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COMMENTARY

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Heart and vessels 'on fire'

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Inflammation is a crucial response towards infections and has been determinant for the conservation of our species throughout the millennia. However, the low grade, chronic and sterile activation of such a process seen during ageing (also known as 'inflamm-aging') is a pillar of the pathophysiology of many cardiovascular (CV) afflictions of the elderly including coronary heart disease, heart failure and arrhythmias.[1] Furthermore, the association between inflammation and atherosclerotic disease (30302102), type 2 diabetes mellitus (31656034) or obesity is well established. As a result, inflammation represents a possible target for the development of cardioprotective therapies as shown in recent randomized controlled trials.[2] Several pathways contribute to the development and maintenance of a pro-inflammatory state, including metabolism, lifestyle, environmental and genetic factors (Figure 1).

Genetic accounts for up to 55% of variation of plasma inflammatory molecules.[3] Studies from centenaries found all over the world, such as in Sardinia (Italy) or Okinawa (Japan) islands, confirmed the role of a favourable genetic background on CV ageing. However, while a good genetic certainly helps in favouring healthiness, also the 'context' in which the genetic expression takes place can differ significantly impacting on disease onset and progression. Unhealthy lifestyles lead to CV diseases (CVD) through several mechanisms including epigenetic regulation of inflammatory gene expression.[4] As well known, excess of weight, active smoke, sedentarism and unhealthy diets are crucial risk factors for CV health. The relation between metabolism and CV health is far from being linear and fully described. The so-called metabolically healthy obesity phenotype (i.e. obesity paradox) with the excess of weight counterintuitively favouring a safer CV profile in certain conditions is a good example.[5] The metabolic profile (including lipid, insulin and inflammatory factors) may be the real determinant of CV condition and certain obese individuals may have a protective metabolic profile while living with excess of weight. On the opposite, normal weight individuals or even sarcopenic individuals may show features of adverse metabolism and living with a higher CV risk. As a consequence, while reducing the weight of a subject might be a good preventive strategy, paying more attention to the presence of dysmetabolism is even more crucial. To this end, regular physical activity ameliorates the metabolic status through increasing insulin sensitivity or reducing proprotein convertase subtilisin/kexin type 9 (PCSK9) levels with direct effect on CV prevention.[6] Again, both insulin resistance and increased levels of circulating lipids have been associated with low-grade inflammation.

Accordingly, an impaired metabolism is among the main causes of the chronic inflammation found in elderly subjects. Altered glucose and lipid metabolism together with an excess of dysfunctional and inflamed

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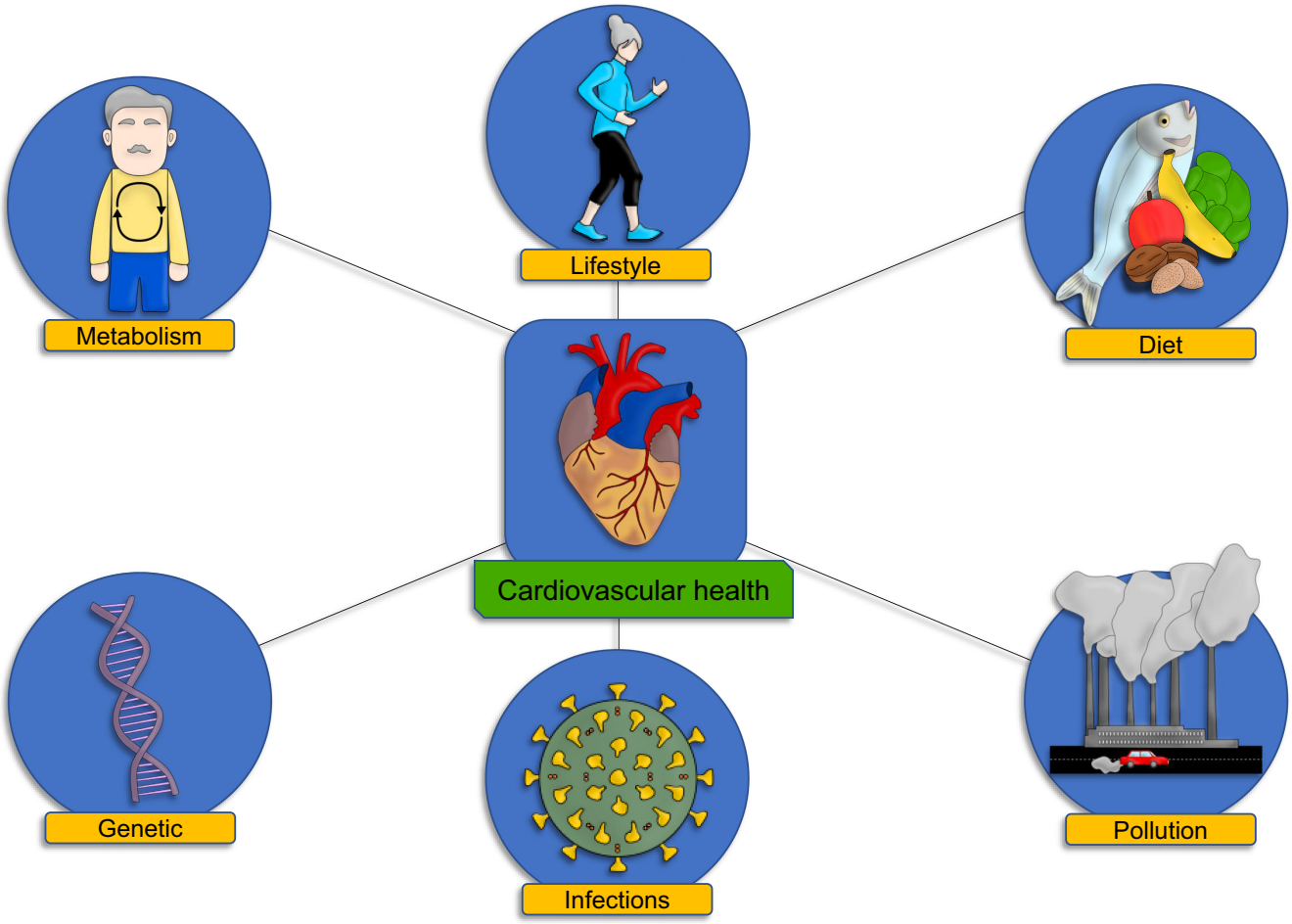

FIGURE 1 Inflammation and cardiovascular health. Several elements concur to inflammation development with detrimental effects on the cardiovascular system.

adipose tissue associates with a reduction of anti-inflammatory adipokines (i.e. adiponectin and omentin) and an increase of pro-inflammatory molecules (such as leptin, interleukin-1β, interleukin-6 and tumour necrosis factor alpha) playing important roles in the development of CVD.[7–9] Hypertension, impaired circulation of lipid particles and/or glucose in the bloodstream, excess of visceral adiposity, and insulin resistance tend to develop with ageing thanks to facilitating role of unfavourable genetic background and unhealthy lifestyle. The melting pot of such alterations is a condition called metabolic syndrome which indeed is characterized by increased inflammation and associates with many CV conditions. Accordingly, balanced dietary behaviour contributes to the maintenance of good health not only by preventing obesity but also by blunting the onset of inflamm-ageing in a direct way. In this sense, Mediterranean diet is currently seen as a paradigm for healthy food intake associating with blunted inflammatory tension and reduced mortality for CVDs.[10] Similarly, recently described dietary regimens mimicking fasting condition also were shown to impact on mortality for different CV and non-CV conditions (i.e. tumours).

As mentioned, the environment is another important contributor to CV health or diseases onset. Accordingly, the environmental pollution is gaining importance in the field of CV prevention. While short-term exposure to air pollution does not associate with systemic inflammation, the long-term exposure might be. Indeed, air particulate holds pro-inflammatory and oxidant effects being able to increase circulating levels of inflammatory molecules including interleukin-6 and tumour necrosis factor-alpha, as showed in both pre-clinical and clinical studies.[11] Beside air pollution, recent works link different kind of pollution such as the noise to inflammation and CV risk.[12] Among external agents causing inflammation and increasing CV risk, infections need of course to be mentioned. While the detrimental effect of chronic infections such as those from Epstein–Barr virus (EBV), hepatitis viruses or *Helicobacter pylori* has been longtime described, recent evidence demonstrates an effect also for acute infections including SARS-CoV-2 (severe acute respiratory

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syndrome–related coronavirus-2) pandemic. Acute complications of COVID-19 include arrhythmia, myocarditis and heart failure,[13] possible mechanisms by which such respiratory virus can cause cardiac disease include direct viral cellular infection and indirect damage via increased systemic inflammation. Long-term detrimental effects of COVID-19 on the CV system remain to be characterized but might include arrhythmia, arterial stiffness, coronary atherosclerosis and heart failure.[14]

Longtime hypothesized, targeting inflammation to reduce CV risk burden got recently proven thanks to the Colchicine Cardiovascular Outcomes Trial (COLCOT) and the Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS).[15,16] Those trials were the first ones to convincingly demonstrate the role of anti-inflammatory therapies on the CV health. The COLCOT study is a randomized control trial that evaluated the role of low-dose colchicine (0.5 mg per os, once a day) in patients that had myocardial infarction in the previous 30 days from the enrolment, evaluating the composite endpoint of CV death, myocardial infarction, stroke, urgent hospitalization because of angina with necessity for revascularization, or resuscitated cardiac arrest. In treated patients vs. controls, the composite primary endpoint showed a reduction of about 23%, indicating the preventive role of colchicine in the reduction of CV risk.[15]

Similarly, CANTOS evaluated the CV effect of the administration of a specific monoclonal antibody that target the interleukin-1β. More than 10,000 patients with stable coronary artery disease and C-reactive protein plasma levels higher than 2 mg/L were enrolled in the study. The treated group received Canakinumab at three different dosages: 50, 150 or 300 mg every 3 months and were followed for more than 3 years. The composite endpoint consisted in the absence of fatal myocardial infarction, fatal stroke or CV death. Actually, the highest dose regimen satisfied the criteria of the endpoint. Several other anti-inflammatory therapies have been proposed, and more trials are planned with new drugs potentially impacting on the future of CV risk management.

Systemic inflammation plays a crucial role in the development of several CVDs. Ageing associates with increased levels of inflammatory mediators; the so-called inflammageing is a critical contributor to CV burden in the elderly. Prevention and treatment of systemic inflammation and its determinants (Figure 1) represent an import step towards a better CV health, especially in the currently growing elderly population.

CONFLICT OF INTEREST STATEMENT

LL is co-inventor on the International Patent WO/2020/226993 filed in April 2020. The patent relates to the use of antibodies which specifically bind IL-1α to reduce various sequelae of ischemia–reperfusion injury to the central nervous system. LL reports speaker fees outside of this work from Daichi-Sankyo. The other authors report no conflicts of interest.

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REFERENCES

1. Liberale L, Bonetti NR, Puspitasari YM, et al. TNF-alpha antagonism rescues the effect of ageing on stroke: perspectives for targeting inflamm-ageing. *Eur J Clin Invest*. 2021;51:e13600. doi:10.1111/eci.13600
2. Liberale L, Montecucco F, Schwarz L, Luscher TF, Camici GG. Inflammation and cardiovascular diseases: lessons from seminal clinical trials. *Cardiovasc Res*. 2021;117:411-422. doi:10.1093/cvr/cvaa211
3. de Maat MP, Bladbjerg EM, von Hjelmborg J, Bathum L, Jespersen J, Christensen K. Genetic influence on inflammation variables in the elderly. *Arterioscler Thromb Vasc Biol*. 2004;24:2168-2173. doi:10.1161/01.ATV.0000143856.01669.e7
4. Srivastava RAK. Life-style-induced metabolic derangement and epigenetic changes promote diabetes and oxidative stress leading to NASH and atherosclerosis severity. *J Diabetes Metab Disord*. 2018;17:381-391. doi:10.1007/s40200-018-0378-y
5. Carbone S, Canada JM, Billingsley HE, Siddiqui MS, Elagizi A, Lavie CJ. Obesity paradox in cardiovascular disease: where do we stand? *Vasc Health Risk Manag*. 2019;15:89-100. doi:10.2147/VHRM.S168946
6. Tirandi A, Montecucco F, Liberale L. Physical activity to reduce PCSK9 levels. *Front Cardiovasc Med*. 2022;9:988698. doi:10.3389/fcvm.2022.988698
7. Unamuno X, Gómez-Ambrosi J, Rodríguez A, Becerril S, Frühbeck G, Catalán V. Adipokine dysregulation and adipose tissue inflammation in human obesity. *Eur J Clin Invest*. 2018;48:e12997. doi:10.1111/eci.12997
8. Liberale L, Montecucco F. Adipocytokines and cardiovascular diseases: putative role of neuregulin 4. *Eur J Clin Invest*. 2020;50:e13306. doi:10.1111/eci.13306
9. Liberale L, Bonaventura A, Vecchiè A, et al. The role of adipocytokines in coronary atherosclerosis. *Curr Atheroscler Rep*. 2017;19:10. doi:10.1007/s11883-017-0644-3
10. Tirandi A, Montecucco F, Carbone F. Apolipoprotein E genetic variants in Mediterranean diet: CORDIOPREV study. *Eur J Clin Invest*. 2020;50:e13213. doi:10.1111/eci.13213
11. Araujo JA. Particulate air pollution, systemic oxidative stress, inflammation, and atherosclerosis. *Air Qual Atmos Health*. 2010;4:79-93. doi:10.1007/s11869-010-0101-8
12. Munzel T, Sorensen M, Daiber A. Transportation noise pollution and cardiovascular disease. *Nat Rev Cardiol*. 2021;18:619-636. doi:10.1038/s41569-021-00532-5

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13. Buckley BJR, Harrison SL, Fazio-Eynullayeva E, Underhill P, Lane DA, Lip GYH. Prevalence and clinical outcomes of myocarditis and pericarditis in 718,365 COVID-19 patients. *Eur J Clin Invest*. 2021;51:e13679. doi:10.1111/eci.13679
14. Sato K, Sinclair JE, Sadeghirad H, Fraser JF, Short KR, Kulasinghe A. Cardiovascular disease in SARS-CoV-2 infection. *Clin Transl Immunol*. 2021;10:e1343. doi:10.1002/cti2.1343
15. Tardif JC, Kouz S, Waters DD, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med*. 2019;381:2497-2505. doi:10.1056/NEJMoa1912388
16. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017;377:1119-1131. doi:10.1056/NEJMoa1707914

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