Acute myocardial infarction (AMI) is one of the major causes of sudden cardiac death. The mechanism of AMI is just an occlusion of a coronary artery.1 In some cases, severe coronary organic stenosis leads to total occlusion and results in AMI. For these cases, percutaneous coronary intervention (PCI) for severe coronary stenosis is applied to prevent AMI. Some medications, such as statins and antiplatelet therapy, are also used.

On the other hand, in most AMI cases, rupture or erosion of atherosclerotic plaque is the leading cause of acute thrombotic coronary occlusion.2 The condition of the coronary artery just before the rupture has been reported not to be severely stenotic.3 Therefore, such a lesion does not make patients feel typical angina symptoms like chest compression or dyspnea on effort. For that reason, it is quite challenging to know the appropriate timing of treatment for patients to avoid AMI. Detection of such a vulnerable plaque and its stabilization is a pivotal step to resolve the situation. However, molecular markers or therapeutic targets of the plaque have not been fully unveiled.

Cyclophilin A is a functional protein conserved over many species and is associated with many diseases such as cardiovascular diseases, diabetes, viral infection, Alzheimer’s disease through T cell activation and/or function as a chaperone protein. Especially in cardiovascular disease, Cyclophilin A is known to affect atherosclerosis and aortic aneurysms. Nakai, et al. reported the increased level of Cyclophilin A in a coronary artery plaque with intra-plaque hemorrhage (IPH) in patients with impaired kidney diseases in this issue.4 According to previous reports, IPH is a characteristic of vulnerable plaque, leading to AMI due to a rupture or erosion of atherosclerotic plaques.5 Several factors are known features of unstable atherosclerotic lesions, such as large necrotic cores with thin fibrous caps, inflammatory cells, and cholesterol deposits.6 The increased number of foam cells is also a representative feature of unstable atherosclerotic lesions. The fibrous cap becomes thin and finally ruptures due to the depletion of matrix components by activating enzymes, such as matrix-metalloproteinases (MMPs), cysteine, and aspartate proteases.6 The reduction of smooth muscle cells also induces the instability of the fibrous cap.7

Among these factors, IPH is a significant contributor to unstable atherosclerotic plaque. Atherosclerotic neovascularization can be a source of IPH and influx of inflammatory mediators, resulting in unstable atherosclerotic lesions.8 A study by Nakai, et al. indicated that Cyclophilin A, an indirect matrix-metalloproteinase inducer, could be a new target for vulnerable plaque and hyperlipidemia.9 This study offers a new treatment strategy idea not only about Cyclophilin A, and it can be a turning point in atherosclerosis treatment.

Statins are strongly recommended to control cholesterol levels in patients with CAD in the current guidelines.10 The benefits of statins, especially strong statins such as rosuvastatin, atorvastatin, and pitavastatin, have been demonstrated in clinical trials.11 A low-density lipoprotein cholesterol level below 70 mg/dL is recommended for secondary prevention.10 Recently, as a new type of drug for hyperlipidemia, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have been used in patients who cannot reach their target level of cholesterol even with other kinds of drugs, including strong statins.12 Furthermore, cholesterol absorption inhibitors, bile acid sequestrants, lomitapide, fibrates, and n-3 fatty acids are also used.13

However, these drugs used in clinical practice also have adverse effects. As the major adverse effects of statins, muscular pain, and tenderness often develop, and it is reported that statin-associated muscle symptoms occurred in up to 10% of patients treated with statins.14 The elevation of alanine aminotransferase is also a side effect of statins. While such adverse effects occur less often with PCSK9 inhibitors, itching at the site of injection and flu-like symptoms have been reported.15 Moreover, PCSK9 inhibitors are somewhat expensive; therefore, their cost-effectiveness may be limited to only patients with a very high risk of CAD. With these adverse effects and disadvantages, a new treatment strategy for vulnerable plaque that involves treating hyperlipidemia is needed (Figure).

MMPs play an essential role in the development of...
In the present clinical practice

**Statins**
- PCSK9 inhibitors
  - Cholesterol absorption inhibitors, bile acid sequestrants, fibrates, ...

**New targets?**
- Cyclophilin A inhibitors
- MMPs inhibitors (eg. tetracyclin)
- Anti-inflammatory drugs

**Figure.** Current anti-hyperlipidemia drugs and the prevention of vulnerable plaque. The present treatment strategy including statins and proprotein convertase subtilisin/kexin type 9 inhibitors is quite effective. However, it also has adverse effects; therefore, a new treatment is required. Cyclophilin A and inflammatory cytokines are potential new treatment targets.

Atherosclerosis through degradation of the extracellular matrix. Moreover, MMPs induce smooth muscle cell migration within a vessel wall, resulting in the accumulation of other cellular materials and occlusion of the vessels. Several kinds of MMPs, such as MMP-1, MMP-2, MMP-3, MMP-8, and MMP-9, have been shown to facilitate vascular remodeling by reducing matrix and migration of smooth muscle cells within a vessel wall. The antibiotic and zinc chelator tetracycline can inhibit the activity of MMPs; therefore, tetracycline has the potential to prevent vulnerable plaques. However, no clinical trials have been conducted.

Inflammatory cytokines also can be a target for the treatment of vulnerable plaques and hyperlipidemia. Interferon γ, produced by Th1-type T cells and natural killer cells, inhibits collagen fiber formation, resulting in vulnerable phenotype plaque formation due to reduced collagen. Tumor necrosis factor (TNF) and TNF receptor superfamily members promote atherothrombosis by increasing platelet aggregates and clots. Stimulation of the ligand-receptor systems leads to increased expression of MMPs. Therefore, these cytokines and their downstream signals can be targets of vulnerable plaques and hyperlipidemia.

Anti-hyperlipidemia drugs such as statins and PCSK9 inhibitors have great benefits and advantages for preventing vulnerable plaque and AMI. These drugs still have disadvantages; therefore, new treatment targets are necessary, and MMPs and the inflammatory process could be potential treatment targets.

**Disclosure**

**Conflicts of interest:** None.

**References**

1. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018; 392: 1736-88.
2. Akasaka T, Kubo T, Mizukoshi M, et al. Pathophysiology of acute coronary syndrome assessed by optical coherence tomography. J Cardiol 2010; 56: 8-14.
3. Shah PK. Mechanisms of plaque vulnerability and rupture. J Am Coll Cardiol 2003; 41: 15-22S.
4. Nakai M, Shimokado A, Kubo T, et al. Expression of cyclophilin A in coronary artery plaque with intraplaque hemorrhage is more frequent in deceased patients who had impaired kidney function. Int Heart J 2020; 61: 1129-34.
5. Parma L, Baganha F, Quax PHA, de Vries MR. Plaque angiogenesis and intraplaque hemorrhage in atherosclerosis. Eur J Pharmacol 2017; 816: 107-15.
6. Vacek TP, Rehman S, Neamtu D, Yu S, Givimani S, Tyagi SC. Matrix metalloproteinases in atherosclerosis: role of nitric oxide, hydrogen sulfide, homocysteine, and polymorphisms. Vasc Health Risk Manag 2015; 11: 173-83.
7. Bennett MR. Apoptosis of vascular smooth muscle cells in vascular remodelling and atherosclerotic plaque rupture. Cardiovasc Res 1999; 41: 361-8.
8. Mach F, Baigent C, Catapano AL, et al.; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020; 41: 111-88.
9. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease,
and stroke: systematic review and meta-analysis. BMJ 2003; 326: 1423.
10. Robinson JG, Farnier M, Krempf M, et al.; ODYSSEY LONG TERM Investigators. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med 2015; 372: 1489-99.
11. Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients—the PRIMO study. Cardiovasc Drugs Ther 2005; 19: 403-14.
12. Cicero AF, Tartagni E, Ertek S. Safety and tolerability of injectable lipid-lowering drugs: a review of available clinical data. Expert Opin Drug Saf 2014; 13: 1023-30.
13. Heo SH, Cho CH, Kim HO, et al. Plaque rupture is a determinant of vascular events in carotid artery atherosclerotic disease: involvement of matrix metalloproteinases 2 and 9. J Clin Neurol 2011; 7: 69-76.
14. Bench TJ, Jeremias A, Brown DL. Matrix metalloproteinase inhibition with tetracyclines for the treatment of coronary artery disease. Pharmacol Res 2011; 64: 561-6.
15. Takata K, Imaizumi S, Zhang B, Miura S, Saku K. Stabilization of high-risk plaques. Cardiovasc Diagn Ther 2016; 6: 304-21.
16. Mallat Z, Taleb S, Ait-Oufella H, Tedgui A. The role of adaptive T cell immunity in atherosclerosis. J Lipid Res 2009; 50: S364-9.
17. Mach F, Schönbeck U, Bonnefoy JY, Pober JS, Libby P. Activation of monocyte/macrophage functions related to acute atheroma complication by ligation of CD40: induction of collagenase, stromelysin, and tissue factor. Circulation 1997; 96: 396-9.
18. Hansson GK, Libby P, Tabas I. Inflammation and plaque vulnerability. J Intern Med 2015; 278: 483-93.
19. Tedgui A, Mallat Z. Cytokines in atherosclerosis: pathogenic and regulatory pathways. Physiol Rev 2006; 86: 515-81.