

Review

The Pivotal Role of Thymus in Atherosclerosis Mediated by Immune and Inflammatory Response

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Abstract

Atherosclerosis is one kind of chronic inflammatory disease, in which multiple types of immune cells or factors are involved. Data from experimental and clinical studies on atherosclerosis have confirmed the key roles of immune cells and inflammation in such process. The thymus as a key organ in T lymphocyte ontogenesis has an important role in optimizing immune system function throughout the life, and dysfunction of thymus has been proved to be associated with severity of atherosclerosis. Based on previous research, we begin with the hypothesis that low density lipoprotein or cholesterol reduces the expression of the thymus transcription factor Foxn1 via low density lipoprotein receptors on the membrane surface and low density lipoprotein receptor related proteins on the cell surface, which cause the thymus function decline or degradation. The imbalance of T cell subgroups and the decrease of naive T cells due to thymus dysfunction cause the increase or decrease in the secretion of various inflammatory factors, which in turn aggravates or inhibits atherosclerosis progression and cardiovascular events. Hence, thymus may be the pivotal role in coronary heart disease mediated by atherosclerosis and cardiovascular events and it can imply a novel treatment strategy for the clinical management of patients with atherosclerosis in addition to different commercial drugs. Modulation of immune system by inducing thymus function may be a therapeutic approach for the prevention of atherosclerosis. Purpose of this review is to summarize and discuss the recent advances about the impact of thymus function on atherosclerosis by the data from animal or human studies and the potential mechanisms.

Key words: atherosclerosis, thymus, aging, inflammatory, immune, mechanisms, Foxn1

Introduction

Atherosclerosis is a complex disease, in which multiple types of immune cells, inflammatory cells and cytokines are involved[1-8] (Fig. 1). Lipid metabolism is the pathological basis of atherosclerosis, which is characterized by involvement of artery lesions from the intima, usually the formation of lipid and compound carbohydrate accumulation, bleeding and thrombosis at first, and hyperplasia of fibrous tissue and calcium deposition, and has gradually degenerated and medial calcification, leading to arterial wall thickening and hardening, vascular stenosis. That increases the

incidence and mortality of patients with heart and cerebrovascular disease. So to reduce the incidence and mortality of heart and cerebrovascular disease in patients with coronary heart disease is the ultimate goal of anti-atherosclerosis therapy. Therefore, it is of great clinical and practical significance to study the mechanism of atherosclerosis.

Epidemiological studies have shown that the higher the incidence of atherosclerosis with age, the higher prevalence is mainly in middle-aged and elderly patients. The immune system function of elderly patients decreased, the number of immune

cells decreased, and the proportion was imbalanced. Previous studies have shown that a series of immune cells and their secreted cytokines are involved in the process of atherosclerosis, especially T lymphocytes. According to previous studies, the thymus will be shrunk with age, and may even disappear. However, with the deepening of the research in recent years, the researchers found that although thymus may deteriorate with age, it will not disappear and still has a certain function. A recent article by Sam Palmer et al. published in PNAS reveals that the vast majority of vertebrates will experience thymic involution (or atrophy) in which thymic epithelial tissue is replaced with adipose tissue, and result in decreasing export of T cell from the thymus[9]. John Murray et al. clearly stated the thymus continued to provide a source of new T lymphocytes through all ages in their research[10]. More importantly, Lynch et al also provided a relatively detailed description of age-related thymus atrophy, in which the authors also recalled that based on their and other previous investigators' results, the thymus would completely cease to produce new T cells at 105 years of age[11]. The thymus as a key organ in T lymphocyte ontogenesis plays an important role in optimizing

immune system function throughout the life[12, 13]. Studies have revealed that thymus is constantly atrophic or hypofunction with age[14]. The thymus is most active early in life but undergoes a steady decline in function over time[15-18]. Those age-associated immune dysfunctions are the consequence of declines in both the generation of new naïve T and B lymphocytes and the functional competence of memory populations[15]. Thymus transplantation can alter or partially reverse some immune related diseases, such as Alzheimer's disease, systemic lupus erythematosus, arthritis, etc[19-22]. It is well known that atherosclerosis is also an immune related disease[23-25]. So atherosclerosis should have a close relationship with thymus.

Our previous study showed that there was a decline in thymus function in atherosclerotic patients[26]. Therefore, the thymus may be involved in the process of atherosclerosis. However, the mechanism of thymus function involved in the process of atherosclerosis is still unclear. The purpose of this review is to summarize and discuss the recent advances in our knowledge of atherosclerosis vascular disease by the impact of thymus function on atherosclerosis, especially for the mechanism.

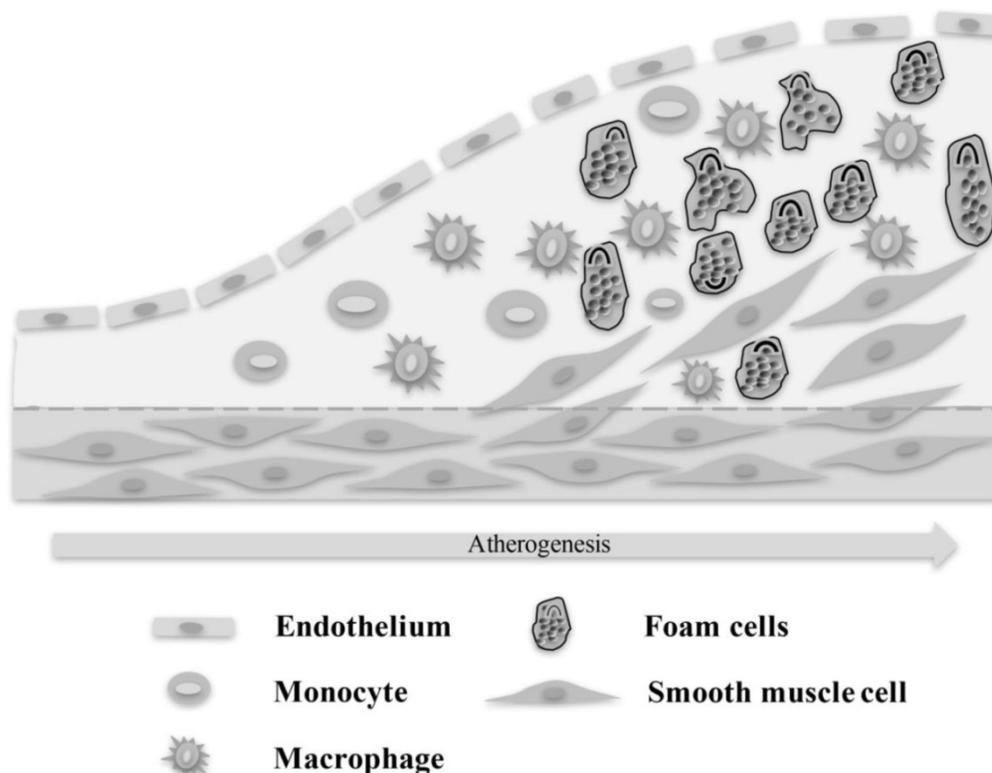


Figure 1. Immune cells including macrophages, T cells and monocyte are involved in the process of blood vessels from normal to atherosclerosis.

Thymus can directly or indirectly modulate inflammatory procedure

Thymus is an important part for T cell development and maturation. Indeed, the thymus is both where the T cell repertoire is generated and where the T cells are composed of positive and negative selection, leading to a wide range of functional MHC-restricted naïve TCR $\alpha\beta$ repertoire[27, 28]. As the development of T cells, they migrate within distinct thymus microenvironments, where they interact with stromal cells that provide signals critical for thymocyte survival, proliferation, differentiation, and selection[29-31].

T cells contain many subgroups. A brief introduction of T cell subgroups and their functions shows as follow. Naive T cells can differentiate into helper T cells(Th), regulatory T cells(Tregs) and cytotoxic T cells (Tc). The generation and maturation of this specific T cell lineage involve particular and complex processes within the thymus, and many signaling pathways participate in these processes. If a thymocyte is auto-reactive against antigens, it undergoes negative selection, via apoptosis, or differentiation into the regulatory T cell lineage. It is now well established that there are two main pathways for the generation of Treg cells in vivo. The majority of functionally mature Treg cells are produced in the thymus, where recognition of self-antigen by certain clones leads to their deviation into the thymus-derived Foxp3+ Treg (tTreg) cell lineage[32, 33]. Th can secrete IL-4, IL-17, and IFN- γ . In addition, Tregs can secrete IL-10. IL-4, a cytokine that stimulates the proliferation of activated B-cells and mast cells and enhances macrophages antigen presenting ability. In the absence of vascular tissue, the presence of IL 4 promotes the substitution of activated macrophages into M2 cells and inhibits the activation of classical activated macrophage M1 cells. Increased macrophage repair (M2) combined with the secretion of IL-10 and TGF- β resulted in a reduction of pathological inflammation[34-36]. The most compelling role of IL-17 is its involvement in the induction and regulation of pro-inflammatory responses. IL-17 induced production of other cytokines (e.g., IL-6, G-CSF, TGF- β , TNF- α , GM-CSF and IL-1 β), chemokines (including IL-8, GRO- α , MCP-1) and prostaglandin (e.g., PGE₂) from many types of cells, such as fibroblasts, endothelial cells, epithelial cells, keratinocytes and macrophages [37-41].

All of these cytokines, chemokines, and inflammatory cells are involved in the inflammatory procedure and atherosclerosis[42, 43]. Previous studies have shown that some cytokines(such as

TNF- α , IL-1,8,12 and IFN- γ etc.) promote the occurrence of atherosclerosis[44-65], while others(such as TNF- β , IL-4 and IL-10 etc.) inhibit the process of atherosclerosis [1, 61, 66-75] (see Table 1). Studies show that IL-6 can support a promotion and inhibition role in the development of atherosclerosis[76-78]. Besides, cytokine therapy with IL-2/anti-IL-2 monoclonal antibody complexes can attenuate the development and progression of atherosclerosis[79-81]. In summary, we learn that the thymus can directly or indirectly affect the above factors or cells, which may affect the atherosclerotic process. Thus, alterations in thymus function may be involved in atherogenesis by modulating inflammatory responses.

Table 1. Cytokines can promote or inhibit atherosclerosis

Cytokines	Whether it promotes or inhibits atherosclerosis?	References
TNF- α	Promotion	Refs: 40-46
TNF- β	Inhibition	Refs: 1,62-65
IL-1	Promotion	Refs: 47-49
IL-4	Inhibition	Refs: 57,66,67
IL-6	Promotion/ Inhibition	Refs: 72-74
IL-8	Promotion	Refs: 50-54
IL-10	Inhibition	Refs: 62,68-71
IL-12	Promotion	Refs: 55-58
IFN- γ	Promotion	Refs: 59-61

Refs stand for References.

Thymus may regulate the immune system by affecting immune cells

The thymus is a privileged and indispensable site for the generation and maturation of T cells in vivo, as this microenvironment induces and supports lineage commitment, differentiation, and survival of thymus-seeding cells. Tregs selection in the thymus is essential to prevent autoimmune diseases[82]. Tregs of the CD4+CD25+FOXP3+ phenotype are generated in the thymus and critical for the maintenance of immune homeostasis and the suppression of naturally occurring self-reactive T cells[83-85].

According to the previous researches, we should learn that the change of thymus function can affect the function of macrophages and B cells. The monocyte-macrophage system has a crucial role in innate immunity and also in the initiation of the adaptive immune response[86-88]. Plasma cells derived from B cells participate in humoral immune response. Moreover, dendritic cells(DCs) play a significant role in establishing self-tolerance and inducing antigen-specific immunity through their ability to present self-antigens to developing T cells in the thymus[89-91]. These cells are involved in the immune response. Hence, changes of the thymus

function can affect the immune system.

Atherosclerosis is a complex disease characterized by smooth muscle cell proliferation, cholesterol deposition, and the infiltration of mononuclear cells. The formation and progression of atherosclerotic plaques result in the disruption of organ perfusion, causing cardiovascular and cerebrovascular diseases. It has been proved that immune responses participate in every phase of atherosclerosis. The presence of leukocytes within atherosclerotic arteries was discovered in the late 1970s[2, 92]. There is increasing evidence show that both adaptive and innate immunity tightly regulate the development and progression of atherosclerosis.

Recent studies have suggested that Tregs, a special T cell subtype, exhibit a weak immune response, have immune-suppressive characteristics of immune-related vascular disease, and play an important role in immune tolerance and immune regulation[1, 2, 93-98]. What was discovered in recent years is that several subsets of Tregs, which are responsible for maintenance of immunological tolerance and suppressing immune over activity of effector T cells, diminish atherosclerosis development by down-regulation of activated T cell responses[99-103]. There are more and more evidences show that CD4⁺ effector T cells may accelerate the development of atherosclerosis. In contrast, CD4⁺ Treg cells play a protective role in atherosclerosis[42, 97, 102, 104-108]. During the occurrence and development of atherosclerosis, diverse types of interactions between immune cells, cytokines, and antibodies form a very complex network of cellular and humoral immune mechanisms[108-110]. Indeed, once Tregs are activated, they can secrete IL-10 and TGF- β 1 to suppress several cell types, including antigen-specific T cells[66-69, 96]. Besides the balance between effector T cells and Tregs, which is sufficient to control atherosclerosis development and progression[111-118]. Tregs inhibit the activation of other lymphocytes via the direct secretion of cytokines or inducing other cells to secrete cytokines, hereby limiting the occurrence and development of atherosclerosis[74, 75]. In addition to Tregs, tolerogenic DCs have a critical role in the regulation of T cell response in atherosclerosis according to previous research[119-123].

In a word, changes in thymus function may take part in atherogenesis by regulating the immune system.

Aging and atherosclerosis

Aging, which many aspects of that involve inflammatory processes, is associated with chronic,

low-grade inflammatory activity leading to long-term tissue damage, and systemic chronic inflammation has been found to be related to all-cause mortality risk in elderly persons[124-129]. Age-related diseases such as Alzheimer's disease, Parkinson's disease, atherosclerosis, and type 2 diabetes are initiated or worsened by systemic inflammation, because the genetic constitution of the organism interacting with systemic inflammation may cause defined organ-specific illnesses, thus suggesting the critical importance of unregulated systemic inflammation in the shortening of survival in humans.

Thymus is an aging associated organ. But evidences have shown that the processes of positive and negative selection qualitatively appear to remain intact, despite the quantitative reductions in cortical and medullary thymocytes in the aged thymus[16-18, 130-134]. Moreover, the naive T cells generated in aged mice appear functionally normal but the decrease in thymic productivity[135, 136]. Increasing the input of functional thymus progenitors can trigger an expansion of thymus epithelial cells (TEC), which in turn create new niches for T-cell lineage commitment and supports increased the proliferation of thymocyte. Alternatively, in aging, the decline in these factors may reinforce a down-ward spiral resulting in thymic involution.

The thymus is the main immune organ and capable of generating T cells throughout life and is crucial for development, selection, and maintenance of peripheral T-cells. It is well documented that aging negatively affects immune responses, leading to an increase in infection and mortality. Aging reduces immune function, part of the reason is thymus involution leads to striking loss of progenitors, epithelial cells, and differentiating thymocytes, causing a decline in the production of naive T cells by the thymus[18, 137-142].

Thymus transcription factors forkhead box N1(Foxn1) is the most important factor for thymus complete physiological function[141, 143-145]. With the atrophy of thymus, the expression of thymus aging-associated gene Foxn1 decreases, that means down-regulation of Foxn1 with age. Increased expression of Foxn1 can improve thymus function, and even promote regeneration of the thymus [146]. Žuklys S et al.[147] determine that Foxn1 regulates the expression of genes involved in antigen processing and thymocyte selection, in addition to the transcriptional control of genes involved in the attraction and lineage commitment of T cell precursors. Therefore, there are reasons to believe that the thymus Foxn1 may be involved in the process of atherosclerosis. In previous studies, the atrophy of thymus organs in patients with coronary heart disease

has been confirmed[26], yet the specific altering of thymus function has not been clearly revealed.

Lipid metabolism is the pathological basis of atherosclerosis. Low density lipoprotein(LDL) in the arterial wall is generally oxidized to oxidized LDL (oxLDL), which is atherogenic, and induces vascular endothelial cells to express adhesion molecules, cytokines and chemokines that attract immune cells[5, 148-152]. *Amy H. Newton et al.*[148] found that naïve cells become activated and differentiate to mature effector T cells that are Th1, Th2 or Treg cells. OxLDL and high density lipoprotein (HDL) regulate activation of macrophages and endothelial cells, and T cells, which perpetuate atherogenesis by promoting cell-mediated responses and inflammation. OxLDL leads to inflammation and nucleation of atherosclerotic plaque in the arterial wall and its incorporation into foam cells, which is opposed by HDL.

LDL receptor-related protein-1 (LRP-1), a member of the scavenger receptor family, is a large endocytic receptor and is a multifunctional cell surface receptor expressed in a wide range of cells, including vascular smooth muscle cells(vSMCs) and

macrophages[153-156]. The early studies have revealed that mice with a selective knockout of LRP in macrophages crossed into an apoE/LDL receptor double knockout mouse[157-160] or vSMCs (LRP^{smc-/-}) on an LDL receptor (LDLR)^{-/-} background lead to an exacerbation of atherosclerosis[161-163]. LRP-1 plays a role in arterial wall physiology and pathology[159, 160, 164-166]. From the study of *Kamel Boukais et al.*, we know that LRP-1 is also a scavenger receptor responsible for the uptake of LDL, especially the aggregation of LDL, leading to intracellular accumulation of lipids and transformation of vSMCs and monocyte-derived macrophages into foam cells in human atheroma[154, 161, 167-169]. Although LDL remains to be the most important risk factor for atherosclerosis, immune and inflammatory mechanisms play a significant and non-redundant role in atherogenesis.

Based on the above statement, we propose the hypothesis of the mechanism of thymic function to participate in the process of atherosclerosis (Fig. 2). Hence, the change of thymus function provides a new target for the treatment of atherosclerosis.

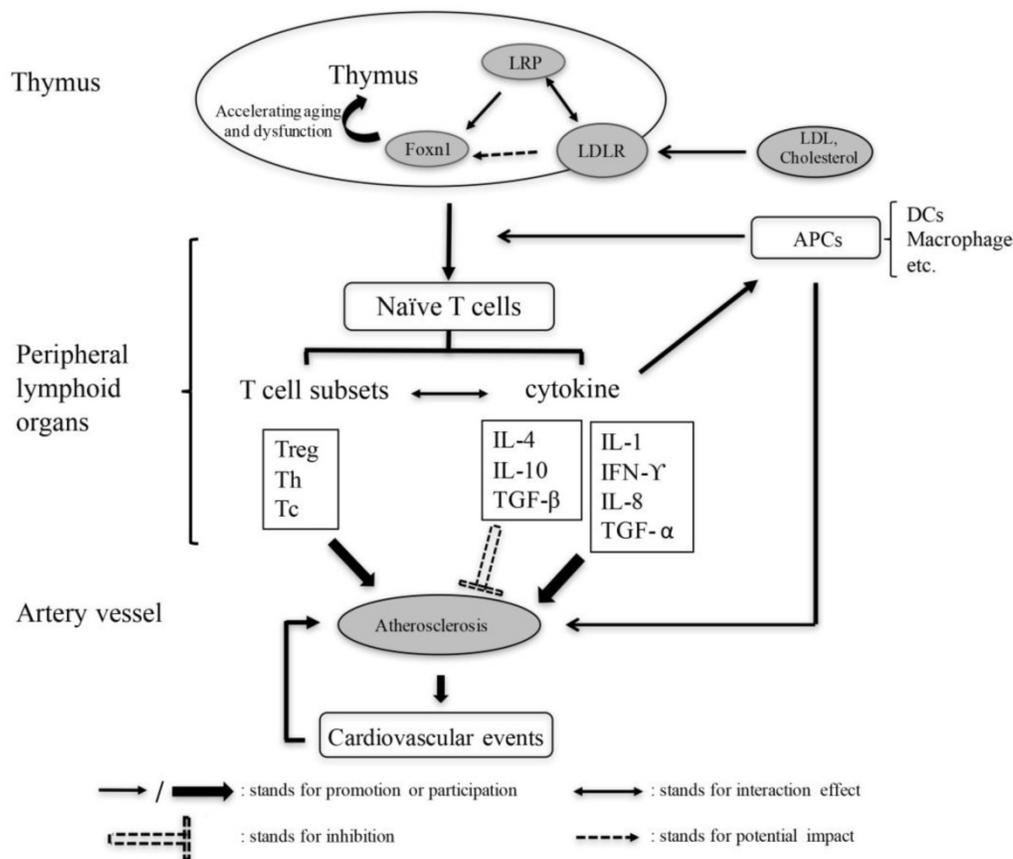


Figure 2. The pivotal role of thymus in AS mediated by immune and inflammatory response. Thymus dysfunction leads to the imbalance of T cell subsets and change in secretion of cytokines, thereby aggravating or inhibiting the progression of atherosclerosis, and as well as other cardiovascular events. LRP: Low density lipoprotein receptor-related proteins, LDLR: Low density lipoprotein receptors, APC: Antigen presenting cell, DC: Dendritic cell, Foxn1: Forkhead box N1, Treg: Regulatory T-cell, Th: Helper T cell, Tc: Cytotoxic T cell.

Conclusion and perspective

Atherosclerosis is considered as an immune inflammatory disease, and the T cell-mediated immune inflammatory response plays an important role in the pathogenesis of atherosclerosis[170]. T cells mature in the thymus site and are involved in the process of atherosclerosis induced by inflammation and immune response. Inflammatory mechanisms and immune system mechanisms are crucially involved in the pathophysiology of atherosclerosis and cardiovascular disease. T lymphocytes are involved and play an important role in both the inflammatory response and the immune response. An imbalance of the degree of activation of the protective Treg lymphocytes, the pro-inflammatory and cytotoxic macrophages and T-effector lymphocytes could thus be at the origin of the triggering or not of progression of vascular injury. However, all of these processes are closely associated with thymus function. In other words, changes in the function of thymus will be deeply affecting the process.

Based on previous research, we can speculate that the changes of thymus function may have an impact on the process of atherosclerosis. The mechanism of thymus involvement in the process of atherosclerosis is assumed as follows: Low density lipoprotein or cholesterol reduces the expression of the thymus transcription factor Foxn1 via low density lipoprotein receptors (LDLR) on the membrane surface and low density lipoprotein receptor-related proteins on the cell surface, which cause the thymus function decline or degradation. The imbalance of T cell subgroups and the decrease of naive T cells due to thymus dysfunction cause the increase or decrease in the secretion of various inflammatory factors, which in turn aggravates or inhibits atherosclerosis progression and cardiovascular events. NK T cell, DCs and macrophages can affect the process of atherosclerosis by affecting the production of naive T cells through the thymus. Furthermore, these cells can also participate in the progression of atherosclerosis via the direct secretion of cytokines or inducing other cells to secrete cytokines (Fig. 2).

According to our hypothesis, lentiviral transfection, siRNA, gene knockout and thymic transplantation technologies can be selected to improve aging thymus function in animal experiments. In the clinical treatment of atherosclerosis, and even other immune-related diseases, we may consider using a vaccine, or a similar alternative to foxn1 to improve the expression of foxn1 in the human body, thereby improving or restoring aging thymus function and resisting the related-diseases caused by the decline of immunity.

In summary, novel data increasingly suggests the potential for new targets of the thymus function for therapeutic intervention to modify the course and reduce events in atherosclerosis and cardiovascular disease, as studies increasingly implicate thymus-related mechanisms. Further investigation on changes of thymus function will help to develop new therapeutic targets that may improve outcomes in atherosclerosis and cardiovascular disease and discover novel approaches in the treatment of atherosclerosis and vascular disease.

Of course, the underlying mechanism of the hypothesis still has some shortcomings in this review. We also need to investigate that how low density lipoprotein affects the expression of the thymus transcription factor Foxn1 via low density lipoprotein receptors on the membrane surface and low density lipoprotein receptor-related proteins on the cell surface.

Abbreviations

Treg-cell/Tregs: Regulatory T-cell(s); Th: Helper T cells; Tc: Cytotoxic T cells; APC: Antigen presenting cell; DC: Dendritic cell; NK T: Natural killer T cells; Foxn1: Forkhead box N1; LDL: Low density lipoprotein; HDL: High density lipoprotein; LDLR: Low density lipoprotein receptors; LRP: Low density lipoprotein receptor-related proteins; vSMCs: Vascular smooth muscle cells; apoE: Apolipoprotein E; oxLDL: Oxidized LDL.

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Authors' contributions

Xianliang Dai, Zonggui Wu and Chun Liang conceived and designed the paper. Xianliang Dai, Danfeng Zhang and Chaoqun Wang analyzed the relevant literature and drew the figures. Xianliang Dai wrote the paper.

Competing Interests

The authors have declared that no competing interest exists.

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