Ischemic heart failure (HF) is a common complex clinical syndrome following myocardial infarction and is characterized by cardiac and non-cardiac features [1]. It is also the cause of mortality in high-risk patients undergoing non-cardiac surgery [2]. Despite the wide use of different drugs, such as beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, or of devices, such as implantable cardioverter-defibrillator and left ventricular assist devices [3], the 5-year survival is worse than cancer. The past three decades have witnessed incessant research aimed at protecting the adult myocardium against ischemic injury, but the development of effective strategies to prevent the maladaptive tissue remodelling is still a desirable achievement. Recent findings reveal that the dietary intake of natural bioactive components with known antioxidant activity improves the intercellular communication and increases the tolerance of both cardiomyocytes and coronary endothelial cells against the ischemic microenvironment. The Epigenetic activation of rescue genes prevents the decay of function of the abovementioned cardiac cells. Consequently, this scenario would reduce the myocardial accumulation of collagen responsible for the thickening of the heart walls. Whereas the non-invasive delivery of cardioprotectant epigenetic compounds through diet is a promising approach, regulatory mechanisms need to be unravelled.

Key words: epigenetics; myocardial remodelling; cardioprotection; diet.

INTRODUCTION

Ischemic heart failure (HF) is a common complex clinical syndrome following myocardial infarction and is characterized by cardiac and non-cardiac features [1]. It is also the cause of mortality in high-risk patients undergoing non-cardiac surgery [2]. Despite the wide use of different drugs, such as beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, or of devices, such as implantable cardioverter-defibrillator and left ventricular assist devices [3], the 5-year survival is worse than cancer. The past few decades have witnessed incessant research aimed at protecting the adult myocardium against ischemic injury, but the development of effective strategies to prevent the maladaptive tissue remodelling is still a desirable achievement [4]. Therefore, it is clinically relevant to address further studies to dissect alternative pathophysiological issues, such as cell-to-cell and cell-to-microenvironment cross-talk during the exposure to ischemic insult. Epigenetic modifications mediate mechanisms underline cellular tolerance against ischemic microenvironment, as cell survival and angiogenesis [5]. Despite the threshold of adaptive epigenetic effects is difficult to be safely modulated by synergistic drug combinations, the intramyocardial delivery of low doses of specific natural compounds has protected the ischemic myocardium through the modification of the epigenetic profile of cardiomyocytes, endothelial and interstitial cells [6]. Our first experimental evidence demonstrates the feasibility of cardioprotection by biocative compounds also present at higher concentrations in conventional plant foods named functional foods. To date, the regular intake of functional foods may be helpful to reduce cardiovascular risk factors [7] and to prevent the onset of the remodelling process of ischemic myocardium.

OVERVIEW OF MYOCARDIAL TARGETS OF CARDIOPROTECTION

The cardiac remodeling recapitulates cellular, interstitial, molecular and genetic changes after an initial injury.
The cardiac remodelling process itself is compensatory at early stage and detrimental in the long term [8]. The early inflammatory cell-mediated response is helpful to remove cell debris and to counteract the release of pro-apoptotic mediators, which leads to the activation of endothelial cells and fibroblasts to form new vessels and to promote adaptive hypertrophy respectively. Afterwards, collagen-rich scar replaces the loss of mature myocardium. The chaotic and rapid stimulation of intracellular pathways triggers cardiomyocytes and progenitor cells death, rarefies the native net of the coronary microcirculation, which is replaced by immature vessels, and deregulates the extracellular matrix turnover as well. This rescue scenario becomes over time a vicious circle leading to irreversible myocardial damage. Specific targets for the prevention of cardiac failure will be revised within interplay between dynamic and pleiotropic signaling pathways.

THE SURVIVAL OF CARDIOMYOCYTES AND PROGENITOR CELLS

Cardiac progenitor cells and cardiomyocytes survive in the presence of hostile microenvironment by multiple mechanisms and the magnitude of cell survival varies regardless the etiology and exposition time. The regulation of survival of cardiac cells is very important both to maintain the homeostasis of normal adult myocardium [9] and to limit the remodeling process during the exposure to insults [10-14]. To date, the prosurvival pathways counteract different form of cell death, such as apoptosis, oncosis and autophagy, in normal and injured adult myocardium [15].

Apoptosis is an active and highly regulated biological process. Two main apoptotic pathways transduce death signals in cardiac cells: i) the intrinsic pathway occurs through the opening of the mitochondrial permeability transition pore or the rupture of outer mitochondrial membrane. The cleavage of caspase-9/caspase-3 cascade is mediated by cytochrome c, which is released by mitochondria after exposure to hypoxia, ischemia–reperfusion injury, and oxidative burst. Finally, the active caspase-3 cleaves cardiac cytoskeletal proteins, such as α-actin, α-actinin, α/β-myosin heavy chain, myosin light chain 1/2, tropomyosin and troponins [16]; ii) the extrinsic pathway involves the stimulation of pathways mediated by death-receptors, such as the Fas receptor or the tumor necrosis factor α receptor-associated death domain protein (TRADD) [17]. Even if the death-receptors do not necessarily cause cell death, the binding of each death-receptor to its ligand induces the formation of a death-inducing signaling complex (i.e.: TL1A/DR3; TRAIL/TRAILR) which activates caspase-8 [18]. The magnitude of apoptosis into the heart is regulated through the expression of: a) anti-apoptotic factors, such as Bcl-2, XIAP (X chromosome-linked Inhibitors of Apoptotic Proteins), ARC (apoptosis regulator with caspase recruitment domain), c-FLIP(L) (an endogenous inhibitor of death receptor-induced apoptosis through the caspase-8 pathway), Foxo3a (a regulator of calcium level) and microRNA (miRNA)-702 (a downregulator of activating transcription factor 6); b) pro-apoptotic factors, such as Bax and Bak, Smac/DIABLO, XIAP-interacting protein-1 and Omi/HtrA2 (IAPs inhibitors) [19].

Oncosis, conversely, is a non apoptotic cell death characterized by rapid depletion of intracellular ATP [19], mitochondria swelling due to the failure of the surface ionic pumps and progressive plasma membrane disruption, followed by an inflammatory reaction [19]. Oncosis is a major contributor to myocardial ischemic cell death [20] and may be independent of caspases activation [20].

Although, autophagy is a process characterized by lysosome-dependent degradation and recycling of intracellular elements, such as dysfunctional mitochondria [21]. It characterizes a conservative response to different insults. Macroautophagy is the main form of autophagy, where plasma membrane enveloping a large portion of the cytosol forming the autophagosomes. The autophagosomes fuse with lysosomes to form autolysosomes [22]. Further studies also detected the occurrence of microautophagy, which is the transfer of small cytosolic components into the lysosome by membrane vesicles [23], and chaperone-mediated autophagy, which is the direct shuttling of soluble cytosolic proteins into lysosomes by chaperone (i.e.: heat shock protein of 70 kDa) [24].

Deregulated autophagy leads to cell death and cardiac dysfunction through uncontrolled self-digestion of cellular constituents [25]. Even if much remains to be elucidated, AMP-activated protein kinase (AMPK), an important regulator of cardiac metabolism [26], serves as an activator of myocardial autophagy through activation of E3 ligases expression [27]. miRNA-325 contributes also to promote autophagic cell death [25].

THE TURNOVER OF CORONARY VESSELS

The capillary density and the capillary-to-myocyte ratio influences the effectiveness of the myocardial blood perfusion in response to increasing load, which is critical to support cardiac contractile function [28]. The rarefaction as well as the dysfunction of the microcirculatory net following myocardial ischemia impairs the restoration of the blood supply in infarcted myocardium [29]. The capillary density is maintained by a balanced turnover of endothelial cells proliferation and migration, sprouting and tube formation. New coronary microvessels are generated from pre-existing mature endothelial cells in response to different sig-
nals, such as hypoxia [30], oxygen free radicals (ROS) [31], growth factors (VEGF, HGF, FGF, Notch-1 and PDGF-β) [16,32], C-type natriuretic peptide [33] or nitric oxide (NO) [34]. Conversely, the coronary angiogenesis is hampered by chronic inhibition of endothelial NO synthase [35] and by different soluble factors. The main endogenous inhibitors of angiogenesis are angiostatin, endostatin [36] and miRNA-24 [37].

Interestingly, the endothelial ability to renew the capillary network architecture is controlled via cell-matrix mechanical interactions [38] and shear stress [39].

THE TURNOVER OF EXTRACELLULAR MATRIX

The turnover of cardiac extracellular matrix (ECM) provides a balance of elastic and plastic structures supporting cardiomyocytes, interstitial cells and capillaries in order to optimize the mechanotransduction, the electrical conductivity and permissivity, the intercellular cross-talk, and metabolic activity in the presence of different microenvironment [40]. This issue is critical because the features of ECM change during early and late remodeling process. In particular, glycosaminoglycans (i.e.: heparan sulfate, hyaluronan), glycoproteins (i.e.: tenascin-C) and proteoglycans (i.e.: lumican) play a key role in ECM formation [40]. Extracellular Granzyme B and metalloproteinases (MMPs), bioactive serine proteases, contribute to the loss of myocardial structural integrity through cleavage of ECM proteins [41,42]. Other factors may interfere with the renew of ECM in normal heart and with fibrosis during remodelling. In particular, the connective tissue growth factor (CTGF), a secreted cysteine-rich protein, highly expressed in both cardiac fibroblasts and cardiomyocytes of failing heart [43], enhances the expression of fibronectin and collagen type 1 through the activation of TGF-beta-dependent pathways. Finally, CTGF expression is epigenetically down regulated by selective microRNAs, such as miRNA-133 and miRNA-30 [44].

THE INNATE IMMUNITY APPARATUS: CROSS-TALK BETWEEN MYOCARDIAL SENSORS

Innate immune apparatus triggers inflammatory response. In particular, toll-like receptor-mediated pathways and cardiac progenitor cells modulate the release of soluble auto-/paracrine factors, such as chemokines, cytokines and exosomes in the injured heart [45].

Cardiac progenitor cells, endothelial cells, fibroblasts and mast cells, which are resident in the adult heart [46], express auto-/paracrine mediators able to activate or to silence gene profile and function in response to changes of microenvironment and tissue geometry [32].

Toll-like receptors (TLRs), such as TLR-2, TLR-3 and TLR-4, are recognition receptors expressed by all cells resident into the adult heart and mediates immune-mediated pathways activity during myocardial remodelling [47]. Endogenous products of myocardial remodelling, such as free radicals, heat shock proteins and hyaluronan, activate several kinases and NF-κB through TLRs, which promote the expression of inflammatory mediators [47] acting as endogenous preconditioning agents [48].

Even though clinical trials have reported unconvincing results on the renew of cardiomyocytes in infarcted myocardium by progenitor/stem cells [49], cardiac progenitor cells are able to polarize human macrophages into an anti-inflammatory phenotype promoting the release of angiogenic and anti-inflammatory cytokines, such as VEGF, IL-10 and IL-13, to inhibit the release of pro-inflammatory cytokines, such as IL-1α, IL-1β and interferon gamma [50] and to induce the release of membrane-surrounded nanovesicles, termed exosomes, activating pro-survival signaling pathways in cardiomyocytes involving TLR 4 and HSP27 [48]. This mechanism highlights the role of myocardial progenitor cells as critical regulator of cell-to-cell communication in the adaptive response of cardiac cells to ischemic microenvironment [51].

EPIGENETIC MODULATION OF CARDIOPROTECTION

The epigenetic code refers to specific heritable chromatin-based regulatory mechanisms underlie the regulation of gene expression without altering DNA sequence [52]. Epigenetic pathways mediate the transcriptional and post-transcriptional modifications of gene profile also in cardiac cells. Three main pathways regulate the epigenetic state of the heart: DNA methylation, histone modifications, and RNA-based silencing.

DNA methylation refers mainly to the addition of a methyl group to the 5-position of cytosine of CpG sequence of promoter regulatory regions through selective enzymes [5]. The cells use DNA methylation to lock gene transcription in the off position by three mechanisms: i) the blocking of recruitment of transcription factors to correspondent cis-DNA binding elements by steric hindrance, ii) the specific co-binding of proteins to methylated DNA that compete with the specific transcriptional factors [53] and iii) the recruitment of histone deacetylases (HDACs) to silence gene expression [54]. The gene downregulation through the global gene promoter methylation is a typical feature of the end-stage failing myocardium in humans [55]. Histone modifications alter the gene expression through changes in the nucleosome conformation in
order to control DNA accessibility. The nucleosome represents the chromatin unit and is composed of 146-bp DNA wrapped around octamers formed of four couple of different highly alkaline nuclear proteins termed histones (H2A, H2B, H3, and H4). Histones undergo different posttranslational modifications at level of lysine (acytlation, ubiquitination, methylation, sumoylation) or arginine (methylation) or serine and threonine (phosphorylation) residues [5]. Reversible histone acetylation plays a key role in the development of postischemic myocardial remodelling. The magnitude of myocardial histone acetylation, which usually activates gene transcription, is regulated by the balance of the activity of two different enzymes: a) histone acetyltransferase (HAT), such as p300/CREB-binding protein, which transfers acetyl group to histones and prevent chromatin compaction, and b) histone deacetylase (HDAC), which removes acetyl group from conserved lysine residues of H3 and H4 histone and leads to the formation of unreadable chromatin. There are four major classes of HDACs, which randomly act to control gene expression in cardiac cells exposed to hostile microenvironment. We and other investigators have demonstrated that the inhibition of the class I HDACs in cardiac cells is able to inhibit apoptosis and to stimulate angiogenesis through acetylation of H4 histone. Taken together, these biological events limit structural remodelling and improve the cardiac function in vivo [6,56]. Finally, phosphorylation of histone H2A(X) is essential to repair damaged DNA [57]; although, phosphorylation of histone H3 promotes cell proliferation and promotes gene transcription through acetylation of H3K14 by the Gcn5 acetyltransferase [58].

MicroRNA (miRNAs) and the RNA interference machinery are endogenous key repressors of chromatin-based gene expression [5]. Most miRNAs genes are located at level of the intergenic, intronic, or exonic regions of DNA and are transported from the nucleus to the cytoplasm as part of mRNA. The mature miRNAs are incorporated into a miRNA-induced silencing complex (RISC) and base-paired to target mRNA for mRNA degradation [59]. Cells secrete miRNAs, small non-coding RNA molecules, into exosomes [60]. To date, it is known that miRNAs profile is altered in failing myocardium [61], which plays a key role in the impairment of the cardiac structure-function relationship. In fact, the upregulation of miRNA25 in failing heart delays myocytes calcium uptake and causes decay of contractility in vivo [62]. Similarly, the over-expression of miRNA 30c and miRNA 155 promote cell loss through alteration of the mitochondrial function [63]. miRNA 21 mediates fibroblast survival and proliferation [64]; although, miRNA21* delivered to cardiomyocytes through fibroblast-derived exosomes induce hypertrophy in response to hostile microenvironment [65]. Other miRNAs might play an activator role in promoting myocyte proliferation in murine infarcted heart. For example, the myocardial overexpression of miRNA 590 and miRNA 199a promote cardiomyocyte proliferation and almost complete recovery of cardiac functional parameters in murine infarcted heart [66]. We have demonstrated that exosomal miRNA 210 prevents cardiomyocytes apoptosis in infarcted heart through downregulation of its known targets, ephrin A3 and protein-tyrosine phosphatase 1B (PTP1b); although, exosomal miRNA 132 enhances the formation of mature coronary vessels through downregulation of RasGAP-p120 [60].

**PRIMARY PREVENTION WITH FUNCTIONAL FOODS**

Primary prevention of cardiac dysfunction is based on the avoidance or attenuation of risk factors in healthy people.

The main risk factors promoting myocardial injury are age, gender, lifestyle factors (i.e.: lower physical activity, occupational stress, smoking, excessive caloric an salt intake, excessive alcohol and coffee consumption, lower socioeconomic status) and comorbidities (i.e.: hypertension, diabetes, obesity, hyperlipidemia, depression and valvular heart disease) [67]. Even if some risk factors cannot be avoided, such as age, gender and genetic susceptibility to cardiomyopathy, lifestyle risk factors and comorbidities might be modulated by intake of functional foods, such as plant or marine foods, which contain higher amount of bioactive compounds (nutraceuticals).

**Foods lowering hypertension**

In young subject, the diastolic blood pressure is a risk factor for HF more relevant than systolic blood pressure; although, the impact of systolic blood pressure increases in older patients [1]. Despite the conventional anti-hypertensive medications are effective in normalizing blood pressure with combination of two or more drugs, natural dietary compounds are emerging as inhibitor of vascular and myocardial remodelling following the exposure to high blood pressure. Recent double-blind randomised placebo-controlled trials have demonstrated that the daily intake of non-fresh garlic extract (at average dose of 2.4mg/day for 12 weeks) causes a significant reduction of the mean systolic blood pressure in patients with refractory systolic hypertension [68]. The anti-hypertensive effects of garlic is partly due to production of NO [69]. However, so far, there is no clinically relevant evidence to claim that regular garlic intake reduces the risk of mortality and cardiovascular morbidity in hypertensive patients [70].

Other pilot study has shown that oral pea protein hydrolysate has a weak and significant blood pressure-lowering effect in hypertensive subjects through inhibition of renin and angiotensin converting enzyme [71]. Conversely, no blood pressure-lowering effect was observed in hypertensive patients following di-
etible epoxide hydrolase and reduces circulating level of oxylipins, which cause endothelial dysfunction and the time exposure to hyperlipidemia, it is conceivable to prevent myocardial injury through diet supplementation with specific functional foods lowering lipids in the bloodstream.

Recent randomized controlled clinical trials have demonstrated that daily intake of functional foods containing high levels of plant-derived protein hydrolysates and peptides reduces the circulating cholesterol levels in a dose-dependent manner [78]. In particular, regular intake of plant stanols and sterols (2 g/day) [79], barley β-glucans (3 g/day) [80] or tree nuts [81,82] reduces circulating LDL-cholesterol (LDL-c) serum levels. In hyperlipidemic patients, 6-months intake of diet containing both of the abovementioned compounds was more effective in LDL-C lowering compared to the intake of low-saturated fat diet [83]. Therefore, the hypcholesterolemic effects of these compounds are independent of the caloric intake. Other dietary plant-derived compounds normalize the lipid profile in dislipidemic patients with normal cardiac function. For example, pectin with high molecular weight and high degree of esterification (contained in lemon and apple), when taken at dose of 6 g/day for 3 weeks, are effective in reducing LDL-c levels in mildly hypercholesterolemic patients [84]. Similarly, red grape seed extract, when consumed at dose of 200 mg/day for 8 weeks, decreases both the oxidized-LDL levels and the risk of atherosclerosis and cardiovascular disorders in mild hyperlipidemic subjects [85]. Grape seeds contain high levels of flavonoids, such as gallic acid and procyanidins, with epigenetic properties (HAT inhibitors) [86]. Conversely, the cholesterol-lowering effects of phenolic-rich virgin olive oil, which is an important component of the Mediterranean diet, are still controversial and need further investigations [87]. This finding is surprising if we consider that a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduces the incidence of major cardiovascular events in persons at high cardiovascular risk [88]. Similarly, some animal-derived functional foods have shown significant effects in reducing human cardiovascular risk due to exposure to hyperlipidemia. Recent randomized placebo-controlled study has demonstrated that daily intake for 10 weeks of yoghurt supplemented with 3 g of n-3 long-chain polyunsaturated fatty acids (PUFA) significantly reduced the circulating levels of inflammatory mediators and the cardiovascular risk in mildly hypertriacylglycerolemic patients [89]. The comparison between the cholesterol-lowering efficacy of plant- and animal-derived foods remain to be fully assessed. So far, it is known that long-term dietary intake of fish oil (17 g/day for 8 weeks), which is rich of n-3 PUFA, decreases only triglyceride serum levels in patients with metabolic syndrome; although, the dietary intake of similar dose of echiom oil, a plant extract of Echium plantagineum rich of stearidonic acid, causes a marked reduction of serum triglyceride and oxidized LDL in the same class of patients [90].

**Foods lowering hyperlipidemia**

Hyperlipidemia, in particular high levels of non-high-density lipoprotein cholesterol, is a primary risk factor for myocardial injury [77]. Since the progression of myocardial injury towards heart failure depends on the time exposure to hyperlipidemia, it is conceivable to prevent myocardial injury through diet supplementation with specific functional foods lowering lipids in the bloodstream.

Recent randomized controlled clinical trials have demonstrated that daily intake of functional foods containing high levels of plant-derived protein hydrolysates and peptides reduces the circulating cholesterol levels in a dose-dependent manner [78]. In particular, regular intake of plant stanols and sterols (2 g/day) [79], barley β-glucans (3 g/day) [80] or tree nuts [81,82] reduces circulating LDL-cholesterol (LDL-c) serum levels. In hyperlipidemic patients, 6-months intake of diet containing both of the abovementioned compounds was more effective in LDL-C lowering compared to the intake of low-saturated fat diet [83]. Therefore, the hypcholesterolemic effects of these compounds are independent of the caloric intake. Other dietary plant-derived compounds normalize the lipid profile in dislipidemic patients with normal cardiac function. For example, pectin with high molecular weight and high degree of esterification (contained in lemon and apple), when taken at dose of 6 g/day for 3 weeks, are effective in reducing LDL-c levels in mildly hypercholesterolemic patients [84]. Similarly, red grape seed extract, when consumed at dose of 200 mg/day for 8 weeks, decreases both the oxidized-LDL levels and the risk of atherosclerosis and cardiovascular disorders in mild hyperlipidemic subjects [85]. Grape seeds contain high levels of flavonoids, such as gallic acid and procyanidins, with epigenetic properties (HAT inhibitors) [86]. Conversely, the cholesterol-lowering effects of phenolic-rich virgin olive oil, which is an important component of the Mediterranean diet, are still controversial and need further investigations [87]. This finding is surprising if we consider that a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduces the incidence of major cardiovascular events in persons at high cardiovascular risk [88]. Similarly, some animal-derived functional foods have shown significant effects in reducing human cardiovascular risk due to exposure to hyperlipidemia. Recent randomized placebo-controlled study has demonstrated that daily intake for 10 weeks of yoghurt supplemented with 3 g of n-3 long-chain polyunsaturated fatty acids (PUFA) significantly reduced the circulating levels of inflammatory mediators and the cardiovascular risk in mildly hypertriacylglycerolemic patients [89]. The comparison between the cholesterol-lowering efficacy of plant- and animal-derived foods remain to be fully assessed. So far, it is known that long-term dietary intake of fish oil (17 g/day for 8 weeks), which is rich of n-3 PUFA, decreases only triglyceride serum levels in patients with metabolic syndrome; although, the dietary intake of similar dose of echiom oil, a plant extract of Echium plantagineum rich of stearidonic acid, causes a marked reduction of serum triglyceride and oxidized LDL in the same class of patients [90].

**Foods restoring insulin sensitivity**

The insulin resistance (IR) strongly characterizes the type 2 diabetes as well as the more complex metabolic syndrome, which are independent risk factors for HF. Recent findings confirmed that chronic insulin resistance itself impairs cardiac homeostasis through the induction of inflammatory and oxidative burst related to the metabolic myocardial state following endothelial dysfunction [91]. Conventional therapies for insulin resistance partly fail to prevent and to reverse both high fasting plasma glucose and myocardial injury. Therefore, it is conceivable to develop innovative dietary-based strategies against IR based on the intake of functional foods [92]. It has been demonstrated that daily intake for one month of both whole and fractionated pea flour (50 g/day) is effective in reducing IR in overweight patients with metabolic syndrome [93]. Similarly, the daily supplementation of low cholesterol diet with 40g of ground flaxseed-containing baked products improves the insulin sensitivity in hyperlipidemic adults [94]. The IR-lowering effects were observed in obese population with pre-diabetes and in patients with metabolic syndrome long-term treated with plant-derived n-3 ALA (flaxseed, rapeseed oil) [95,96].

Even though the benefits require further investigations, the use of antioxidants seems to be a promising approach to reduce the insulin resistance in an epigenetic manner. In fact, long-term dietary intake of broccoli sprouts powder (10 g/day), which contains high levels of sulphoraphane, a potent inhibitor of class I HDACs, significantly reduces serum insulin levels and homoeostasis model assessment of IR (HOMA-IR) index in type 2 diabetic patients [97]. However, further studies are mandatory to exclude the inhibition of glucose-induced insulin secretion after the long-term intake of lower dose of sulphoraphane [98].
SECONDARY PREVENTION WITH FUNCTIONAL FOODS

Secondary prevention of cardiac dysfunction is focused on the prevention of late myocardial remodelling in patients with current symptoms of ischemic heart diseases (i.e.: angina, myocardial infarction, recipients of coronary revascularisation, cardiac amyloidosis, arrhythmias) or with symptoms of other vascular diseases (such as stroke, peripheral vascular diseases). The aim of secondary prevention is to prevent progression of the primary myocardial injury. The conventional interventions of secondary prevention are based on drugs (i.e.: low dose aspirin, statins, β-blockers, angiotensin converting enzyme (ACE) inhibitors, inhibitors of platelet aggregation) and changes of lifestyle habits (i.e.: physical activity, diet, meticulous control of blood pressure and glucose, cognitive activity). Emerging pre-clinical evidences have shown that regular intake of selected functional foods might hamper the post-ischemic myocardial remodelling in damaged hearts. Flavonoids, such as anthocyanins, are common anti-oxidant compounds of plant-derived functional foods and their regular intake after ischemia-reperfusion injury improves cardiac function in rats [99]. Similar benefits are induced with short-term oral administration of beta-glucan in a swine model of myocardial ischemia/reperfusion [100] and in a canine model of myocardial infarction [101]. In addition, short-term dietary intake of cooked broccolis can limit the infarct size of murine hearts exposed to ischemia-reperfusion injury [102]. While the mechanisms are still under investigation, it is conceivable that the cardioprotection is due to the inhibition of class I HDACs by sulforaphanes contained in broccolis [103]. We have demonstrated that long-term treatment of cultured endothelial cells and Tg (kdrl: EGFP) s843Tg zebrafish embryos with 3% barley beta-glucan enhances the formation of new vessels in the presence of ischemic microenvironment through the increased acetylation of histone H4, which is related to higher levels of manganese superoxide dismutase, a key antioxidant enzyme, and NO [104]. Similarly, our recent preliminary data have shown that the long-term intake of low-fat diet supplemented with functional pasta delivering 3% barley beta-glucan increases the VEGF-mediated myocardial capillary density and attenuates the ischemia/reperfusion injury in murine heart through the increase of native collateral formation after 5-weeks of diet [105]. In addition to these recent pre-clinical evidences, placebo-controlled, double-blind randomised clinical trial has demonstrated that the supplementation of diet with vitamin D, able to induce histone acetylation and DNA demethylation [106], did not improve the endothelial function in patients with myocardial infarction [107]. It is conceivable that this negative finding is related to the hormetic regulation of the epigenetic state. In fact, the co-treatment of cells with active vitamin D, HDACs inhibitors and DNA methyltransferase inhibitors induces apoptosis of cancer cells [108], an effect induced by the exposure to highest dose of chromatin openers. Similarly, the broad use of antioxidants increases the risk of HF in patients with acute myocardial ischemia [109]. These findings suggest that the cardioprotective efficacy of functional foods mainly depends on the epigenetic magnitude of natural compounds in the presence of different microenvironment, but it does not depend on antioxidant activity. Finally, the epigenetic role of dietary antioxidant compounds in modulating the expression of myocardial microRNAs is emerging. The synergistic action of antioxidant resveratrol, a constituent of red wine, and alpha-tocotrienol, a compound of palm oil, is able to increase the myocardial expression of anti-angiogenic miRNA20b, which is not reflected in the cardioprotection against ischemia/reperfusion injury [110]. In fact, other investigators have demonstrated that the anti-angiogenic properties of the resveratrool are counteracted by its ability to increase NO-dependent vasodilation [111]. Otherwise, the intake of anti-inflammatory curcuminoids (4 g/day from 3 days before until 5 days after the surgery), polyphenols able to demethylate the DNA [112], prevented the onset of myocardial infarction in 121 patients undergoing coronary artery bypass grafting [113]. Experimental and clinical investigations are on-going in order to further unravel epigenetic mechanisms underlie cell-to-cell and cell-to-matrix interactions in injured hearts, which are candidate targets of dietary bioactive compounds.

CONCLUSIONS AND PERSPECTIVES

Dietary functional compounds have been gaining interest, so far. Since the relationship between epigenetic state and myocardial remodelling becomes more well-defined, the identification of key molecular targets is helping to reveal new natural epigenetic compounds mainly contained in conventional plant-derived foods. These findings will be useful to design hitherto unexpected dietary approach in order to prevent both the myocardial injury and the development towards heart failure. Moreover, some relevant issues on pleiotropic epigenetic effects of natural compounds will also encourage further studies in order to reduce the dose of conventional drugs and to improve the outcome of subjects exposed to high cardiovascular risks.

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