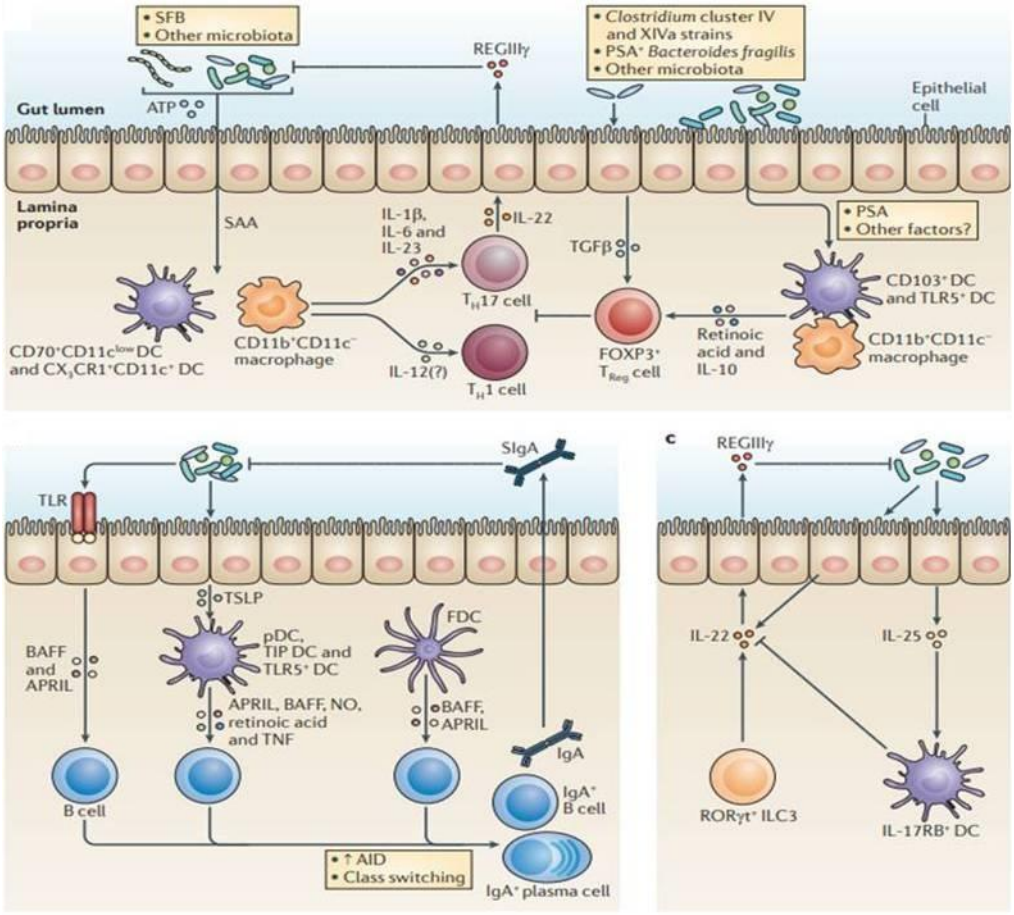

Fig. 2: gut microbiota-mediated development of the intestinal immune system

The gut microbiota mediated development of the intestinal immune system

- Segmented filamentous bacteria (SFB) and other commensal microorganisms activate lamina propria dendritic cells (DCs) and macrophages to induce the T helper 17 (TH17) cells and TH 1 cells by the assembly of interleukin 1β, Interleukin 6 and interleukin 23 just in case of TH 17 cells, and IL-12 just in case of TH 1. TH 17 cells regulate the gut microbe community and re-generate islet derived protein. Clostridium species and other microbiota stimulate intestinal epithelial cells, T cells, and lamina propria dendritic cells and macrophages to promote the development and activation of cells.
- The microbiota stimulates the epithelial cells of the intestine and dendritic cells to promote IgA producing B cell and plasma cell differentiation in the LP. The TLR receptor activation on intestinal epithelial cells which induces the secretion of a "BAFF factor" and proliferation inducing ligand which promotes the differentiation of IgA producing plasma cells. The intestinal epithelial cells produce a protein called thymic stromal lymphoprotein to stimulate a BAFF factor and a proliferation inducing ligand by dendritic cells. Dendritic cells secrete BAFF, Ligand, NO, retinoic acid, and TNF factor to ease the articulation of AID and B cells.The follicular dendritic cells induce IgA producing plasma cells in the payer's patches and lymphoid follicles. Lamina propria B cells produces IgA is secreted into intestinal lumen where it changes the composition and function of microbiota.
- The innate lymphoid cells which expresses the retinoic acid receptor and produce IL-22 which regulates the gut micro biome through the epithelial cells of intestine. Microbiota regulates production of IL-22 by an unknown mechanism; it also induces IL-25 SECRETION by the endothelial cells and acts on lamina propria (Fig:2).

Microbiota and Resistance to Pathogens

This is known from many years that the germ free mice are more susceptible to the infections than that of the conventionally raised mice. Additionally, the treatment with antibiotics is associated with increased colonization of the pathogens in mice and humans. The observation and results specify that an important function of the indigenous microbe to protect the host from infections. The techniques by which the mechanisms commensal bacterium achieved this is unknown,

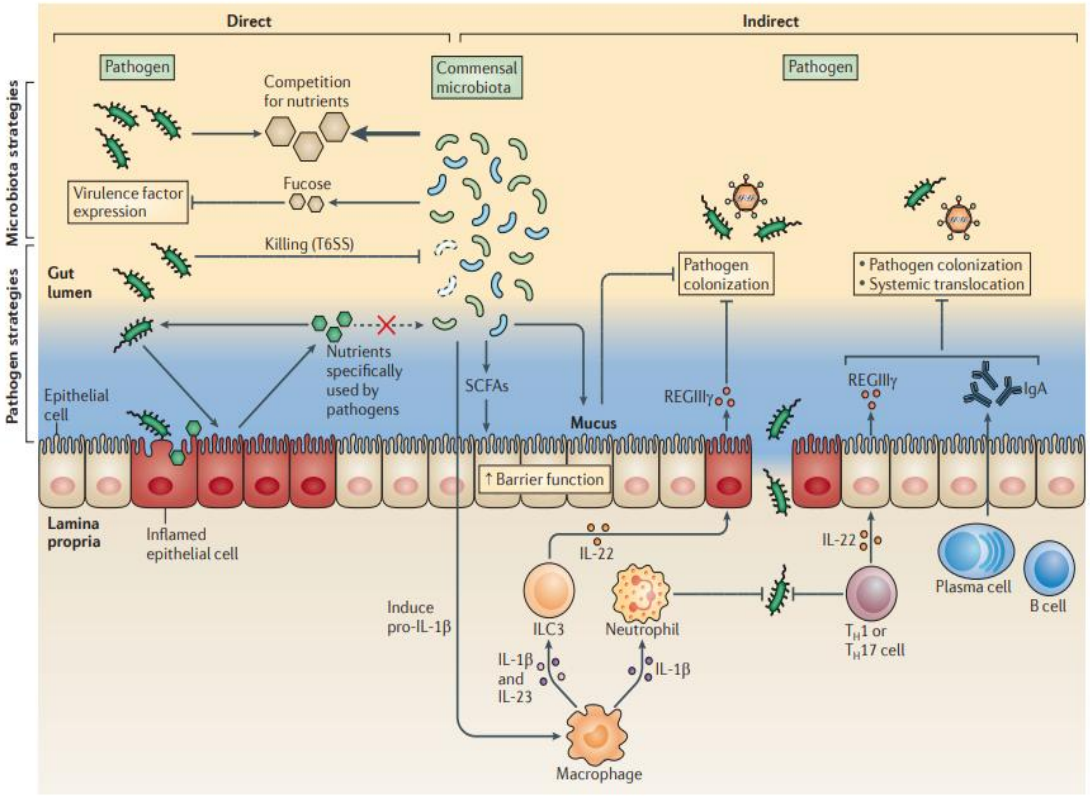

Fig. 3: Resistance of the microbiota to colonization by enteric pathogens

there is manifestation to indicate that direct and indirect are involved as shown in Fig. 3 [18].

Direct Competition for the Nutrients

There are many studies done and have shown the commensal bacteria can inhibit the colonization of pathogen through competing for the less supply of nutrients which are present in the intestine. There is competition between E. coli with other species of E. coli for organic acids, nutrients and amino acids. The E. coli stains have distinct metabolic profiles where each strain can differently compete with the pathogens. For example: - The Citrobacterium rodentium is mediated by the competition for the simple sugars which are used by the bacteria in intestine.

Direct mechanism

The gut microbiota promotes a direct colonization resistance by killing, and through competition for nutrients (resources). The Bacteria competes for the nutrients and for the space in the intestine. With that they develop an arrangement to fight and kill the competitors. These mechanisms occur simultaneously and the bacteria, tends to utilize the resources and evolving in the killing process to fight with their own kind of bacteria or microbe.

Indirect Mechanism

In indirect mechanism the microbes can compete with one another by indirectly acting on the host. This mechanism includes both innate and adaptive immune response systems. Its mechanism includes mucus and glycosylation, regulation of myeloid cells, neutrophils, eosinophils, macrophages, Th17 cells regulation of T cell response. Enterobacteriaceae is evolved with many strategies to remove the host's immune response and to prevail in the inflamed gut [19-20].

Many other diseases can occur like:

Gastrointestinal diseases	Autoimmune diseases	Metabolic diseases	Multiple sclerosis
Diarrhea	Asthma	Obesity	Neurologic disorders
Irritable bowel syndrome	Allergies	Diabetes type 1 Diabetes type 2	MS Autism
Inflammatory bowel diseases	Diabetes type 1	Atherosclerosis	Parkinson's disease

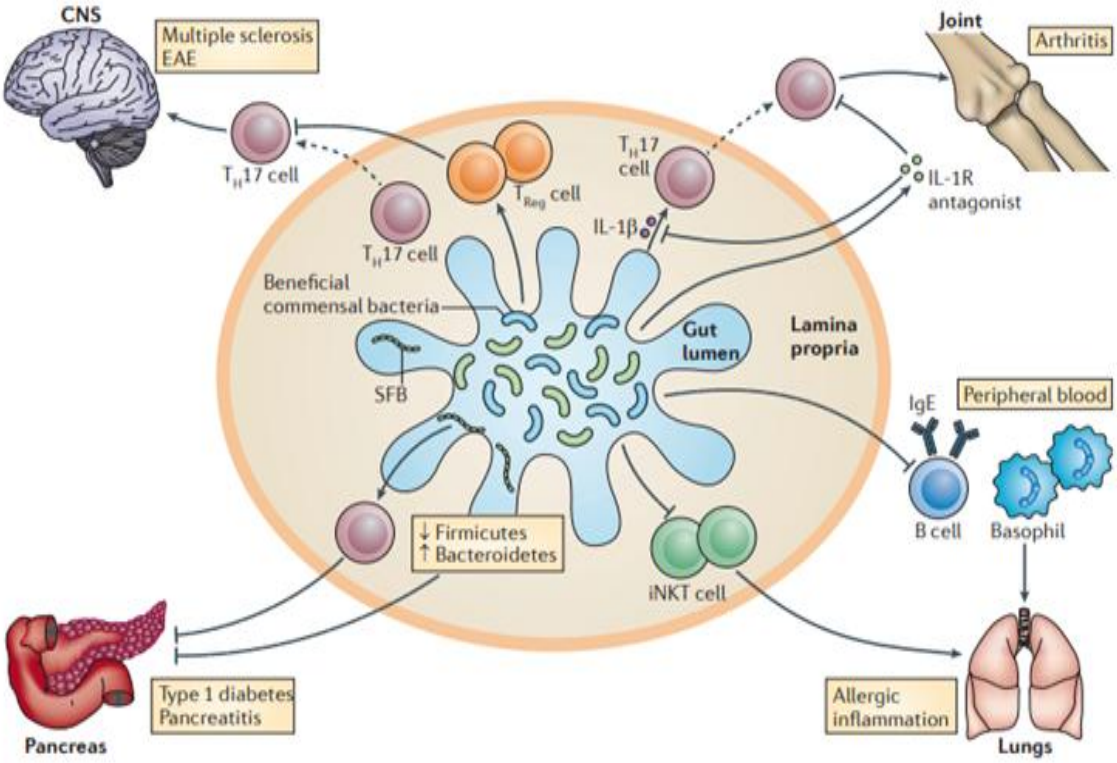

Fig. 4: Participation of gut microbiota in modulating immune systems in various organs and tissues.

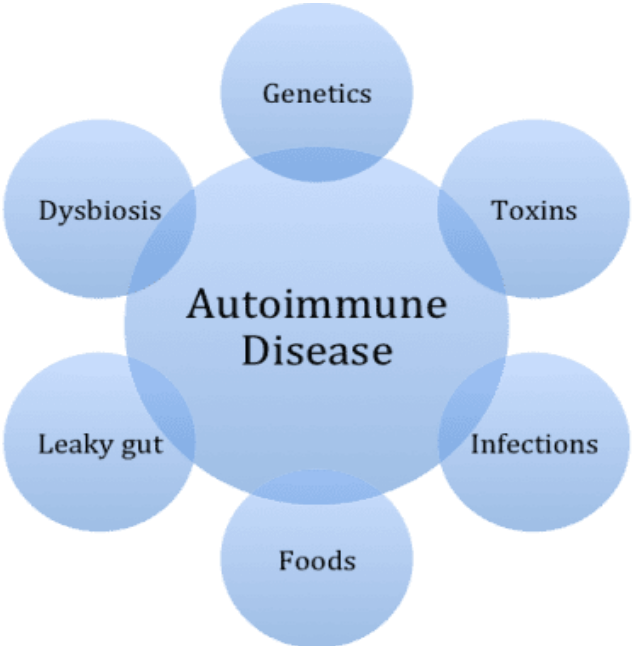

Fig 5: Autoimmune Diseases

Extra-Intestinal Diseases

The imbalance of gut microbiota which is linked with GIT diseases or conditions which are IBD and IBS, Inflammatory bowel disease and irritable bowel disease [21].

Conclusion

The gut microbiota plays major roles within the maintenance of the human health. The gut microbiota is involved within the progress and development of infections and human diseases. They include various diseases like metabolic, inflammatory diseases, IBD, IBS, diabetes type 2, and depression. The gut microbiome is especially composed of anaerobes and therefore microbial colonization in the gut of humans begins at birth.

Conflict of Interest

The authors declare no conflict of interest.

References

1. L. V. Hooper, A. J. Macpherson, Immune adaptations that maintain homeostasis with the intestinal microbiota, Nature Rev. Immunol. 10 (2010) 159–169.
2. H. Renz, P. Brandtzaeg, M. Hornef, The impact of perinatal immune development on mucosal homeostasis and chronic inflammation, Nature Rev. Immunol. 12 (2011) 9–23.
3. B. Stecher, W. D. Hardt, Mechanisms controlling pathogen colonization of the gut, Curr. Opin. Microbiol. 14 (2011) 82–91.
4. D. R. Littman, E. G. Pamer, Role of the commensal microbiota in normal and pathogenic host immune responses, Cell Host Microbe 10 (2011) 311–323.
5. K. Honda, D. R. Littman, The microbiome in infectious disease and inflammation, Annu. Rev. Immunol. 30 (2012) 759–795.
6. K. Smith , K. D. McCoy , A. J. Macpherson, Use of axenic animals in studying the adaptation of mammals to their commensal intestinal microbiot,. Semin Immunol 19 (2007) 59-69.
7. I. Sekirov, N.M. Tam, M. Jogova, M. L. Robertson, Y. Li, C. Lupp, et al., Antibiotic-induced perturbations of the intestinal microbiota alter host susceptibility to enteric infection, Infect Immune 76 (2008) 4726-36.
8. D. A. Hill, C. Hoffmann, M. C. Abt, Y. Du , D. Kobuley, T. J. Kirn, et al., Metagenomic analyses reveal antibiotic induced temporal and spatial changes in intestinal microbiota with associated alterations in immune cellhomeostasis, Mucosal Immunol 3 (2010) 148-58.
9. S. Rakoff-Nahoum, J. Paglino, F. Eslami Varzaneh, S. Edberg, R. Medzhitov, Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis, Cell 118 (2004) 229-41.
10. A. Iwasaki, B. L. Kelsall, Freshly isolated Peyer's patch, but not spleen, dendritic cells produce interleukin 10 and induce the differentiation of T helper type 2 cells, J Ext Med 190 (1999) 229-39.
11. L. E. Smythies, M. Sellers , R. H. Clements, M. MOs teller Barnum, G. Meng, W. H. Benjamin, et al., Human intestinal macrophages display profound inflammatory anergy despite avid phagocytic and bacteriocidal activity, J Clin Invest 115 (2005) 66-75.
12. L. E. Smythies, R. Shen, D. Bimczok, L. Novak, R. H. Clements, D. E. Eckhoff , et al., Inflammation anergy in human intestinal macrophages is due to Smad-induced I kappaB alpha expression and NF-kappa B inactivation, J Biol Chem 285 (2010)593-604.
13. A.J. Macpherson, M. M. Martinic, N. Harris, The functions of mucosal T cells in containing the indigenous commensal flora of the intestine, Cell Mol Life Sci 59 (2002) 2088-96.
14. M. S. Anderson, E. S. Venanzi, L. Klein, Z. Chen, S. P. Berzins, S. J. Turley et al. Projection of an immunological Self-shadow within the thymus by the Aire protein, Science 298 (2002) 1395-401.
15. D. H. Gray, I. Gavanescu, C. Benoist, D. Mathis, Dangerfree autoimmune disease in Aire-deficient mice, ProcNatl Acad Sci USA 104 (2007) 18193-8.
16. M. A. Maldonado, V. Kakkanaiah, G. C. MacDonald, F. Chen, E. A. Reap, E. Balish, et al., The role of environmental antigens in the spontaneous development of autoimmunity in MRL-lpr mice, J Immunol 162 (1999) 6322-30.
17. K. Hase, D. Takahashi, M. Ebisawa, S. Kawano, K. Itoh, H. Ohno, Activation-induced cytidine deaminase deficiency causes organ-specific autoimmune disease, PLoS One 3 (2008) e3033.
18. Y. Bertin, Enterohaemorrhagic Escherichia coli gains a competitive advantage by using ethanolamine as a nitrogen source in the bovine intestinal content, Environ. Microbiol. 13 (2011) 365–377.
19. H. J. Wu, Gut-residing segmented filamentous bacteria drive autoimmune arthritis via T helper 17 cells, Immunity 32 (2010) 815–827.
20. P. J. Turnbaugh, V. K. Ridaura, J. J.Faith, F. E. Rey, R. Knight, J. I. Gordon, The effect of diet on the human gut microbiome: a Metagenomic analysis in humanized gnotobiotic mice, Sci Transl Med 1 (2009) 6-14.
21. J. F. Bach, The effect of infections on susceptibility to autoimmune and allergic diseases N Engl J Med 347 (2002) 911-20.