INTRODUCTION

Atherosclerosis is one of the major risk factors for a variety of cardiovascular illnesses (CVD), including myocardial infarction, ischemic stroke and pulmonary disease. The concept of atherogenesis has evolved, from a focal lipid accumulation or an extended cellular-lipid matrix formation to a cascade inflammatory or immunological event (Libby *et al.*, 2019). Although various factors are known to trigger atherogenesis, vascular cell senescence due to age is considered to be a predominant risk factor for atherosclerosis (Tyrrell and Goldstein, 2021). Several epidemiological and clinical investigations have highlighted that the incidence of CVD and related fatal events is comparatively higher in post-menopausal women than in pre-menopausal women and age-matched men.

Various epidemiological and clinical studies accentuated that incidence of CVD and associated fatal events are more prominent in post-menopausal women than in pre-menopausal women and age-matched men (Zhou *et al.*, 2019). While hormone replacement therapy (HRT) has been proven effective in preventing the onset and progression of atherosclerosis in younger post-menopausal women, the "timing hypothesis" sounds like a note of caution for the use of HRT for atherosclerosis in older women (Langer, 2017). Hence, there is a dire need to understand the intertwined molecular mechanisms underlying menopause-induced arterial senescence and atherosclerosis.

Arterial senescence is characterised by an irreversible cell cycle arrest in the arterial vasculature, which is associated with a variety of vascular pathological events including increased inflammation, telomere shortening, abnormal endothelial infiltration, disruption of cell-cell junctions, structural and functional abnormalities in mitochondrial, lysosomes and other sub-cellular components, resistance to apoptosis and defective tissue remodelling (Shimizu and Minamino, 2020). Further, a recent study by Munoz-Cordova *et al*. (2021) depicted that postmenopausal atherosclerosis can be prevented by the augmentation of autophagic flux and the repression of oxidative stress, inflammation, and apoptosis. Chemokines have been associated with atherosclerosis and other age-related disorders (Gencer *et al.*, 2021).

CXCL12, the solitary ligand of CXCR4, is a chemokine and a homeostatic regulator expressed by a wide array of cells. CXCL12 exhibits a dual physiological-pathological role in various conditions, including angiogenesis, tissue repair, hypoxia and growth arrest (Gencer *et al.*, 2021). Hence, CXCR4 and its receptor CXCL12 are known to work in an intricate cell- and the context-specific manner in the atherosclerotic milieu (Murad *et al.*, 2021). A recent study based on the Mendelian randomization analysis revealed that CXCL12 is one of the prime causal mediators of coronary artery disease (CAD) in humans (Sjaarda *et al.*, 2018). In addition, a meta-analysis of genome-wide association studies (GWAS) indicated that endothelial cell-derived CXCL12 accelerates the progression of atherosclerosis in CAD (Butnariu *et al.*, 2022). In addition to the atherogenic role, CXCL12 acts as a topological central node in the differentially expressed genes' network related to senescence (Avelar *et al.*, 2020). Grootaert *et al*., (2018) showed that autophagic dysfunction in vascular smooth muscle cells (VSMCs) upregulates CXCL12 and other factors, hastens senescence in VSMCs, and triggers neointimal thickening and atherogenesis.

Telomeres, the chromosomal ends comprising DNA-protein complexes, offer protection against genome instability in various pathological conditions, including senescence and atherosclerosis (Amir *et al.*, 2020). Reduced telomere length, increased telomere attrition rate, and repressed telomerase reverse transcriptase (TERT) activity are known to increase the risk for atherosclerosis (Amir *et al.*, 2020). Li *et al.* (2018) demonstrated that CXCL12 controls endothelial progenitor cell senescence by modulating telomerase. Recently, Gao *et al.* (2019) revealed that CXCL12 causes atherosclerosis by suppressing ATP-binding cassette transporter A1 (ABCA1). Therefore, the current investigation was carried out to clarify the functioning mechanism of CXCL12 and its association with telomeres in the context of atherosclerosis and arterial senescence brought on by menopause.

MATERIAL AND METHODS

Study area

The present study was carried out in the Department of Cardiovascular Disease, Jinling Hospital, Medical School, and Nanjing University from January to May 2022.

Animals and experimental design

In this investigation, 20 female C57BL/6 mice (8-9 weeks old) were obtained from the animal house facility of the Center at Jinling Hospital, Nanjing University. During the animal assay, test animals were isolated in wide, clean cages with a constant temperature of 23±1°C, 40-60% humidity, and exposed to a 12-hour dark-light sequence. Animals were subjected to either sham surgery or bilateral ovariectomy (OVX). 20 animals were randomly assigned into 2 OVX groups (n=10) as follows: Early postmenopausal (EPM) and late postmenopausal (LPM) groups (1 and 5 weeks post-OVX, respectively), as described earlier by Campos *et al.* (2020). Both EPM and LPM groups were further treated with the selective CXCR4 antagonist, POL5551 (Polyphor Ltd., Switzerland), as a continuous infusion (0.05µL;

*Corresponding author: e-mail: jianbingong04@gmail.com