

Editorial

# Inflammation and cardiovascular diseases



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Despite great advances in the diagnosis and therapy of cardiovascular diseases (CVDs) over the last few decades, they remain the leading causes of morbidity and mortality worldwide and have emerged as the leading causes of death in China.<sup>1</sup> This is partly due to the fact that the exact pathogenic mechanisms remain poorly understood in most cases, which significantly limits the effectiveness of therapy. Thus, identification of the key mechanisms that regulate cardiovascular function and the novel preventable risk factors of CVDs is urgently needed.

## Inflammation and atherosclerosis

Mounting evidence suggests that vascular inflammation plays a critical role in the development of atherosclerosis, which in turn can cause clinically important CVDs, including coronary artery disease, stroke, and peripheral arterial disease. Inflammation has been linked to multiple stages of the remodeling process of atherosclerotic plaque formation and thrombogenicity. Cytokines, including tumor necrosis factor- $\alpha$ , interleukin 1 $\beta$  (IL-1 $\beta$ ), and IL-6, play critical roles throughout the pathogenetic

process of atherosclerosis, from early endothelial activation to plaque rupture.<sup>2</sup> Mendelian randomization studies suggest that the IL-6 signaling system plays a causal role in the development and progression of atherosclerosis.<sup>3</sup> Further upstream from IL-6, activation of the nucleotide-binding oligomerization domain-like receptor family, pyrin domain-containing protein 3 inflammasome, also appears to be causally involved in the development and progression of atherosclerotic cardiovascular disease.<sup>4</sup> Laboratory and observational studies have also identified a number of other inflammatory, oxidative, and adhesion pathways in the development and progression of atherosclerosis, including lipoprotein-associated and secretory phospholipase A2, p38 mitogen-activated protein kinase, and P-selectin.<sup>5</sup>

## Infection, inflammation, and cardiovascular diseases

Various infectious microbes have been linked to atherosclerotic disease in epidemiological studies.<sup>6</sup> Infections have been known to cause atherogenesis or to precipitate acute cardiovascular events.<sup>7</sup> Recently, a highly pathogenic novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide and presently reached the dimension of a pandemic. Cappannoli et al<sup>8</sup> summarized the

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evidence of a potential association between SARS-CoV-2 and cardiovascular involvement.

First, CVDs are a common comorbidity in patients with coronavirus disease (COVID-19). A recently published meta-analysis of six studies highlighted that CVDs were present in up to 16.4% of patients with COVID-19,<sup>9</sup> and the presence of these comorbidities significantly increased the risk of death.<sup>8</sup> The mechanism of these associations remains unclear. Potential explanations include the fact that CVDs are prevalent in elderly patients or that patients with CVDs have functionally impaired immune systems, elevated levels of angiotensin-converting enzyme 2 (ACE2), or predispositions to COVID-19 infection.<sup>10</sup>

Second, myocardial injury is commonly seen in patients with COVID-19 and is associated with worse prognosis and mortality,<sup>8</sup> although the exact mechanism remains under investigation. One potential mechanism is direct myocardial involvement mediated by ACE2.<sup>10</sup> SARS-CoV-2 infection is caused by the binding of the viral surface spike protein to the human ACE2 receptor. ACE2 is highly expressed in the heart and is associated with excessive activation of the renin-angiotensin system, which results in conditions such as hypertension, congestive heart failure, and atherosclerosis.<sup>10</sup> A recent hypothesis suggests that the inhibition of the angiotensin 1 receptor (AT1R) may provide benefits to patients with COVID-19.<sup>11</sup> Other suggested mechanisms of COVID-19-related cardiac injury include cytokine storms and systemic hyperinflammation, hypoxia-induced excessive intracellular calcium leading to cardiac myocyte apoptosis, microvascular injury, and/or stress cardiomyopathy.<sup>10,12</sup> In addition, Cappannoli et al<sup>8</sup> demonstrated that SARS-CoV-2 can also affect acute coronary syndromes through systemic inflammatory activation and cytokine release. Indeed, it has been posited that these immune injuries may be risk factors for the development of future CVDs through fibrosis or accelerated atherosclerosis. This identifies a critical need for long-term study of patients with COVID-19 to understand the cardiovascular sequelae of this disease.<sup>13</sup>

### **Environment, inflammation, and cardiovascular diseases**

Environmental pollutants may also induce inflammation and enhance the risk of CVDs.<sup>7</sup> The underlying mechanisms may be due to the overproduction of

reactive oxygen species and increases in inflammation markers.<sup>7</sup> In this issue, Yang et al<sup>14</sup> demonstrated that environmental degradation and exposure to heavy metals may have a direct impact on CVD development. More importantly, Yang et al<sup>14</sup> also suggested that oxidative stress and systemic inflammation induced by exposure to toxic metals contribute to the progression of atherosclerosis and CVDs. This work has provided evidence linking environmental heavy metal exposure to increased risks of CVDs and has suggested that inflammation may be the key mechanism. As CVDs and environmental degradation are major public health problems worldwide, further studies are needed to elucidate the real mechanism linking environmental exposure to heavy metals and CVD risk in order to establish appropriate intervention strategies for prevention.

### **Inflammation and heart failure**

Inflammation has also been recognized as a common pathobiologic feature of heart failure (HF), another important CVD with high morbidity and mortality. Studies have demonstrated that immune-inflammatory activation plays a critical role in the development and progression of HF and is predictive of poor outcomes.<sup>15</sup> In the recent CANTOS trial, anti-cytokine therapy with a monoclonal antibody targeted against IL-1 $\beta$  resulted in improved heart failure outcomes.<sup>16</sup> These results suggest that more precisely targeted anti-inflammatory therapeutic strategies may reduce HF mortality when applied to more specific subpopulations.

### **Inflammation and cardiomyopathy**

Along with the recognition of inflammation as a major factor that modulates HF, the role of inflammatory processes in the pathogenesis of cardiomyopathy has also become widely accepted. An up-to-date review by Tian et al<sup>17</sup> provided a framework to deepen our understanding of the genetic basis, pathogenetic phases, and clinical faces of cardiomyopathy, including dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), arrhythmogenic cardiomyopathy (ACM), and restrictive cardiomyopathy.

As the most common type of cardiomyopathy, the etiology of DCM can be genetic, acquired, or mixed, and it may result from genetic mutations, infections, inflammation, exposure to toxins, or endocrine or

neuromuscular causes. Progression from myocarditis to DCM has long been hypothesized and is supported by studies that used endomyocardial biopsy to provide evidence of inflammation and/or viral infection within the myocardium in patients with DCM.<sup>18</sup> Due to these findings, the term ‘inflammatory DCM’, which refers to a subgroup of DCM associated with inflammation, has become commonly used.<sup>19</sup>

A variable myocardial and systemic inflammatory response associated with myocardial fibrosis was demonstrated in patients with HCM, suggesting that myocardial fibrosis in HCM is an active process modified by an inflammatory response.<sup>20</sup> The phenotypic variability observed in HCM is the end-result of many factors; however, leukocyte-derived extracellular traps, apoptosis, proliferation of matrix proteins, and impaired or dysfunctional regulatory pathways also contribute to tissue-level inflammation.<sup>21</sup>

ACM is an incurable genetic disease characterized by arrhythmia, fibrosis, and cardiac dilation, which may lead to HF and sudden cardiac death. A recent study has shown that specific immune cell populations and chemokine expression profiles modulate inflammatory and repair processes throughout ACM progression.<sup>22</sup> This suggests that inflammation may be a major component of disease pathogenesis.

## Conclusions

Emerging data suggest that dysregulation of inflammatory and immune pathways may be the leading mechanisms in a large number of CVDs, including coronary disease, HF, cardiomyopathies, and heart rhythm disorders.<sup>19,23,24</sup> In this regard, understanding how inflammation contributes to CVDs is critical for establishing appropriate intervention strategies for disease prevention and control. Further studies will be needed to determine the specific inflammatory mechanisms that contribute to CVDs in order to better understand the pathological crosstalk between inflammation and the cardiovascular system and to identify novel therapeutic strategies.

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## Conflicts of interest

None.

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