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論文内容の要旨

Background

Epidemiological data consistently rank atherosclerotic diseases as among the leading causes of mortality worldwide, even accounting for the recent excess deaths attributed to the COVID-19 pandemic.¹ These diseases often remain asymptomatic until they progress to advanced stages. Patients frequently present with severe complications, such as myocardial infarction, ischemic stroke, or aortic rupture, at which point outcomes are often poor, marked by high mortality, permanent disability, and substantial healthcare costs. These trends highlight the immediate need for improved strategies for the early detection and treatment of atherosclerosis and its complications to mitigate their significant global health burden.

Recent studies have upgraded the conventional understanding of atherosclerosis, highlighting the pivotal role of inflammation in its development.^{2, 3} Immune cell activity is intricately involved at nearly every stage of atherosclerosis. Initiation of atherosclerosis begins with the innate immune response, where circulating monocytes are recruited to the vascular endothelium through interactions with adhesion molecules upregulated in aged or injured vessels. These monocytes infiltrate the vessel wall and differentiate into macrophages or dendritic cells (DCs). Low-density lipoprotein (LDL) cholesterol transferred by endothelial cells into the subendothelial space undergoes oxidation, facilitated by recruited macrophages. Oxidized LDL is internalized by macrophages via scavenger receptors, triggering their transformation into foam cells—the hallmark

of early atherogenesis (**Figure 1**). As atherosclerosis progresses, resident DCs, including those derived from monocytes, initiate the adaptive immune responses by presenting antigens to T cells. Upon presentation of antigen—whether self or pathogenic-derived—naïve CD4⁺ T cells differentiate into several helper T cell subsets. Key subsets observed in atherosclerotic lesions include type 1 T helper (Th1), type 2 T helper (Th2), type 17 T helper (Th17), and regulatory T cells (Tregs). While Th1, Th2, and Th17 cells collectively constitute effector memory T cells (Teffs) that promote inflammation, Tregs serve an anti-inflammatory role, underscoring the dynamic role of adaptive helper T cells between immune activation and regulation in atherosclerosis.^{4, 5}

The verdict on Th1 cell-mediated roles in atherogenesis is unanimous as consistent evidence demonstrates the proinflammatory proatherogenic activities of Th1 cells and their related cytokines, interferon-gamma (IFN- γ) and tumor necrosis factor-alpha.^{6, 7} A recent translational study indicated the likely proatherogenic role of Th1 cells in humans.⁸ Meanwhile, opinions are divided due to contradictory findings on Th2 cell-mediated responses. Th2 cells are likely antiatherogenic because most of their activities counteract Th1 cell-mediated inflammation, causing a collective belief that a lower Th1 cell/Th2 cell ratio is beneficial.⁹ Conversely, a strong clinical association exists between allergic diseases, conditions in which Th2 cell-mediated inflammation predominates, and an increased risk of cardiovascular events related to atherosclerosis. This risk is likely related to the Th2 cell-dependent activation of proinflammatory B cells and the upregulation of immunoglobulins.

The initial trigger for an aneurysmal lesion may resemble the early development of atherosclerosis, beginning with intimal injury followed by innate and adaptive immune responses with a predominance of Th1 cell activities. The establishment of aortic plaque seems essential for causing aortic dilation, particularly in the angiotensin II-induced abdominal aortic aneurysm (AAA) model in LDL receptor-deficient mice, in which a high-fat, high-cholesterol diet is

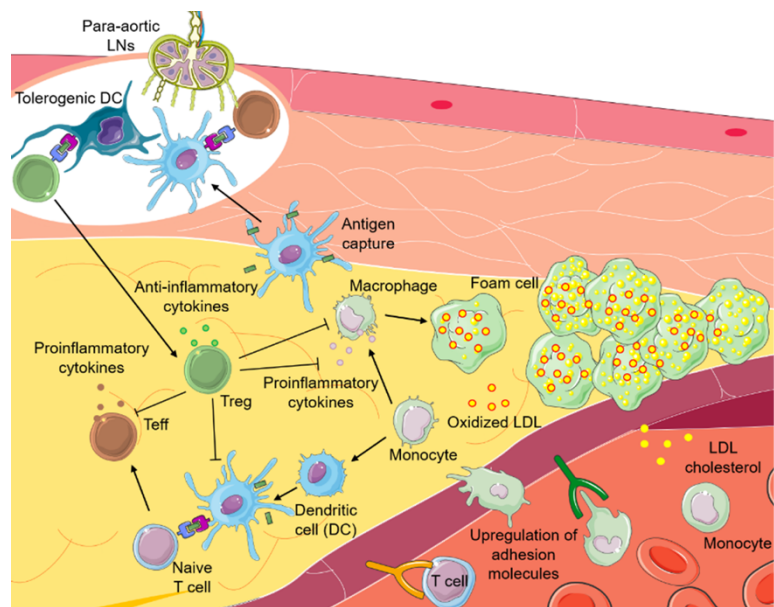


Figure 1. Immunoinflammatory responses in atherogenesis. This figure was partly generated using Servier Medical Art, by Servier (<http://smart.servier.com>).

required to sustain plaque progression. Switching to a normal chow diet in these mice halted angiotensin II-induced AAA dilation.¹⁰ However, the influence of Th1 cell/Th2 cell balance in AAA progression likely differs from that of atherosclerosis (**Figure 2**). Surgically removed human AAA tissue demonstrated a predominance of Th2 cell-related cytokines.¹¹ Additionally, induction

of Th2 cell-mediated inflammation promoted aneurysm in allografted aorta in mice.¹² Consequently, a shift to Th2 cell predominance after establishing early atherosclerosis induces AAA development, whereas persistent Th1 cell predominance proceeds to a stenotic lesion.¹²

Th17 cells primarily produce interleukin (IL)-17, particularly the major isoform IL-17A. Inciting vascular inflammation thus are considered proatherogenic and known to cause aneurysm aggravation.¹³⁻¹⁵ Studies have linked the IL-23/Th17 axis to AAA development, as IL-23 promotes Th17 differentiation.¹⁶ The relationship between obesity and increased IL-23 levels highlights the broader role of cardiometabolic factors in Th17 cell-driven inflammation.¹⁷

In contrast, Tregs exhibit consistent anti-inflammatory and antiatherogenic properties in both atherosclerosis and AAA development. Tregs suppress immune activation through cell-to-cell contact via cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and produce anti-inflammatory cytokines such as IL-10 and transforming growth factor (TGF)- β . The balance between helper T cell subsets, such as Th1/Th2, Th1/Treg, and Th17/Treg ratios, determines the inflammatory trajectory in atherosclerosis and AAA.

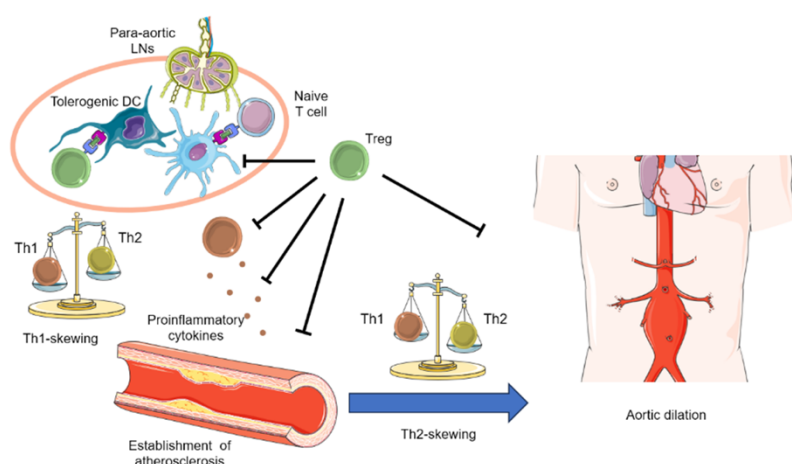


Figure 2. The roles of the Teff /Treg and Th1/Th2 balance in atherosclerosis and abdominal aortic aneurysm. This figure was partly generated using Servier Medical Art, by Servier (<http://smart.servier.com>).

Given the crucial role of helper T cells, the laboratory I belong to has focused on identifying novel targets for the treatment of atherosclerosis and related diseases through the regulation of immune responses. As an immunotherapy target, the modulation of the helper T cell subset balance is the topic of interest. Experimental approaches targeting T cell balance have included antibodies,^{9, 18, 19} cytokines,⁹ an active form of vitamin D₃,²⁰ vaccination,²¹ overexpression of CTLA-4,^{22, 23} and ultraviolet B (UVB) phototherapy.²⁴⁻²⁶

Among the above interventions, UVB phototherapy has been widely used to manage inflammatory skin conditions. To minimize risks such as skin irritation, immune suppression, and skin cancer, recent studies have investigated single-wavelength UVB irradiation using distinct wavelengths.²⁷ Among these, 282 nm UVB significantly reduced atherosclerosis by promoting Treg responses, including increased expression of C-C chemokine receptor 4 (CCR4), whereas 312 nm UVB, resembling narrowband UVB (NB-UVB) used clinically, demonstrated a tendency toward atheroprotection, suggesting its therapeutic potential.

A different approach involving a chemokine receptor likely responsible for facilitating T cell migration into inflammatory sites is also promising. CCR4, expressed predominantly in Tregs and Th2 cells but absent in Th1 cells, making it a promising target for modulating immune responses. While already targeted in cutaneous T cell lymphomas,²⁸ its role in vascular inflammation and atherosclerosis remains unexplored.

Based on these findings, this thesis aimed to explore novel therapeutic strategies utilizing CCR4 and 312 nm UVB irradiation with particular focus on modulation of helper T cell responses in atherosclerotic diseases. Given that UVB irradiation increased Treg expression of CCR4, this thesis also sought to evaluate the possibility applying synergistic effect of both interventions.

1. Unveiling the role of CCR4 in atherosclerotic disease: insights from gene deletion models and implications for novel therapeutic strategies

Given the high specificity of CCR4 expression in helper T cell subsets, targeting CCR4 may selectively modulate T cell responses and their balance. Several inflammatory disease models have highlighted the importance of CCR4 in modulating inflammation through its role in Treg recruitment to related organs.^{29, 30} From a clinical perspective, CCR4 has been a target for the treatment of the cutaneous form of T cell lymphoma (mycosis fungoides and Sezary syndrome) through the administration of the clinically approved recombinant humanized monoclonal anti-CCR4 antibody called mogamulizumab.³¹ However, the roles of CCR4 in vascular inflammation, atherosclerosis, and related diseases are unknown. Therefore, experiments were conducted to explore the role of CCR4 in atherosclerotic diseases using mouse models of atherosclerosis and AAA.

Methods

CCR4-deficient (*Ccr4*^{-/-}) mice³² were crossed with hypercholesterolemic apolipoprotein E-deficient (*Apoe*^{-/-}) mice¹⁸ to generate *Ccr4*^{-/-}*Apoe*^{-/-} mice on a C57BL/6 background. For atherosclerosis, mice were fed regular chow throughout the experiments. Mice were sacrificed at 18 weeks of age to observe atherosclerosis formation in the aortic sinus and thoracoabdominal aorta.

In AAA experiments, mice were fed regular chow until 6 weeks of age before switching to a high-cholesterol diet. Six weeks after diet conversion, infusion of angiotensin II (aneurysm-induced groups) or saline (sham-operated groups) was initiated by implanting a miniosmotic pump. Mice were sacrificed 4 weeks after implantation to collect blood and observe AAA formation. Some mice were sacrificed 1 week after pump implantation to examine immune responses during the early phase of AAA development.

The analysis included, but was not limited to, assessment of aneurysm morphology, histological analysis of atherosclerosis and aneurysmal lesions with and without immunostaining, flow cytometric analysis of immune cells, enzyme-linked immunosorbent assay (ELISA), quantitative real-time polymerase chain reaction, and intracellular cytokine staining.

Results

Ccr4 gene deletion accelerated early atherosclerosis while unexpectedly exhibiting a protective effect on AAA development. The protective effect was attributed to the endorsement of a Th1 cell-skewed immune response.

The high expression level of CCR4 on CD4⁺Foxp3⁺ Tregs was confirmed as opposed to CD4⁺Foxp3⁻ non-Tregs. Additionally, the expression of CCR4 ligands, C–C chemokine ligand 17 and C–C chemokine ligand 22, in atherosclerotic plaque and angiotensin II-treated aortic tissues was confirmed through immunostaining. However, no detectable ligands were detected in the aortic tissue of saline-treated mice. These results indicate the importance of the CCR4 axis in the inflammatory response of the aorta.

Observations of atherosclerotic lesions in the aortic sinus of 18-week-old *Ccr4*^{-/-}*Apoe*^{-/-} mice distinctively demonstrated a notable size increment compared with the control *Apoe*^{-/-} mice. Lesion size was quantified as mean \pm standard deviation (s.d.). An aortic sinus mean \pm s.d. plaque area of $1.46 \pm 0.50 \times 10^5 \mu\text{m}^2$ was obtained for control *Apoe*^{-/-} mice *versus* $2.04 \pm 0.82 \times 10^5 \mu\text{m}^2$ for *Ccr4*^{-/-}*Apoe*^{-/-} mice.

In addition, 93.2% of angiotensin II-infused *Apoe*^{-/-} mice developed AAA. This strikingly high incidence was reduced by CCR4 deficiency, decreasing the incidence by nearly half (52.3%), as observed in angiotensin II-infused *Ccr4*^{-/-}*Apoe*^{-/-} mice. Moreover, when the severity of AAA was analyzed using the accepted grading scale, the AAA phenotype of angiotensin II-infused *Ccr4*^{-/-}*Apoe*^{-/-} mice scored much lower severity compared with angiotensin II-infused *Apoe*^{-/-} mice.

The angiotensin II-induced AAA mouse model has consistently demonstrated that aortic inflammation initiates AAA development.³³ Macrophages and CD4⁺ T cells are the main constituents of infiltrating cells in aneurysmal tissues. Through MOMA-2 and CD4 immunostaining, this study observed that the aneurysmal lesions of angiotensin II-infused *Ccr4*^{-/-}*Apoe*^{-/-} mice had significantly lower accumulation of macrophages and CD4⁺ T cells than those of angiotensin II-infused *Apoe*^{-/-} mice.

Remodeling of structural proteins in the aortic wall matrix is widely recognized as the hallmark of AAA pathology. Therefore, histological analysis of the aortic wall of angiotensin II-infused mice was performed which revealed a preserved normal structure of elastin layers and strikingly lower expression of matrix metalloproteinases and their activity in CCR4-deficient mice. Collagen analysis also revealed lower angiotensin II-induced abnormal deposition in CCR4-deficient mice. This result is supported by lower expression of profibrotic TGF- β 1, which induces collagen deposition by fibroblasts.

Flow cytometric analysis revealed expansion of Tregs and Tregs in lymphoid tissues of CCR4-deficient mice. However, this study confirmed the lower suppression capacity of CCR4-deficient Tregs. Evaluation of helper T cell subsets displayed Th1 cell-skewed responses through cytokine staining analyses of lymphoid tissues. Additionally, ELISA revealed that quantification of plasma immunoglobulin E (IgE) levels correlated with Th2 cell activity showed lower levels in CCR4-deficient mice. These results indicate that the Th1 cell-skewed responses at the systemic level likely result from impaired Treg suppression of Th1 cells. Investigation of the local response in the aorta reported consistent results with pronounced inhibition of angiotensin

II-induced Th2 cell recruitment to the aorta, resulting in skewing of the Th1 cell/Th2 cell ratio calculation toward Th1. Similarly, the observation of angiotensin II-induced B cell recruitment to the aorta exhibited a remarkable reduction in CCR4-deficient mice.

2. Evaluating the efficacy of clinically feasible 312 nm UVB irradiation as phototherapy for atherosclerosis

In previous studies, broadband UVB irradiation protected mice from atherosclerosis and aortic aneurysms via an induced increase in Treg proliferation.^{24, 26} This increase was associated with the activity of Langerhans cells, which responded to UVB irradiation and promoted Treg activation. Concerns have arisen regarding the side effects of UVB treatment. Chronic exposure to UVB irradiation may cause irritation, infection, immune suppression, and the most serious adverse effect of irradiation: skin cancer. Therefore, careful planning of the dose and irradiation conditions is required to reduce the probability of such side effects. The UVB spectrum consists of a range of wavelengths, using a narrower band or, when possible, a single wavelength may help in reducing adverse effects while maintaining optimal benefits, as previously demonstrated with 282 nm UVB.²⁷ UVB irradiation has long been used in clinical settings to manage inflammatory skin conditions, such as psoriasis and vitiligo. Narrowband 311 nm peak NB-UVB irradiation is currently the most widely endorsed UVB phototherapy. However, a previous study using 312 nm UVB, which closely resembles clinical NB-UVB, showed only a tendency toward atheroprotective effects.²⁷ Given that the dose used in the previous study (2 kJ/m²) was considerably lower than those typically used in clinical settings, the current study investigates the atheroprotective potential of higher doses of 312 nm UVB and its underlying mechanisms.

Methods

Atherosclerosis-prone *Apoe*^{-/-} mice on a C57BL/6 background were assigned to three groups: nonirradiated control, 5 kJ/m², and 10 kJ/m². Irradiation was delivered using a light-emitting diode device that emits a specific wavelength of 312 nm UVB. Irradiation began at 6 weeks of age; it was performed weekly until 20 weeks of age (14 times). At the end of treatment, mice were sacrificed and analyzed for their atherosclerosis plaque phenotype. Some mice were irradiated for 6 weeks to examine the effects of 312 nm UVB irradiation on immune responses.

Results

The high dose of 10 kJ/m² 312 nm UVB irradiation reduced plaque development associated with the Treg/Teff balance shift toward Treg responses and reduced the Th1 cell/Th2 cell ratio. In comparison with the nonirradiated control mice, a notable size reduction of aortic sinus atherosclerotic lesions was observed in the 10 kJ/m² 312 nm UVB-irradiated mice when the aortic sinus plaques at five different levels were analyzed in detail. The change in plaque size was

accompanied by reduced recruitment of immune cells (macrophages and CD4⁺ T cells) into the plaque and increased collagen content.

The 312 nm UVB irradiation induced an increase in CD4⁺Foxp3⁺ Tregs cellularity in the lymphoid tissues of hypercholesterolemic mice while reducing the cellularity of splenic CD4⁺CD44^{hi}CD62^{lo} T effs. The evaluation of helper T cell subsets revealed an unchanged proportion of IFN- γ -producing Th1 cells, IL-4-producing Th2 cells, IL-17-producing Th17 cells, and IL-10-producing CD4⁺ T cells. However, the calculation of the Th1 cell/Th2 cell ratio revealed a reduction in 5 and 10 kJ/m² 312 nm UVB-irradiated mice. In addition, the upregulation of Treg-enhancing proresolving lipid mediators (resolvin D1, resolvin D2, and maresin 1) was observed in the skin sample of UVB-irradiated mice.

Summary

This thesis investigates the modulation of helper T cell-mediated immune responses as a therapeutic strategy for atherosclerotic diseases. Emphasizing the immunoinflammatory basis of these diseases, the work explores two complementary approaches: targeting CCR4 to manipulate T cell migration and responses, and utilizing UVB irradiation to directly influence immune cell balance. Despite their differences, both strategies converge on the central theme of the thesis: the critical importance of adaptive immune regulation in the progression of atherosclerotic diseases. CCR4 deficiency and UVB irradiation independently demonstrate that favorably altering the balance of helper T cell subsets can attenuate chronic vascular inflammation. Together, these findings pave the way for multimodal immunotherapeutic approaches, combining molecular and physical interventions to address the diverse immune mechanisms underlying atherosclerosis and AAA.

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論文審査の結果の要旨

動脈硬化性疾患の発症及び進展には、マクロファージやT細胞などの免疫細胞が深く関わっている。主にT細胞が関与する獲得免疫応答を調節して腹部大動脈瘤と動脈硬化を防ぐ新規治療法の開発を目的に、病態モデルマウスを作出して研究を実施した。ケモカイン受容体 CCR4 の欠損マウスでは、ヘルパーT細胞が Th1 細胞優位となることで、アンジオテンシンⅡにより誘導される腹部大動脈瘤の形成が抑制されることを見出し、その詳細な機序について FACS や免疫染色などの実験手法を用いて明らかにした。また、皮膚疾患の治療に臨床使用されている 312nm の紫外線 B 波を LED を用いて動脈硬化モデルマウスに照射すると、制御性 T 細胞が増加してエフェクターT細胞が減少することで、大動脈基部における動脈硬化病変の形成が抑制されることを明らかにした。

本学位論文に示されている研究成果は、薬物療法のない腹部大動脈瘤に対する新規治療法の開発、及び動脈硬化に対する紫外線療法の開発に多大な貢献を果たすと期待できることから、本研究の臨床的有益性は高く、重要な知見を得たものとして価値ある研究であると認める。

上記の論文は博士（薬学）論文として、適当と判定する。