Elucidation of the mechanism of the disruption of the crosstalk between host and gut microbiota with aging

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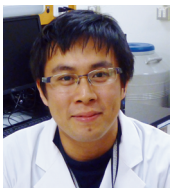

Abstract

We have demonstrated that one of the causes of age-related disruption of the gut microbiota is cellular senescence of germinal center B cells in the ileum induced by the gut microbiota (Fig.1). Namely, long-term stimulation by the gut microbiota causes the induction of cellular senescence in germinal center B cells of the ileum, leading to a decrease in IgA production and diversity, which in turn yields a disruption of the gut microbiota during aging. Furthermore, we found that lipopolysaccharide (LPS), a component of Gram-negative bacteria, is responsible for the induction of cellular senescence of B cells. These findings indicate that a vicious cycle is formed between host and gut microbiota via cellular senescence of B cells, which leads to gut aging (Fig.2).

Background & Results

Aging is accompanied by a decline in biological functions and the onset of age-related diseases, leading to an increasing number of unhealthy elderly people and causing a major problem that threatens the sustainable social systems in developed countries. In recent years, two age-associated phenomena, i.e., accumulation of cells inducing cellular senescence (senescent cells) and disruption of the gut microbiota, are likely to play a central role in the aging process. Cellular senescence, which is irreversible cell-cycle arrest induced by heavy DNA damage, acts as a cancer suppression mechanism but causes chronic inflammation, thereby promoting the development of age-related diseases. On the other hand, the gut microbiota plays an essential role in maintaining health but becomes imbalanced with aging, leading to various age-related diseases. However, it has yet to be clarified whether there is a relationship between the two phenomena.

Therefore, we compared mice in which senescent cells could be visualized by luminescence maintained under normal or sterile conditions and found that senescent cells accumulated in the ileum and that cellular senescence was induced, especially in germinal center B cells in the ileum in a bacteria-dependent manner (Fig.1). We also found that a decrease in the quantity and quality of IgA and a disruption of the gut microbiota simultaneously occurred with aging. Furthermore, comparative analysis revealed that age-related changes in IgA and gut microbiota are caused by B cell senescence. Thus, we proved that the induction of cellular senescence of germinal center B cells by the gut microbiota promotes the disruption of the gut microbiota with aging.

Significance of the research and Future perspective

Although it has long been believed that there is a link between age-related disruption of the gut microbiota and the progression of aging, the cause of the disruption of the gut microbiota has remained unclear. This study revealed that long-term stimulation by the gut microbiota accelerates gut aging and suggested that there may be gut bacteria promoting disruption of the gut microbiota (Fig.2). In the future, we would like to confirm whether a similar mechanism exists in humans, identify bacteria that have the potential to induce cellular senescence of B cells, and establish an artificial control method for them, leading to the development of new preventive methods against age-related disruption of the gut microbiota.

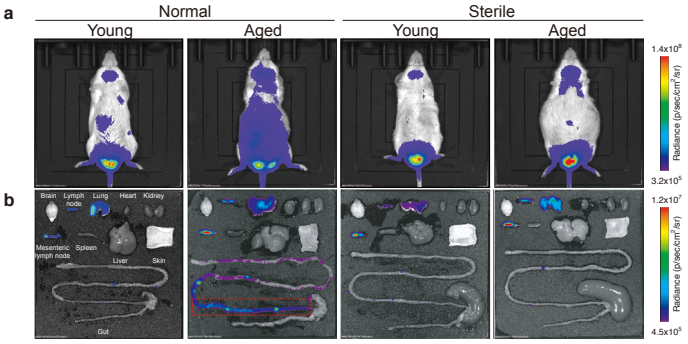

Fig. 1. Gut bacteria-dependet accumulation of senescent cells with aging
(a)Mice in which senescent cells could be visualized with luminescence were maintained under normal or sterile conditions and used for *in vivo* imaging at young or old ages. Accumulation of senescent cells was observed in the abdomen with aging under normal conditions.
(b)Imaging images of the organs collected from each mouse. A significant accumulation of senescent cells was observed, especially in the ileum of the small intestine (red dot box).

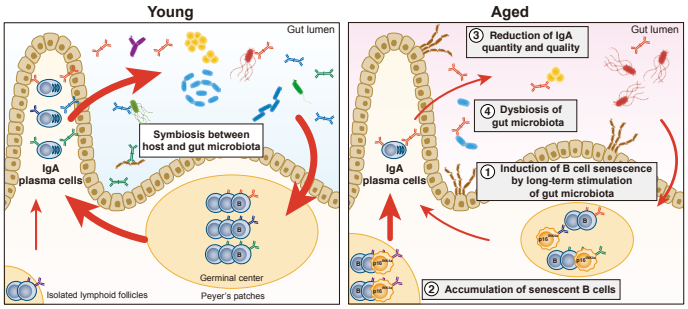

Fig.2. Age-associated changes of the interaction between host and gut microbiota
Left: In young age, IgA induced by the gut microbiota regulates the gut microbiota; thereby, a symbiotic regulatory loop between the host and gut microbiota through IgA is formed.
Right: In old age, long-term stimulation of the gut microbiota induces cellular senescence in ileal germinal center B cells, which leads to the reduction of IgA production and function, causing dysbiosis of gut microbiota through aging.

Patent

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Keyword aging, gut microbiota, cellular senescence, B cell, IgA