Introduction

Tissue and cellular microenvironment is a complex of interactions between small molecules like interleukins, cytokines, chemokines, SirNA, hormones acting in autocrine and paracrine manner in cardiomyocytes [1]. The cardiac tissue is a pluricellular organ composed of cardiomyocytes, fibroblasts, endothelial cells, smooth muscle cells, neurons and immune cells regulating the homeostasis of the matrix deposition, neo-vascularization, inflammation and mitochondrial metabolism [2]. In the field of oncology, several work focalize their attention on the role of cancer microenvironment, also by using phytotherapics and anti-inflammatory drugs of synthetic or natural origin.

Discussion

In recent years, clinical research in cardiology focalize the attention on the importance of cardiac and vascular microenvironment.
microenvironment in the incidence and recurrence of cardiovascular diseases and cardiotoxicity. Pro-inflammatory microenvironment principally based on IL-1, IL-6, IL-8, with are overexpressed in patients affected by Metabolic Syndrome or in treatment with Aldosterone Receptor Antagonists, increased Doxorubicin-Induced cardiotoxicity and cardiovascular diseases [9-12]. As shown in Figure 1, these interleukins activate multiple pathways leading to dysregulation of Sarcoplasmatic reticulum and calcium homeostasis. Another key player of the cardiomyocyte microenvironment is the receptor of the Advanced Glycation End Products (AGEs). Patients with Metabolic Syndrome have high plasma levels of AGEs [13]. As, example, plasma pentosidine levels, one of the crosslinking AGEs, has been shown to be an independent predictor of both re-hospitalization and mortality in heart failure patients independent from other known risk factors such as brain natriuretic peptide (BNP), age and renal function [14].

**Figure 1:** Multiple biochemical effects of Interleukin 1, 6 and 8, Tool Like receptor type 4, Lipid peroxidation and Advanced glycation End Product in cardiomyocyte metabolism.

Glycated Hemoglobin (HbA1c) is a common AGE easily detectable in the blood. HbA1c is a reliable risk factor for all-cause mortality and cardiovascular mortality in both non-diabetic and diabetic populations. Notably, glycation of proteins like the hemoglobin determine specific pro-inflammatory effects also in the vascular district [15] with alteration of erythrocyte membrane properties leading to erythrocyte aggregation, consequent increase in blood viscosity, and impaired blood flow with phenomena of shear stress. Shear stress trigger inflammatory response (same of them based on iron-dependent peroxidation of proteins and lipids) to the vascular endothelium enhancing atherogenic risk. Based on these information, dietary or pharmacologically strategies are strictly required to decrease AGE levels in patients with high risk of cardiovascular diseases or stroke. As example, following a diet based on the World Cancer Research Funding (WCRF, 2007) principles, several metabolic and cardiovascular improvements have been reached. In fact, these type of diet is based on high intake of anti-inflammatory fatty acids and aromatic glycoproteins able to decrease glucose, AGEs levels and lipid peroxidation [16]. Moreover, foods suggested in WCRF recommandations are very rich in Quercetin and other flavonoids (like the tricin founded in brown rice) able to decrease cellular pro-inflammatory interleukins production and secretion by acting on the promoters of regulatory genes [17].

With the growing pathophysiological relevance of IL-1 in cardiotoxicity, new biologic drugs have been introduced in clinical world to restrict the actions of these inflammatory cytokines. As example, a recent clinical trial called CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) has shown interesting results. During the trial, 10,061 patients with previously diagnosed myocardial infarction were randomized to receive three doses (50, 150, and 300 mg, administered subcutaneously every 3 months) of Canakinumab, an IgG1k monoclonal antibody able to neutralizes soluble IL-1β. Notably, at 4 years of treatment, patients receiving Canakinumab at 50, 150 and 300 mg, had a median reduction from baseline in the high-sensitivity C-reactive protein (HS-PCR) level of 26, 37, and 41 percentage points greater, compared to placebo group, respectively [18]. Moreover, the incidence rate of CVs-related death or stroke or non-fatal myocardial infarction was 4.1, 3.8, and 3.9 events (per 100 person-years) in the groups receiving...
Canakinumab at 50, 150 and 300-mg, respectively, compared to 4.5 events observed in the placebo group. These results indicate a key role of interleukin 1 in the etiopathogenesis of cardiovascular diseases promoting therapeutic strategies towards these pro-inflammatory molecules involved in cardiac microenvironment.

Conclusion

Accumulating evidence suggests that a pro-inflammamatory cardiac and vascular microenvironment trigger a vicious cycle of oxidative/inflammatory responses between cardiomyocytes, endothelial cells, pericardial adipose tissue and immune cells. Recruitment of inflammatory mediators like Interleukin 1, 6, 8 and AGEs contributes to the progression of atherogenesis, cardiovascular disease, stroke and higher cardio-sensitivity to anticancer drugs (like the anthracyclines). Designing preventive and therapeutic measures that target glyco-oxidative stress and pro-inflammatory interleukins may be useful tools for the management and control cardiovascular diseases. Natural bioactives and nutraceuticals derived from healthy foods, like same flavonoids, antioxidant and omega 3 fatty acids are also possible strategies for the management of cardiovascular risk factors, mainly through improvement of cardiac and vascular microenvironment.

References

1. Kanda T, Takahashi T (2004) Interleukin-6 and cardiovascular diseases. Jpn Heart J 45(2): 183-193.
2. Brutsaert DL (2003) Cardiac endothelial-myocardial signaling: its role in cardiac growth, contractile performance, and rhythmicity. Physiol Rev 83: 59-115.
3. Barbarisi M, Iaffaioli RV, Armenia E, Schiavo L, De Sena G, et al. (2017) Novel nanohydrogel of hyaluronic acid loaded with quercetin alone and in combination with temozolomide as new therapeutic tool, CD44 targeted based, of glioblastoma multiforme. J Cell Physiol 233(10): 6550-6564.
4. Quagliariello V, Iaffaioli RV, Armenia E, Clemente O, Barbarisi M, et al. (2017) Hyaluronic Acid Nanohydrogel Loaded With Quercetin Alone or in Combination to a Macrolide Derivative of Rapamycin RAD001 (Everolimus) as a New Treatment for Hormone-Responsive Human Breast Cancer. J Cell Physiol 232(8): 2063-2074.
5. JT Willerson, PM Ridker (2004) Inflammation as a cardiovascular risk factor. Circulation 109: 2-10.
6. J Galea, J Armstrong, P Gadsdon, H Holden, SE Francis, et al. (1996) Interleukin-1 beta in coronary arteries of patients with ischemic heart disease. Arterioscler Thromb Vasc Biol 16(8): 1000-1006.
7. Davies R, Choy E (2014) Clinical experience of IL-6 blockade in rheumatic diseases- implications on IL-6 biology and disease pathogenesis. Semin Immunol 26(1): 97-104.
8. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH (2000) Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. Circulation 101(15): 1767-1772.
9. De Vecchis R, Cantarotra C, Mazzei D, Barone A, Maurea N, et al. (2017) The Impact Exerted on Clinical Outcomes of Patients With Chronic Heart Failure by Aldosterone Receptor Antagonists: A Meta-Analysis of Randomized Controlled Trials. J Clin Med Res 9(2): 130-142.
10. Maurea N, Coppola C, Piscopo G, Galletta F, Riccio G, et al. (2016) Pathophysiology of cardiotoxicity from target therapy and angiogenesis inhibitors. J Cardiovasc Med 17(1): 19-26.
11. Capasso I, Esposito E, De Laurentiis M, Maurea N, Cavalcanti E, et al. (2014) Metabolic syndrome-breast cancer link varies by intrinsic molecular subtype. Diabetol Metab Syndr 6(1): 105.
12. Quagliariello V, Rossetti S, Cavaliere C, Di Polo R, Lamantia E, et al. (2017) Correction: Metabolic syndrome, endocrine disruptors and prostate cancer associations: biochemical and pathophysiological evidences. Oncotarget 8(37): 62816.
13. Baye E, De Courten MP, Walker K, Ranasinha S, Earnest A, et al. (2017) Effect of dietary advanced glycation end products on inflammation and cardiovascular risks in healthy overweight adults: a randomised crossover trial. Sci Rep 7(1): 4123.
14. Koyama Y, Takeishi Y, Arimoto T, Nizetzi T, Shishido T, et al. (2007) High serum level of pentosidine, an advanced glycation end product (AGE), is a risk factor of patients with heart failure. J Card Fail 13(3): 199-206.
15. Li YS, Haga JL, Chien S (2005) Molecular basis of the effects of shear stress on vascular endothelial cells. J Biomech 38(10): 1949-1971.
16. Bruno E, Gargano G, Villarini A, Taina A, Johansson H, et al. (2015) Adherence to WCRF/AICR cancer prevention recommendations and metabolic syndrome in breast cancer patients. Int J Cancer 138(1): 237-244.
17. Quagliariello V, Iaffaioli RV, Armenia E, Clemente O, Barbarisi M, et al. (2017) Hyaluronic Acid Nanohydrogel Loaded With Quercetin Alone or in Combination to a Macrolide Derivative of Rapamycin RAD001 (Everolimus) as a New Treatment for Hormone-Responsive Human Breast Cancer. J Cell Physiol 232(8): 2063-2074.
18. Cavelli-Weder C, Timper K, Seelig E, Keller C, Osranek M, et al. (2016) Development of an interleukin-18 vaccine in patients with type 2 diabetes. Mol Ther 24(5): 1003-1012.