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Protective role of the longevity-associated BPIFB4 gene on cardiac microvascular cells and cardiac aging

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ABSTRACT

In recent years, the role of the cardiac microvasculature in modulating the symptoms and disease progression of patients affected by cardiac pathology has been reconsidered. The term cardiac microvascular disease (CMD) describes the set of functional and/or structural alterations of the cardiac microvasculature that reduce the ability of the heart to adequately increase its coronary blood flow to keep up with increased metabolic demand. CMD is involved in the evolution of heart disease of both ischemic and non-ischemic origin as well as in cardiac aging. The primary actors involved in this process are the cells of the stromal compartment, whose nature and biology are now investigated to a new level of detail thanks to single-cell omics studies. Recent studies on the genetics of extreme longevity have identified a polymorphic haplotype variant of the BPIFB4 gene that confers prolonged life span and health span, atheroprotective advantages, and an improved immune response.

The aim of this review was to focus on the beneficial effects of the longevity-associated variant (LAV) of BPIFB4 on cardiac microvascular cell biology, providing novel and exciting mechanisms of its action directed against the development or progression of many age-related cardiovascular diseases, thus emphasizing its translational therapeutic potential.

1. Introduction and aim of the review

Although it has been overlooked for many years, the cardiac microvasculature is crucial for modulating the symptoms and disease progression in patients affected by cardiac pathology. The term cardiac microvascular disease (CMD) describes the set of functional and/or structural alterations of the cardiac microvasculature that reduce the ability of the heart to adequately increase its coronary blood flow to keep up with the increased metabolic demand. This may be due to alterations in physiological mechanisms involving gasotransmitters (e.g., nitric oxide, carbon monoxide, or sulfidic acid) or structural alterations in the microvessels.

The myocardium is composed of cardiomyocytes, vascular cells, and interstitial cells, whose anonymous morphology and the absence of specific markers hampered their study until single-cell RNA sequencing (scRNA-seq) experiments became available. Therefore, we are beginning to decipher the role of the microvascular cell niche in the modulation of inflammation and fibrosis.

Aging is associated with an increased prevalence of chronic diseases, among which cardiovascular diseases are one of the most relevant. By

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investigating the molecular mechanisms associated with extreme longevity, the relevant role of the longevity-associated variant (LAV) of human bactericidal/permeability-increasing protein (BPI)-fold-containing family member 4 (BPIFB4) has emerged.

Intriguingly, LAV-BPIFB4 plays a prominent role in cardiovascular health by improving healthy longevity and vascular cell homeostasis through the activation of endothelial nitric oxide synthase (eNOS) as well as novel molecular mechanisms.

This review summarizes recent evidence of LAV-BPIFB4-mediated effects on microvascular structure and function in relation to age-related cardiovascular disorders, opening new avenues for the prevention and treatment of these diseases.

2. Microvascular dysfunction in heart failure

2.1. Coronary anatomy and pathophysiology

The coronary vessel tree is composed of three anatomically and physiologically distinct districts: large epicardial conductance vessels, characterized by endothelial shear-stress-dependent vasodilation and minimal drop in perfusion pressure; pre-arterioles, characterized by higher resistance and a measurable drop in perfusion pressure; and arterioles, characterized by the highest resistance and dilation in response to changes in oxygen demand [1]. Under physiological conditions, coronary blood flow (CBF) is kept constant over a wide range of perfusion pressures owing to both myogenic and metabolic mechanisms that regulate the vascular tone of the microvessels [2]. Finally, sympathetic and parasympathetic innervation regulate arteriolar vasoconstriction and vasodilation [3]. The difference in CBF between the baseline value and maximal vasodilation is defined as the coronary flow reserve (CFR) and may be experimentally assessed using vasoactive drugs [2].

2.2. Non-obstructive coronary artery disease

Although obstruction of the epicardial coronary arteries has received much attention, 20–50 % of patients with angina (i.e., chest pain due to myocardial ischemia) or other evidence of cardiac ischemia have a normal coronary angiogram (angina with non-obstructive coronary artery disease [ANOCA] and ischemia with non-obstructive coronary artery disease [INOCA]). These episodes can be caused by coronary vasospasm or CMD in nearly two-thirds of the patients. Percutaneous coronary intervention (PCI) has minimal impact on symptom relief and medium-term prognostic benefit in patients with stable angina, suggesting that CMD is a major pathogenic factor in this setting [4]. In extreme cases, myocardial infarction can occur in the absence of obstructed coronary arteries (MINOCA) [5]. The term CMD was first used to define microcirculation abnormalities that lead to inadequate vasodilative responses or pathological vasoconstrictive responses to physiological or pharmacological stimuli, and can be assessed as CFR impairment [6]. The diagnostic workup of ANOCA and INOCA involves angiography to rule out significant epicardial stenosis [7], whereas both noninvasive diagnostic tools (e.g., transthoracic Doppler echocardiography and cardiac magnetic resonance) and invasive diagnostic techniques to determine CFR (e.g., intracoronary Doppler or intracoronary thermodilution) and to rule out vasospasm (i.e., acetylcholine provocation test) are required for a correct etiological classification [8].

2.3. Coronary microvasculature in cardiovascular disease

Acute stenosis of the epicardial arteries leads to potent vasodilation of the resistance vessels as a compensatory mechanism to preserve CBF [2]. Conversely, chronic coronary artery stenosis leads to remodeling of the microvascular compartment, which decreases the CFR and determines the metabolic and structural changes in the myocardium that induce chronic depression of cardiac contractility in a pathological condition called myocardial hibernation [9]. Indeed, in pigs subjected to left anterior descending artery (LAD) constriction, arterioles distal to the stenotic region show a reduced myogenic response and an exaggerated vasoconstrictive response to endothelin-1 [10]. Similarly, pigs exposed to 4 weeks of LAD stenosis that developed chronic myocardial hibernation were characterized by structural remodeling of the small intramyocardial coronary arteries, with an increased wall thickness-to-lumen ratio and reduced lumen area per arteriole. These changes are correlated with CBF reduction and myocardial fibrosis [11]. Although a transient compensatory increase in arteriolar density has been described, arteriolar remodeling persists even after the resolution of chronic stenosis by PCI, leading to a reduction in maximum perfusion [12].

A pathogenic role of CMD has also been observed in hypertensive and valvular heart disease and hypertrophic and dilated cardiomyopathy [13,14]. CMD is also observed in the presence of systemic diseases (e.g., diabetes mellitus, obesity, autoimmune diseases, and chronic kidney disease) [13]. Overweight and obesity affect epicardial coronary arteries, increasing the risk of coronary artery disease (CAD) independently, at least in part, from arterial blood pressure and lipid profiles [15]. Known mechanisms involve adipokine secretion, insulin resistance, inflammation, and oxidative stress [16]. However, in addition to CAD, CMD is emerging as a pathogenic mechanism of obesity-associated heart diseases. Indeed, in obese patients without evidence of CAD, an inverse relationship exists between CFR and body mass index (BMI), whereas CFR is associated with cardiovascular events independent of BMI [17]. Concerning the mechanisms responsible for this, systemic inflammatory molecules were independently associated with CFR in obese patients without signs of cardiovascular disease [18], while endocannabinoids were inversely correlated with the variation of myocardial blood flow to cold pressor test or dipyridamole [19]. Additionally, obesity is associated with insulin resistance and hyperglycemia, which promotes the formation of reactive oxygen and nitrogen species, thus reducing the production and bioavailability of NO [20].

Sex-related differences were also observed. Angina pectoris is less frequently associated with obstructed coronary arteries in women [21], whereas women-specific cardiovascular risk factors include pregnancy-associated conditions (e.g., preeclampsia, gestational diabetes, and preterm labor), premature menopause, and a history of autoimmune disease [3]. From an anatomical standpoint, although women have smaller epicardial coronary arteries, they are protected from focal coronary artery disease [22], especially during the premenopausal period. In middle-aged women, the CFR, assessed using invasive methods, was lower than that in men, mostly because of the higher resting CBF in females [23]. This has been attributed to sex-related differences in the autonomic nervous system [3]. Furthermore, the presence of smaller arteries with higher flow is coupled with high endothelial shear stress, which protects arteries from atherosclerosis [24]. Finally, the observation that premenopausal women have a better CBF response than postmenopausal women and age-matched men suggests a protective role of estrogen in the microvasculature [25]. The net effect of these protective factors on focal atherosclerosis may be associated with the development of more diffuse coronary artery disease later in life [24].

Aging is the most relevant risk factor for cardiovascular diseases, even in the absence of traditional factors, and is associated with both structural and functional impairment of the microvessels [26]. Consequently, impairment of flow-mediated vasodilation, angiogenesis, and microvascular rarefaction characterizes the aged microvasculature [26]. Age-related changes in the microvasculature alter the immune and endocrine systems, primitive cell trafficking, and cardiac neurovascular interface [26,27]. From a mechanistic perspective, cellular senescence (i.e., a cellular response to stressors characterized by cell proliferation arrest coupled with the release of an altered secretome rich in pro-inflammatory molecules) is a potential mechanism responsible for age-related vascular dysfunction [26]. Indeed, chronic accumulation of senescent cells characterizes age-related pathologies [28], whereas in the heart, fibroblast senescence is associated with tissue fibrosis [29]. Conversely, the selective elimination of senescent cells has been

associated with attenuation of the aging phenotype, including atherosclerosis and cardiac fibrosis [30,31]. Cardiac fibrosis has prominent clinical relevance since a 3 % increase in extracellular volume is associated with a 50 % increase in all-cause mortality [32].

Heart failure (HF) is a syndrome caused by distinct etiologies, characterized by either the inability of the heart to provide peripheral tissues with an output commensurate to their metabolic requirements or by pathologically elevated intracardiac pressures [33]. HF can be classified based on the measurement of left ventricular ejection fraction (EF) into HF with reduced EF (HFrEF) and HF with preserved EF (HFpEF) [33]. These two entities differ in the epidemiological characteristics of affected patients, as HFpEF patients are usually older, often female, and affected by comorbidities (e.g., atrial fibrillation, obesity, diabetes mellitus, hypertension, and chronic kidney disease) [33]. An association between HFpEF and CMD has been reported previously. A longitudinal study conducted on 201 patients without significant CAD and an EF $\geq$ 40 % followed up for 4.1 years showed that a CFR $<$ 2 was an independent predictor of an elevated E/e' (an index of diastolic dysfunction), while patients with elevated E/e' and reduced CFR had the highest cumulative rate for HFpEF hospitalization [34]. Similarly, in different studies performed on patients fulfilling strict criteria for HFpEF, 70–80 % had CMD [35,36]. Two mechanistic links might explain the association between CMD and HFpEF. The first involves defects in myocardial relaxation (lusitropy). Specifically, comorbidities frequently associated with HFpEF (i.e., obesity, diabetes, and hypertension) trigger systemic inflammation that reduces NO bioavailability and protein kinase G activity, thus increasing cardiac hypertrophy and cardiomyocyte stiffness by reducing titin phosphorylation [37]. The second involves defects in matching increased metabolic demands with adequate myocardial perfusion, thus rendering the heart more vulnerable to subendocardial ischemia and promoting myocardial fibrosis [38].

2.4. The cellular components of the microvascular niche cells

The myocardium comprises cardiomyocytes and interstitial cells, including fibroblasts, mural cells (pericytes and vascular smooth muscle cells), and endothelial cells. Single-nucleus RNA sequencing revealed atria have fewer cardiomyocytes but more endothelial cells and fibroblasts compared to ventricles [39]. In ventricles, cardiomyocyte and fibroblast proportions are inversely correlated, while pericytes and smooth muscle cells show positive correlation, suggesting functional organization [39]. Notably, women have a higher proportion of ventricular cardiomyocytes than men [39].

The lack of specific markers historically hampered cardiovascular niche studies until scRNA-seq identified 12 fibroblast and four mural cell clusters, distributed within niches [40]. Some fibroblasts are more involved in producing ECM proteins, which are crucial for wound healing, whereas others may play roles in signaling to immune cells or in influencing vascular remodeling [39]. Mural cells, including pericytes and vascular smooth muscle cells (VSMCs), have also been shown to have diverse functions, including regulating vascular stability to influence angiogenesis and inflammation, maintaining vascular integrity, and responding to pathological stress. Vascular niche remodeling, particularly in HF, involves disrupted interactions between endothelial cells, pericytes, and fibroblasts, leading to increased permeability, reduced capillary density, and impaired perfusion, worsening HF outcomes.

2.5. Coronary microvascular disease pathophysiology

The pathophysiological mechanisms of CMD can be broadly distinguished as structural and functional.

Structural anomalies can be secondary to various causes. First, cardiomyocyte hypertrophy displaces microvascular cells, thus increasing the intercapillary distance and predisposing the heart to ischemia [41]. The second cause is ischemia-reperfusion injury (IRI), which becomes apparent when an adequate level of perfusion cannot be achieved following the reopening of an obstructed epicardial artery (i.e., "no reflow" phenomenon). The pathophysiological mechanisms of this phenomenon include microvascular obstruction (due to thromboembolism, microvascular thrombosis, and cellular plugging) and extravascular compression caused by myocardial edema or hemorrhage [42]. IRI activates leukocytes that release sheddases, damaging the endothelial cell glycocalyx, thus increasing vascular permeability and leukocyte adhesion [43]. Damage to endothelial cells also results in the release of soluble thrombomodulin (sTM) into the bloodstream, which serves as a marker of endothelial injury. Elevated levels of sTM and syndecan-1 (a glycocalyx component) are associated with worse outcomes in patients with AMI, including higher mortality rates and increased likelihood of HF [44]. Furthermore, damage-associated molecular patterns released during reperfusion of ischemic cardiac microvascular endothelial cells can injure non-ischemic endothelial cells, altering their morphology and decreasing eNOS expression [45]. Proinflammatory cytokines elevate microvascular permeability and worsen cardiac damage. Molecules such as nerve growth factor (NGF) and angiopoietin-2 disrupt pericyte-endothelial interactions, enhancing hyperpermeability and infarct expansion [46,47]. The third cause is chronic remodeling of the microvasculature, characterized by either smooth muscle cell hypertrophy and narrowing of the lumen, which is observed in hypertrophic cardiomyopathy, hypertensive and/or ischemic heart disease, and in obese stressed animals [48–50], or rarefaction of microvascular cells occurring in ischemic and failing hearts [51]. Capillary rarefaction and reduced myocardial oxygenation have also been observed in aging mice [52], whereas in human hearts exposed to increased afterload, capillary density decreases as a function of age [53]. Pericyte loss and reduction in capillary coverage by pericytes occur both in ischemic heart disease and in models of HFpEF [51,54]. In the latter condition, this is the earliest alteration documented [54]. Indeed, in the *PDGFR-B*$^{ret/ret}$ mutation model of pericyte loss, diastolic dysfunction spontaneously develops in animals in the absence of other *noxae* [54]. Finally, perivascular fibrosis, caused by the altered balance of matrix deposition and remodeling, impairs the crosstalk between endothelial cells and myocytes and is associated with reduced coronary blood flow [55]. Pericytes play pivotal roles in myocardial ischemia, no-reflow phenomena, fibrosis, and scar stabilization and exert dynamic functions throughout the phases of cardiac repair. During ischemia, destabilization of pericyte-endothelial interactions mediated by matrix metalloproteinase-9 (MMP-9) leads to ECM degradation, vascular destabilization, and impaired angiogenesis [56]. This process, which is vital for capillary remodeling, contributes to the progression of ischemic injury by reducing capillary perfusion and promoting vascular dysfunction. Pericytes are also key players in the no-reflow phenomenon, where their constriction narrows the capillary lumen and obstructs microvascular flow even after coronary reperfusion, leading to the no-reflow phenomenon [57,58]. Experimental studies have shown that adenosine-induced pericyte relaxation can significantly restore perfusion and identify them as critical regulators of microvascular obstruction [57]. In the proliferative phase of repair, pericyte phenotypic plasticity and responsiveness to signaling molecules suggest their involvement in fibrosis [59]. While fibroblasts remain the primary drivers of collagen deposition and myofibroblast activation, lineage-tracing studies have proposed that specific pericyte populations, such as Gli1^{+} cells, contribute to fibrotic remodeling in infarcted hearts [60,61] (see Fig. 1).

Functional anomalies refer to the impairment of vasodilator, anti-inflammatory, and anti-aggregation functions in the healthy endothelium. These actions are promoted by gas mediators such as NO, CO, hydrogen sulfide (H_2S), and eicosanoids such as prostacyclin (PGI_2). In the CMD setting, most studies have focused on anomalies of NO, which diffuses into smooth muscle cells where it induces relaxation by activating soluble guanylate cyclase. NO is generated by NO synthase enzymes (the most relevant for vascular physiology are the constitutive ones, the neuronal isoform nNOS, and the endothelial isoform eNOS),

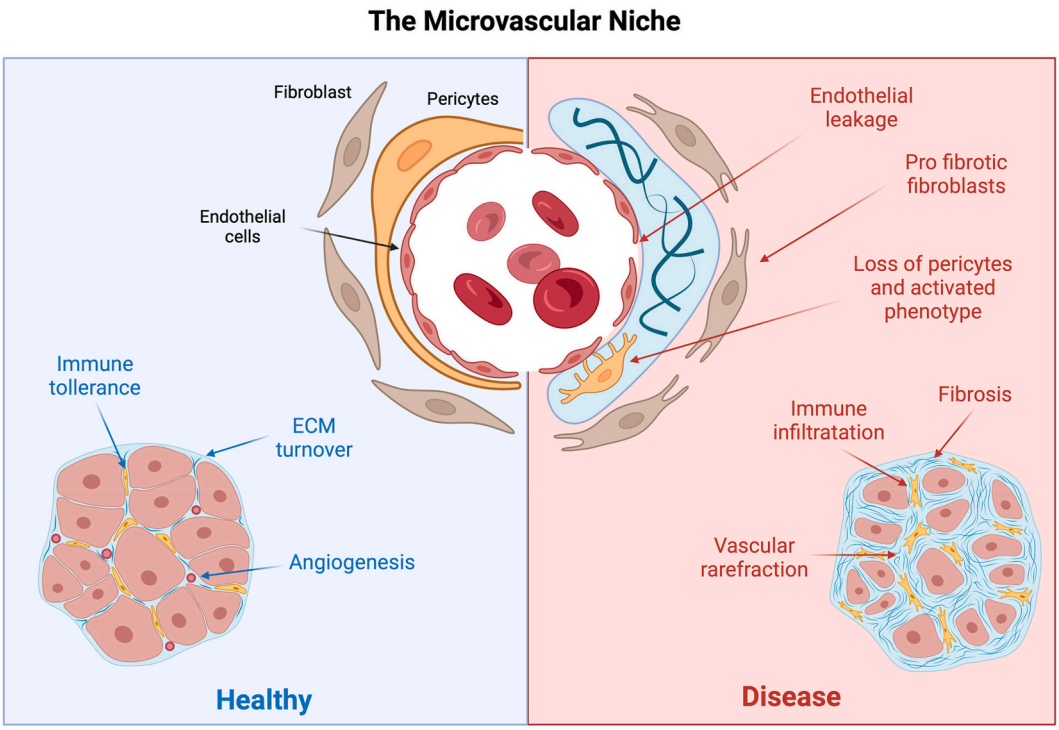

Fig. 1. Cartoon illustrating the dynamics of the microvascular niche in healthy and diseased conditions. In the healthy state, the microvascular niche maintains immune tolerance, extracellular matrix (ECM) turnover, and angiogenesis, ensuring a balanced and functional vascular environment. This state is characterized by the coordinated interaction between endothelial cells, pericytes, and fibroblasts. In contrast, the diseased state is marked by pathological changes, including endothelial leakage, loss of pericytes, and their activation into a profibrotic phenotype. Immune infiltration, fibrosis, and the emergence of pro-fibrotic fibroblasts can be observed in the pathological myocardium. These changes ultimately lead to vascular rarefaction and impaired tissue function.

which convert L-arginine to NO and citrullin. NO is a free radical that can react with oxygen to form more reactive species such as peroxynitrite [62]. Intrinsic and extrinsic regulators of eNOS activity are in place to prevent tissue damage. Among the intrinsic regulators, Ca^{2+}-bound calmodulin is a critical positive regulator of NOS enzymatic activity [63]. Among the extrinsic regulators of constitutive NOS, Ser/Thr kinases (e.g., Akt and AMP-activated protein kinase -AMPK-), and phosphatases (e.g., PP1) regulate the activity of these enzymes by phosphorylation [64]. Other regulatory post-translational modifications include acetylation, S-nitrosylation, S-gluathionylation, palmitoylation, and myristoylation. Furthermore, NOS activity can be modulated by protein-protein interactions with partners, such as Heat Shock Protein 90 (HSP90, activatory) and caveolin-1 and -3 (inhibitory) [64]. Shear stress can also increase eNOS activity via a mechanism that involves, at least in part, AMPK [65]. Therefore, alterations in the glycocalyx, such as those described above, can reduce AMPK activation and eNOS activity [65].

The second and third gasotransmitters are CO and H_2S, respectively. CO is endogenously produced by heme oxygenase (HO)-1 and − 2, whereas H_2S is produced from cysteine by different enzymes (cystathionine β-synthase -CBS-, cystathionine-γ-lyase -CSE-, 3-mercaptopyruvate sulfurtransferase −3-MPST-, and cysteine aminotransferase -CAT-) [66]. HO-1 and -2 catabolize heme to CO, biliverdin-IXα (further metabolized to bilirubin by biliverdin reductase, BR), and Fe^{2+} in the presence of O_2 and NADPH [67]. All gasotransmitters easily diffuse through the cell membranes and exert similar physiological effects (vasodilation, anti-inflammatory activity, and cytoprotection) [66]. CO activates, as NO does, soluble guanylyl cyclase, thus promoting vasodilation [68]. Furthermore, HO and BR metabolites exert protective effects on vascular cells [69]. Specifically, low levels of CO modulate oxidative phosphorylation and mitochondrial quality control, reduce ROS generation, and suppress inflammasome activation and pro-inflammatory cytokine release [70,71]. Positive and negative interactions between CO and NO systems have also been reported [67].

CSE is the main enzyme responsible for H_2S synthesis, and is mostly expressed in vascular cells. Consequently, H_2S levels are ≈100 times higher in the aorta than in other tissues (including the heart and brain) [72]. CSE expression is inhibited by several cardiovascular risk factors such as high-fat diet, hyperglycemia, inflammation, and angiotensin II, whereas it is increased by other factors, including nuclear factor erythroid 2-related factor (Nrf2), hypoxia-inducible factor 1α (HIF-1α), NO, and calcium [73]. The biological effects of H_2S are very broad, including modulation of gene expression and cell metabolism, and depend on its concentration. Three major mechanisms of action have been identified for H_2S. The first is the post-translational modification of proteins, known as the S-sulfhydration of cysteine residues. One of these targets is the ATP-dependent K-channel (K_{ATP}), which hyperpolarizes endothelial and smooth muscle cell membranes, thus promoting vasodilation [74]. Another relevant target is NFκB, whose S-sulfhydration promotes its antiapoptotic activity [75] and reduces LPS-induced inflammation in astrocytes [76]. Moreover, H_2S stimulates angiogenesis and wound healing by upregulating HIF-1α and vascular endothelial growth factor [73]. The second mechanism of action involves the reduction of ROS levels by both direct scavenging and regulation of the Nrf2 pathway by S-sulfhydrating its inhibitor, Keap1 [77]. Finally, H_2S signals by binding and/or reducing the metal centers of iron-heme proteins [78].

3. Molecular biology of BPIFB4

BPIFB4 is a member of the BPIF and mammalian palate lung and nasal epithelium clone (PLUNC) family of proteins, which are crucial antibacterial components that participate in host protection through their immunomodulatory properties [79]. As a member of the BPIFB subgroup, BPIFB4 contains two hydrophobic barrel-shaped structures, the BPI domains, which can specifically bind to lipopolysaccharides

(LPS) and phospholipids (Fig. 2A).

BPIFB4 maps to the long arm of chromosome 20 within a gene cluster containing four *BPIFB* genes (*BPIFB1*, *BPIFB2*, *BPIFB3*, and *BPIFB6*) and two pseudogenes (*BPIFB5P* and *BPIFB9P*) (Fig. 2B) [80]. Based on evolutionary history, protein sequences, genomic organization, and species conservation, it has been speculated that *BPIFB4* is a more recent duplicated gene derived from *BPIFB3*, which in turn has post-dated *BPIFB2* and the ancestral *BPI* gene. *BPIFB4* spans 33 KB of genome sequence organized into 15 exons and 14 introns, encoding a protein of 575 amino acids (Fig. 2C) [80].

According to the Human Protein Atlas consortium, the encoded protein is prominently expressed in the pituitary gland, where it shows high co-expression correlation with a cluster of 60 pituitary-enriched proteins and hormones. Elevated protein levels have also been reported in the brain (choroid plexus), proximal digestive tract (salivary gland), male tissues (testis), muscle tissue (heart muscle), and connective/soft muscles (adipose tissue). Further analysis revealed that *BPIFB4* is highly expressed in developmentally immature cells such as embryonic and induced pluripotent stem cells, stem cell-containing niches of adult tissues, and in the hippocampal dentate gyrus [81]. In addition, studies focusing on extreme longevity have demonstrated that BPIFB4 is a secreted protein with enriched levels in the serum of centenarians. Consistently, *BPIFB4* mRNA levels are reduced in fragile long-living individuals (LLI), indicating that it is a molecular marker associated with longevity and health status of the elderly [81,82].

Notably, the BPIFB4 locus has been shaped by natural selection for successful integration into local stressful environmental factors, including high altitudes and anthropogenic events [83,84]. In line with these evolutionary forces, BPIFB4 plays a crucial role in specific molecular adaptive mechanisms that are linked to improved survival. Indeed, it is instrumental in the maintenance of cellular homeostasis through the regulation of protein synthesis and ribosome biogenesis and in counteracting cellular stress via activation of adaptive stress responses [51,81].

4. Discovery of the longevity associated variant (LAV) of BPIFB4, molecular mechanisms and functional significance

The longevity-associated variant (LAV) of BPIFB4 was discovered using a stringent threshold of statistical significance for genome-wide association studies (GWA) in three independent cohorts of centenarians in Italy, Europe, and the US [81]. Association analysis demonstrated significant enrichment of the minor allele rs2070325 (Ile229Val) of BPIFB4 in LLIs and its linkage disequilibrium with three additional SNPs (rs2889732, rs11699009, and rs11696307). The resulting LAV-BPIFB4 haplotype, characterized by four missense variants (Val229/Thr281/Phe488/Thr494), reached a frequency of 14 % in centenarians as compared to 10 % in young controls. The most common variant (Ile229/Asn281/Leu488/Ile494) called wild-type-WT-BPIFB4, is found in 66 % of the population.

In line with the enrichment in centenarians, the LAV-BPIFB4 haplotype was inversely correlated with frailty in elderly subjects, strengthening its relevance in influencing the health status and longevity of the elderly.

Further analyses showed that the LAV homozygous genotype was positively associated with high endothelial nitric oxide (eNOS) phosphorylation at serine 1177 in mononuclear cells, which translates to augmented NO production and beneficial functions in the cardiovascular system [81]. In keeping with the benefits to the vascular compartment, recombinant LAV-BPIFB4 protein supplementation enhanced the proangiogenic activity of young and senescent endothelial cells by optimizing their ability to form a network on matrigel [51]. Importantly, these advantages can be transferred through LAV-BPIFB4 gene therapy in older mice, whereas eNOS phosphorylation and vessel activity are restored to levels observed in young mice [81].

The vascular protective function mediated by LAV-BPIFB4 arises from a cascade of biochemical events that involve two protein kinases: Protein Kinase R (PKR)-like endoplasmic reticulum kinase (PERK) and Protein Kinase C alpha (PKCα) [81,85]. This suggests that LAV-BPIFB4 is more prone to PERK- and PKCα-dependent phosphorylation than the wild-type isoform, resulting in the augmented cytoplasmic retention of the protein. This favors sustained interaction of the LAV isoform with 14–3-3, a scaffolding protein for phosphorylated proteins, and HSP90, an activator of eNOS. Moreover, LAV-BPIFB4 activated PKCα by increasing calcium mobilization via a feed-forward mechanism. Taken together, the calcium-dependent potentiation of PKCα and multiprotein complex formation triggered by PERK are crucial signals for improved NO availability mediated by LAV-BPIFB4 (Fig. 3).

Alongside the eNOS downstream substrate, the SDF-1/CXCR4 axis is a crucial effector of the cardiovascular protective and immunomodulatory activity of LAV-BPIFB4. In this regard, LAV-BPIFB4 activates SDF-1/CXCR4 signaling to remodel the immune system and resolve

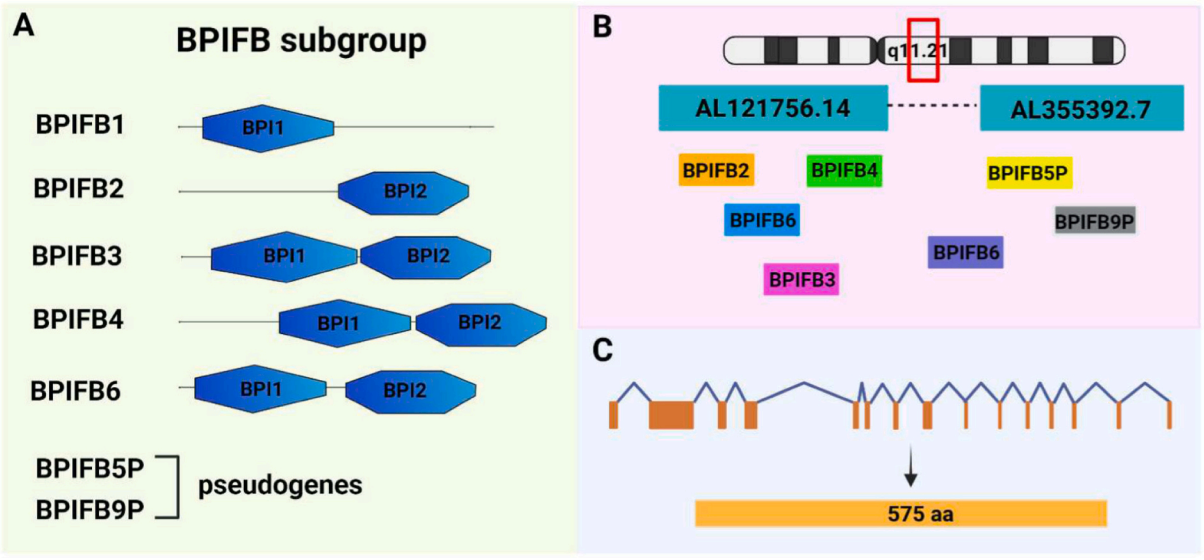

Fig. 2. A) Classification of human BPIFB members; B) Physical mapping of BPIFB members on the chromosome 20; C) Schematization of BPIFB4 transcript and protein.

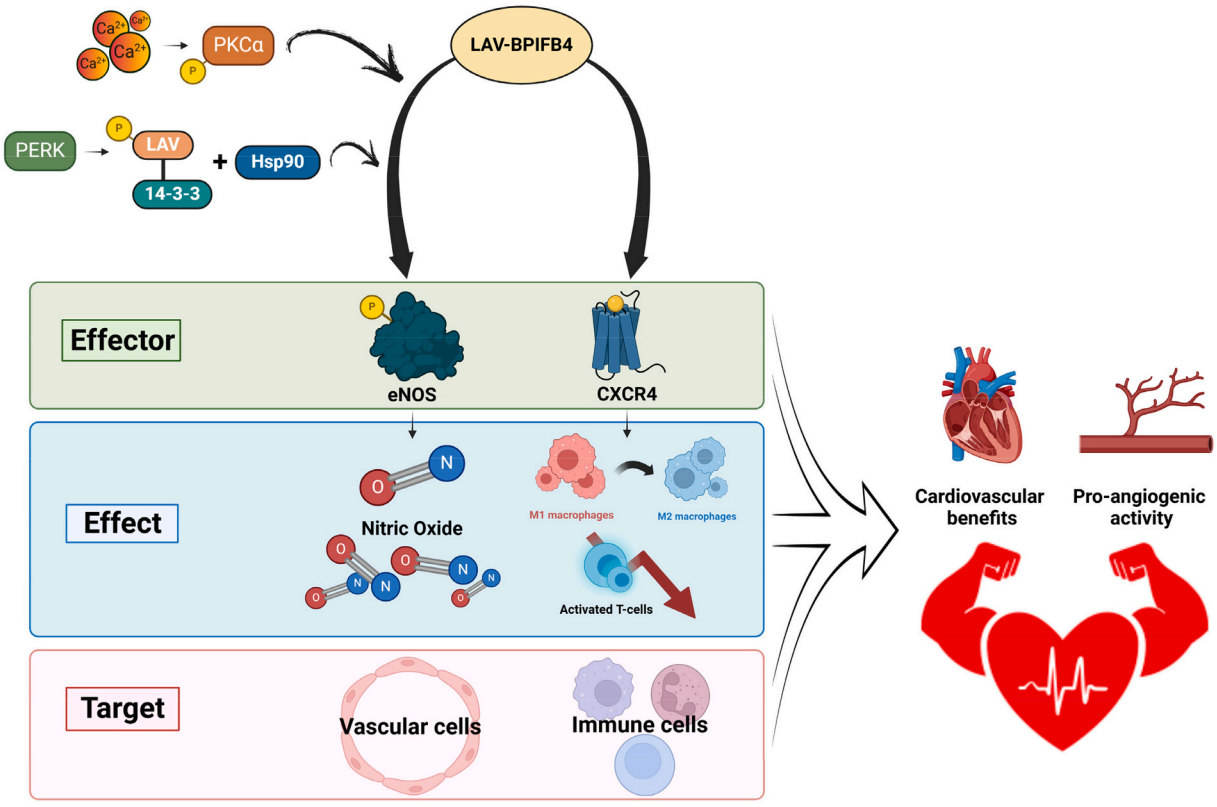

Fig. 3. Schematic representation of the two downstream effectors and the protective effects of LAV-BPIFB4 on the cardiovascular and immune systems.

inflammation through various mechanisms involving protective macrophage polarization toward the pro-resolving M2 phenotype, favorable redistribution of circulating monocyte cell subsets, and reduction in T-cell activation.

Overall, these mechanistic investigations define eNOS and CXCR4 as fundamental downstream effectors of LAV-BPIFB4, strengthening the translational relevance of BPIFB4 in the aging of the immune and cardiovascular systems (Fig. 3).

5. Protective role of LAV-BPIFB4 on the cardiovascular system: from microvascular dysfunctions to heart diseases

Aging is an inevitable process influenced by genetic and environmental factors and is a major independent risk factor for cardiovascular morbidity and mortality [26,86]. Age-related cardiovascular diseases are preceded by gradual microvascular dysfunction caused by chronic exposure to environmental, metabolic, and inflammatory insults that result in capillary loss, impaired blood flow regulation, and diminished barrier function of substance exchange between the blood and organs or tissues [26,86]. Thus, improving microvascular function and structure may be a promising strategy for the treatment of cardiovascular diseases.

Novel solutions may emerge from the genetic studies of LLIs. LLIs and their offspring suffer less microvascular dysfunction and related cardiovascular diseases, and exhibit extraordinary resistance to long-lasting stress [87]. Hence, boosting the influence of genes that support health and fitness in LLIs could represent an effective and safe modality to achieve better aging and prevent microvascular and cardiovascular complications in the general population. This could be the case for the LAV-BPIFB4. In recent years, we have provided evidence of a close link between LAV-BPIFB4 and microvascular function in several cardiac injury models, indicating that the longevity protein is a promising therapeutic tool for counteracting the damage inflicted by age-related cardiovascular diseases [51,81,88,89]. In the following sections, we summarize recent studies on the regulation of microvascular compartments mediated by LAV-BPIFB4 and its underlying mechanisms, including traditional pathways and novel molecular mechanisms involved in optimizing the performance of perivascular cells, microvascular angiogenesis, and capillarization.

5.1. LAV-BPIFB4 protects the heart from the damaging effects of aging and ischemia by targeting microvascular dysfunctions

A recent study aimed at understanding the potential mechanisms underlying the protective effects of LAV-BPIFB4 in age-related cardiovascular disease showed the capacity of this protein to revitalize the function and vascularization of the ischemic heart in the elderly by boosting the performance of microvascular PCs [51]. This study examined the differences in heart tissues obtained from elderly patients with end-stage ischemic HF (IHF) undergoing heart transplantation surgery and those from donors without cardiovascular complications, and showed lower expression of BPIFB4 in both cardiomyocytes and endothelial cells of IHF vs. controls. The BPIFB4 deficit was associated with microvascular defects, including the scarcity of Von Willebrand-positive endothelial cells and reduced density and coverage of PDGFRβ-positive PCs. Importantly, PC pauperization was remarkably attenuated in patients with IHF homozygous for the LAV-BPIFB4 genotype, highlighting microcirculation and cardiac PC as the preferential targets of LAV-BPIFB4 therapeutic action in aging cardiomyopathy (Fig. 4).

To obtain a more exhaustive overview of the microvascular protective effect mediated by LAV-BPIFB4, human cardiac PCs isolated from elderly patients with IHF were used as a cell model to analyze BPIFB4 titrations. Once again, IHF PCs showed low BPIFB4 expression levels, which correlated with an exacerbated senescent phenotype and depressed ribosome biogenesis [51]. Indeed, BPIFB4-deficient older IHF-PCs showed a higher frequency of Ki67 negative and γH2AX positive antigenic phenotype, lower levels of precursor 47S ribosomal RNA (rRNA) transcripts, and smaller nucleoli than controls. Notably,

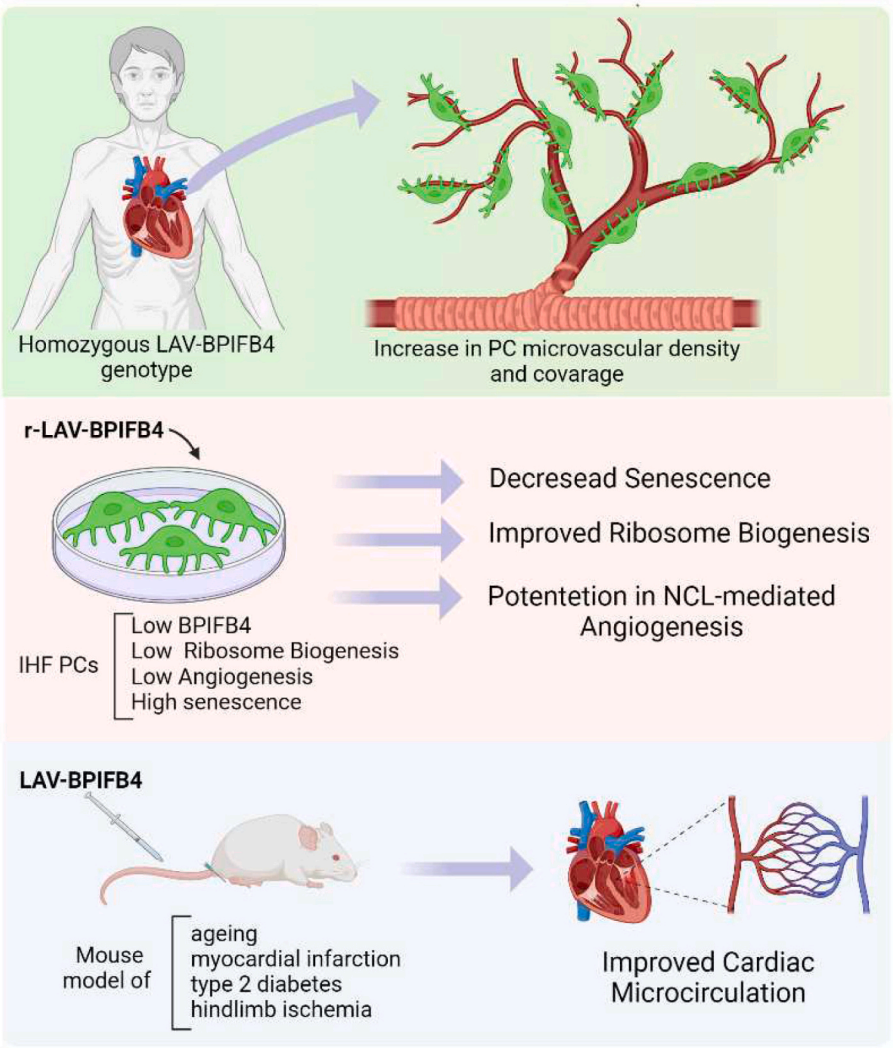

Fig. 4. Schematic representation of the positive association between *i.* IHF patients homozygous for the LAV-BPIFB4 genotype and increased PC ensheathment in the heart; *ii.* LAV-BPIFB4 conditioned IHF PC and improved homeostatic pathways; *iii.* LAV-BPIFB4 gene therapy and improvement in cardiac microcirculation.

supplementation with recombinant LAV-BPIFB4 protein rejuvenated the IHF PCs, induced ribosomal RNA transcription, and preserved the size of the nucleolus.

These findings indicate that BPIFB4 deficiency could accelerate microvascular dysfunction and failure of homeostatic processes in the heart and that boosting LAV-BPIFB4 was effective in correcting pathways implicated in microvascular network formation, vascular senescence, and ribosome biogenesis (Fig. 4).

The possibility that LAV-BPIFB4-mediated signaling may represent a target for treatment was further investigated at the molecular level in the perivascular cells.

Mechanistic investigations have shown that LAV-BPIFB4-mediated benefits in IHF PCs are attributed to the interaction of this molecule with nucleolin (NCL), a multifunctional nucleolar protein that is mainly implicated in the regulation of ribosome biogenesis, senescence, and angiogenesis [51,90]. By physically interacting with NCL through two moieties, the first BPI domain and the amino-terminal stretch of glycine, LAV-BPIFB4 induces mutual participation of endothelial cells and IHF PCs in vascularization. Indeed, focusing on microvascular cell interactions, IHF PCs preconditioned with recombinant LAV-BPIFB4 protein enhanced the release of proangiogenic factors and the capacity to encourage young or senescent endothelial cells to form networks on Matrigel. Conversely, the pro-angiogenic activity induced by LAV-BPIFB4 was blocked by silencing NCL or deleting the LAV-BPIFB4's binding sequence to NCL. These data indicate for the first time that the two proteins function as an on-off switch to modulate cellular crosstalk in angiogenesis (Fig. 4).

Overall, the in vitro study provides compelling evidence for the protective role of LAV-BPIFB4 against microvascular heart disease, suggesting that it is a successful therapeutic instrument capable of correcting molecular and structural dysfunctions occurring in microvascular compartments during aged ischemic heart disease.

5.2. LAV-BPIFB4 gene therapy in animal models of age-heart diseases exerts preventive and reparative action on cardiac microcirculation

In line with the data described above, preclinical studies conducted in animal models of cardiac aging have indicated that treatment with LAV-BPIFB4 has biologically relevant effects on microvascular density [51].

Evidence of its efficacy was recently observed in two animal models of heart aging, represented by early and late intervention studies [51].

In an early intervention study, in which the gene was delivered through an adeno-associated virus to middle age (14 months) and monitored after 4 months (4-month follow-up), LAV-BPIFB4 treatment completely prevented the decline in microcirculation occurring from middle age to the elderly. Indeed, at the anatomical and structural levels, LAV-BPIFB4 treatment increased capillary and arteriole density,

as well as PC ensheathment in cardiac tissues. The quantitative improvement of microvessels was accompanied by a decrease in cardiac cell aging, as determined by the reductive effect of LAV-BPIFB4 on the expression of senescence markers including the β-galactosidase, p16Ink4A and the histones H3.3 and ϒH2AX. Furthermore, this anatomical benefit translated into the recovery of myocardial perfusion under basal conditions and following stress, as assessed using PET/CT imaging.

In the late intervention study, in which the treatment was started at an older age (18 months) and had a 1-month follow-up, LAV-BPIFB4 treatment exerted a reparative action on cardiac microvascular rarefaction that typically occurs in the elderly, confirming the advantages previously observed in the early study.

Similar results were obtained in a mouse model of myocardial infarction, in which a single administration of *LAV-BPIFB4* revitalized myocardial vascularization by increasing the capillary density [88].

These findings extend the positive effects observed in our earlier preclinical studies conducted in a mouse model of type-2 diabetes and peripheral ischemia [81,89]. In the former, LAV-BPIFB4 gene therapy increased cardiac capillary density, whereas in the latter, both capillary and arteriole densities were remarkably improved in the limb muscles.

Overall, in vivo studies demonstrated the capacity of LAV-BPIFB4 to protect the heart from aging and the damaging effects of ischemia by improving microvascular network remodeling (Fig. 4).

5.3. *LAV-BPIFB4 preserves the cardiac function by improving the cardiomyocyte contractility*

Recent preclinical studies conducted in mouse models of cardiac aging and myocardial infarction indicated that LAV-BPIFB4 gene therapy exerts a significant benefit on heart contractile function [51,88].

In middle-aged mice, LAV-BPIFB4 treatment completely prevented the decline in the cardiac index by improving systolic and diastolic function, perfusion, and coronary flow response to β1 adrenergic stimulation [51].

Similarly, the transfer of LAV-BPIFB4 in older mice recovered the contractility indices to levels observed in middle-aged mice, strengthening its translational significance in human disease. Indeed, this success was estimated to be equivalent to reducing the biological age of the human heart by more than ten years [51].

Consistent with aging models, echocardiographic analysis conducted in LAV-BPIFB4-treated infarcted mice indicated reduced volumetric dimensions and improved parameters associated with systolic function [88], which attenuated the damage inflicted by myocardial infarction [88].

These findings complement our previous report regarding the capacity of LAV-BPIFB4 to protect the heart from diabetes-induced damage by improving diastolic and systolic functions.

Investigation of the mechanisms underlying this remarkable advantage indicated that LAV-BPIFB4 exerted a direct effect on the contraction and relaxation of human cardiomyocytes. Indeed, focusing on the functional indexes, LAV-BPIFB4 treatment significantly increased the beating frequency and contraction amplitude of cardiomyocytes [88], indicating its exceptional ability to improve the performance of cardiac muscle cells. Simultaneously, LAV-BPIFB4 gene therapy in diabetic mice induced the upregulation of cardiac MyHC-α, a contractile protein whose downregulation contributes to impaired cardiac performance in diabetes [89]. At a deeper molecular level, the enhancement of contractile capacity may be due to calcium-mediated activation of PKC-α induced by LAV-BPIFB4 [85].

Taken together, by exerting a chronotropic and inotropic effects on cardiomyocytes, LAV-BPIFB4 may protect the cardiac function from the damaging inflected by heart disease (Fig. 5)

5.4. *LAV-BPIFB4 gene therapy reduces the extension of perivascular fibrosis by targeting the activation of cardiac fibroblasts and the subsequent microvascular remodeling*

Perivascular fibrosis is defined as the progressive accumulation of extracellular matrix proteins (ECM) surrounding the vessels between cardiomyocytes following both acute and chronic tissue damage events, resulting in the remodeling and stiffening of heart tissue [55]. Perivascular fibrosis plays an important role in the pathogenesis of many cardiovascular disorders including HF, myocardial infarction, and

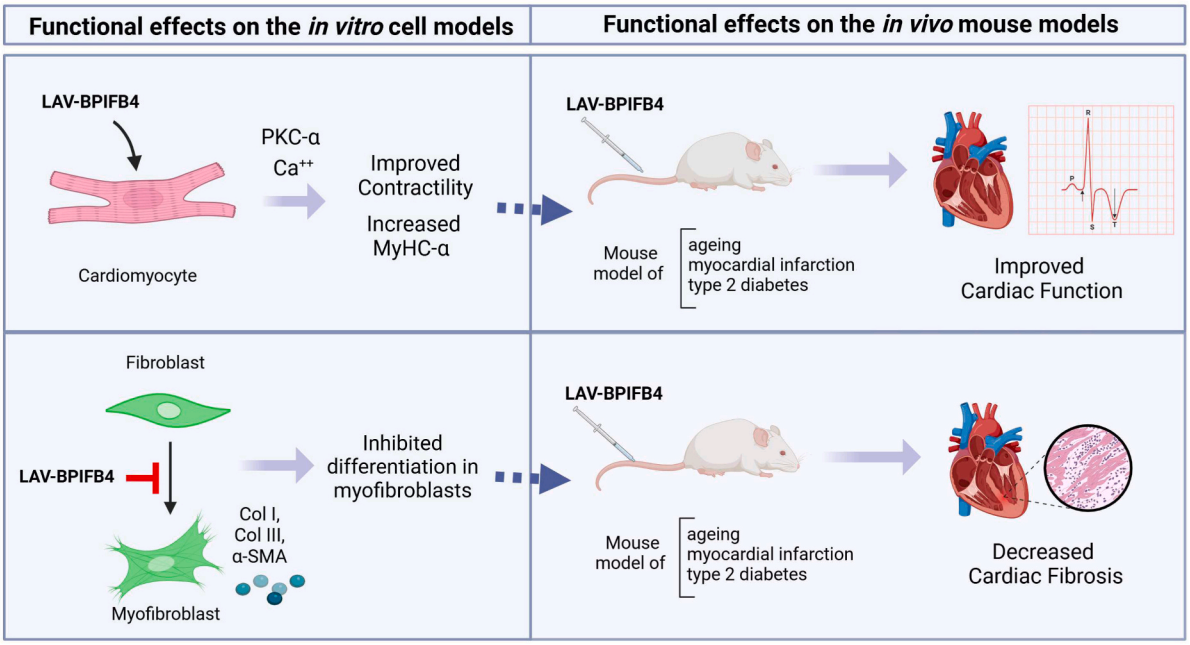

Fig. 5. Top panel: schematic representation of the chronotropic and inotropic effects exerted by LAV-BPIFB4 treatment on cardiomyocytes and translational effects on cardiac function. Panel below: cartoon showing the direct effect exerted by LAV-BPIFB4 on cardiac fibroblast activation and translational effects on cardiac fibrosis.

diabetes [55,91]. Therefore, malfunction or fibrotic remodeling of the microcirculation is a major threat to cardiac health.

Despite encouraging results from experimental studies, aldosterone antagonists are one of the few drugs with primary anti-fibrotic action approved for clinical use, although they reduce the speed of extracellular matrix accumulation rather than reverse fibrosis [92]. A new approach to contrast fibrosis may be the use of LAV-BPIFB4, which has been shown to be effective in attenuating perivascular and/or interstitial fibrosis in the myocardium of diabetic, aged, and infarcted mice [51,88,89]. The mechanism of antifibrotic LAV-BPIFB4 action may be, in part, associated with its direct inhibitory effect on the activation of cardiac fibroblasts. These cells differentiate into myofibroblasts, a specialized cell subtype with contractile action and secretion of ECM elements, in response to various types of damage, thus representing the most important cell types involved in the fibrotic process.

Our in vitro studies on cardiac fibroblasts demonstrated the ability of LAV-BPIFB4 to decrease the protein expression of the main fibrotic markers, including alpha smooth muscle actin and Collagen I and III, either during spontaneous or TGF-β1-stimulated fibrogenesis [88]. Simultaneously, in infarcted mice, LAV-BPIFB4 was effective in modulating circulating soluble pro-inflammatory cytokine levels, particularly soluble ICAM-1 [88].

Taken together, LAV-BPIFB4 may represent a therapeutic option to protect against adverse fibrotic remodeling in heart tissue via the modulation of cardiac fibroblast activation (Fig. 5).

6. Conclusion

CMD, caused by functional and structural alterations in the coronary microvascular tree, shapes the natural history of cardiovascular disease and aging. Single-cell omics analyses revealed with unprecedented detail the dynamics of cardiac stromal cells in pathology, showing the importance of microvascular cells in modulating cardiac inflammation and fibrosis. Genome-wide association studies on the genetics of extreme longevity have identified four polymorphic haplotype homozygous genotypes in BPIFB4 that are enriched in centenarians. LAV-BPIFB4 encodes a secretory protein whose levels are inversely associated with frailty and extent of coronary atherosclerosis. LAV-BPIFB4 promotes eNOS phosphorylation, NO production, and reparative angiogenesis, partially impinging on the SDF-1–CXCR4 axis. LAV-BPIFB4 interacts with nucleolin, promoting the transcription of ribosomal genes and releasing proangiogenic molecules, while inhibiting the release of inflammatory factors. Functionally, LAV-BPIFB4 can be successfully used in models of cardiovascular aging and myocardial ischemia to preserve the microvasculature, promote reparative angiogenesis, increase myocardial contractility, and reduce cardiac fibrosis. Therefore, in this review, we provide compelling evidence for the translational potential of LAV-BPIFB4 in the promotion of cardiovascular health and rejuvenation.

CRediT authorship contribution statement

Matteo Calligaris: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Aneta Aleksova:** Writing – review & editing. **Alessandra Lucia Fluca:** Writing – review & editing, Conceptualization. **Milijana Janjusevic:** Writing – review & editing. **Giada Carpi:** Writing – review & editing. **Daniele Stefanizzi:** Writing – review & editing. **Sara Carnevali:** Writing – review & editing. **Francesco Curcio:** Writing – review & editing. **Annibale Alessandro Puca:** Writing – review & editing, Conceptualization. **Monica Cattaneo:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Antonio Paolo Beltrami:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

Annibale Alessandro Puca has patent pending to Annibale Alessandro Puca. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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