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EDITORIAL

Sialic acid: an important contributor to cardiovascular risk

Ozcan BASARAN [1], Angela DEI GIUDICI [2] *, Massimo FEDERICI [3], Francesco VERSACI [2]

[1]Department of Cardiology, Mugla Sitki Kocman University, Muğla, Turkey; [2]Division of Cardiology, S. Maria Goretti Hospital, Latina, Italy; [3]Tor Vergata Polyclinic Hospital, Rome, Italy

*Corresponding author: Angela Dei Giudici, Division of Cardiology, S. Maria Goretti Hospital, Via Canova snc, 04100 Latina, Italy. E-mail: angela86.adg@gmail.com

Cardiovascular disease (CVD) is the leading cause of death worldwide.[1] Although substantial improvement has been made regarding CVD risk factor management, there is still an unmet need for prevention of disease. Cholesterol, which plays a pivotal role in atherosclerosis has been studied widely. It was proved to be the trigger of atherosclerosis and almost all clinical trials have shown the lower was better for cholesterol. However, there is a residual risk despite aggressive lowering of low-density lipoprotein (LDL) cholesterol. This residual risk was partially addressed by the inflammatory theory. The role of inflammation in atherosclerosis has long been noticed and has been proved recently.[2] There are numerous studies searching for the link between lipids and inflammation.

Metabolomics studies small molecules within cells, fluids and tissues. Specifically, metabolomics in CVD try to underlie disturbances in cardiac metabolism. Over the past decade metabolomics which represent the interaction between environment and genetic of the individual subject have drawn attention in better understanding the pathogenesis of CVD.[3]

Sialic acid is a metabolite that was studied in CVD and found to play an important role in atherogenesis. Sialic acid is also associated with a number of risk factors of CVD, such as dyslipidemia, insulin resistance and immune responses. In a previous issue of *Minerva Cardiology and Angiology*, a review by Poznyak *et al*.[4] tried to evaluate sialic acid metabolism and its relation to atherosclerosis.

Sialic acid is a nine-carbon monosaccharide which binds to glycoproteins and glycolipids. It has been associated with atherosclerosis *via* several mechanisms. Epidemiological studies have shown elevated levels of total plasma sialic acid (TSA) was a risk factor for increased risk of CVD.[5] It is also an important contributor in accumulation of LDL in the arterial wall. The oxidation of desialylated LDL is enhanced and it can cause accelerated atherosclerosis.[6]

Sialic acid is also a component of LDL receptor (LDLR). Desialylated LDLR is more susceptible to degradation and is associated with increased levels of LDL.[7]

Sialic acid has a role in immunomodulation in atherosclerosis via its receptor sialic acid binding immunoglobulin like lectin (Siglec). Sialic acid-Siglec axis has some potential important roles in B lymphocytes, dentritic cells, t-reg cells and monocytes. Siglec might promote atherosclerosis by suppressing the protective functions of B cells and the presence on monocytes was associated with CVD severity.[8, 9]

There are three enzymes in the metabolism of sialic acid: sialidase (NEU), sialyltransferase (ST), and trans-sialidase (TS). Zhang *et al.*[10] have shown NEU1 had a key role in myocardial ischemia injury and pharmacological inhibition

TABLE I.—*The site of action of different drugs on sialic acid metabolism.*

Drug	Site of action	Effect
Statin	Increase sialic acid of LDL cholesterol	
Fibrates	Reduce TSA	
Anti-viral (oseltamivir, zanamivir)	Reduce TSA, block NEU1	Protect from ischemic myocardial damage
iPCKS9	Not known	Hypomorphic sialidase mice has reduced level of PCSK9; LDL degradation is reduced and LDL-R on the surface cell can reabsorb plasma LDL

Neu: N-acetilneuraminic acid = sialidase; TSA: (total plasma sialic acid.

of this enzyme by oseltamivir and zanamivir protected cardiomyocytes from this injury.[10, 11] ST has a dual action in atherosclerosis, overexpression of this enzyme could promote endothelial cell repair however, it might also accelerate atherosclerosis. Desialylation of LDL might be partly catabolized by TS. Desialylated LDL is an important contributor of atherosclerosis. Antiatherosclerotic strategies could arise from deliveries in sialic acid metabolism. Total sialic acid (TSA) is a marker of a sustained inflammatory response in CVD, and oseltamivir and zanamivir usually used for the influenza, reducing sialic acid level, might be potential antiatherosclerotic drugs in CVD through a lipid-independent pathological mechanism. They could lower sialic acid by suppressing NEU1 activity.[10]

Approved drugs to treat dyslipidemia, including statins and fibrate, alter sialic acid levels (Table I). The statin treatment could increase the sialic acid content of LDL in hypercholesterolemic patients[12] and fibrate is shown to reduce the serum sialic acid level in hypercholesterolemic rats.[13] Moreover, PCKS9 inhibitors has a central role in cholesterol treatment (Figure 1). Yang *et al.* have shown that mice with hypomorphic sialidase has lower levels of PCSK9 and it is likely responsible for maintaining steady-state levels of LDL receptors. As a result, reduced level of LDLR degradation enables its recycling and its higher efficiency for LDL internalization. Few studies have analyzed the action of sialidase on PCSK9 metabolism in human cells. Although the exact mechanism is unknown, sialylation of LDLR appears to affect its recycling or internalization, potentially through PCSK9.[14]

In conclusion, sialic acid metabolism seems an attractive target in atherosclerosis. Further research is needed to fully understand this complex metabolism to find potential therapeutic targets.

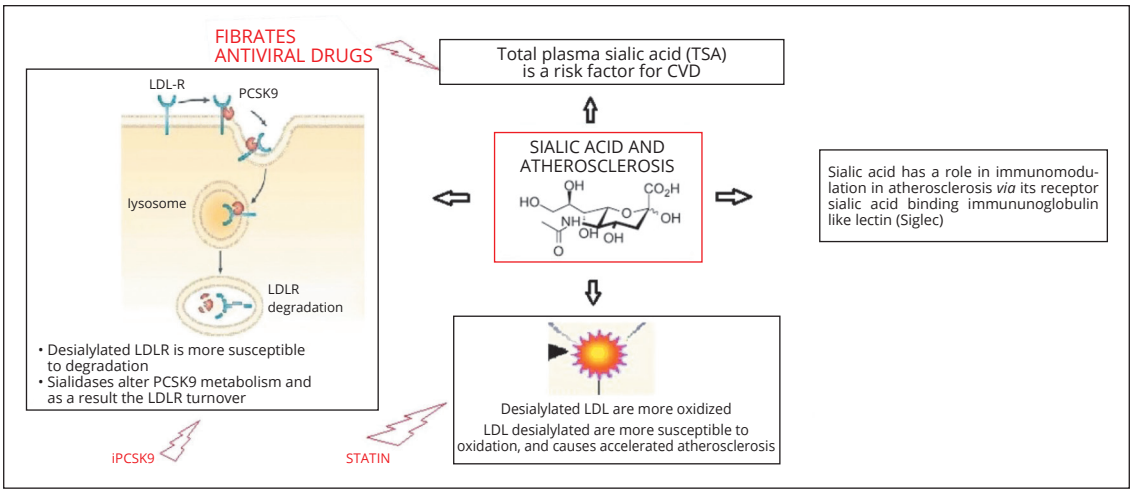

Figure 1.—Effect of sialic acid on atherosclerosis and site of action of statins, anti-viral drugs, fibrates, and iPCKS9.

Key messages

• Sialic acid is a metabolite that was studied in CVD and found to play an important role in atherogenesis.

• Approved drugs to treat dyslipidemia, including statins and fibrates, alter sialic acid levels.

• Sialic acid metabolism seems an attractive target in atherosclerosis, but further research is needed to fully understand this complex metabolism to find potential therapeutic targets.

References

1. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, *et al.*; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. Circulation 2020;141:e139–596.

2. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, *et al.*; CANTOS Trial Group. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med 2017;377:1119–31.

3. Ussher JR, Elmariah S, Gerszten RE, Dyck JR. The Emerging Role of Metabolomics in the Diagnosis and Prognosis of Cardiovascular Disease. J Am Coll Cardiol 2016;68:2850–70.

4. Poznyak AV, Zhang D, Grechko AV, Wu WK, Orekhov AN. The role of sialic acids in the initiation of atherosclerosis. Minerva Cardioangiol 2020;68:359–64.

5. Lindberg G, Eklund GA, Gullberg B, Råstam L. Serum sialic acid concentration and cardiovascular mortality. BMJ 1991;302:143–6.

6. Cuniberti LA, Martinez V, Schachter J, Magariños G, Meckert PC, Laguens RP, *et al.* Sialic acid as a protective barrier against neointima development. Atherosclerosis 2005;181:225–31.

7. Nioi P, Sigurdsson A, Thorleifsson G, Helgason H, Agustsdottir AB, Norddahl GL, *et al.* Variant ASGR1 associated with a reduced risk of coronary artery disease. N Engl J Med 2016;374:2131–41.

8. Xiong YS, Zhou YH, Rong GH, Wu WL, Liang Y, Yang ZX, *et al.* Siglec-1 on monocytes is a potential risk marker for monitoring disease severity in coronary artery disease. Clin Biochem 2009;42:1057–63.

9. Gruber S, Hendrikx T, Tsiantoulas D, Ozsvar-Kozma M, Göderle L, Mallat Z, *et al.* Sialic Acid-Binding Immunoglobulin-like Lectin G Promotes Atherosclerosis and Liver Inflammation by Suppressing the Protective Functions of B-1 Cells. Cell Rep 2016;14:2348–61.

10. Zhang L, Wei TT, Li Y, Li J, Fan Y, Huang FQ, *et al.* Functional Metabolomics Characterizes a Key Role for N-Acetylneuraminic Acid in Coronary Artery Diseases. Circulation 2018;137:1374–90.

11. Gopaul KP, Crook MA. Sialic acid: a novel marker of cardiovascular disease? Clin Biochem 2006;39:667–81.

12. Lindbohm N, Gylling H, Miettinen TE, Miettinen TA. Statin treatment increases the sialic acid content of LDL in hypercholesterolemic patients. Atherosclerosis 2000;151:545–50.

13. Oztürk LK, Yarat A, Emekli N. Effect of fenofibrate on serum and tissue sialic acid levels in short-term experimental hypercholesterolemia. Arzneimittelforschung 2007;57:770–6.

14. Yang A, Gyulay G, Mitchell M, White E, Trigatti BL, Igdoura SA. Hypomorphic sialidase expression decreases serum cholesterol by downregulation of VLDL production in mice. J Lipid Res 2012;53:2573–85.

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