Barzegari, Pavon-Djavid, *BioImpacts*, 2014, 4(3), 111-112
doi: 10.15171/bi.2014.002
http://bi.tbzmed.ac.ir/

Editorial

Carotenoids as signaling molecules in cardiovascular biology

Abolfazl Barzegari[1,2], Graciela Pavon-Djavid[3*]

[1] Research Center for Pharmaceutical Nanotechnology, Tabriz University of Medical Sciences, Tabriz, Iran
[2] Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
[3] Translational Vascular Research Laboratory INSERM U1148, Université Paris13 - PRES Sorbonne Paris Cité, Paris, France

ARTICLE INFO

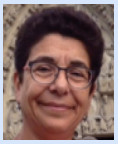
Article History:
Received: 15 Sep. 2014
Accepted: 27 Sep. 2014
ePublished: 29 Sep. 2014

Keywords:
Carotenoids
Cardiovascular disease
MicroRNA
Reactive oxygen species (ROS)

Summary

Oxidative stress and inflammation play important roles in the etiology of cardiovascular disease (CVD). Thus, natural antioxidant carotenoids existing in fruits and vegetables could have a significant role in the prevention of CVD. Nevertheless, clinical data are conflicting about the positive effect of some antioxidant carotenoids in reducing cardiovascular morbidity and mortality. Many biological actions of carotenoids have been attributed to their antioxidant effect; however, the precise mechanism by which carotenoids produce their beneficial effects is still under discussion. They might modulate molecular pathways involved in cell proliferation, acting at Akt, tyrosine kinases, mitogen activated protein kinase (MAP kinase) and growth factor signaling cascades. Screening for a promising cardiovascular protective carotenoids therefore might be performed *in vitro* and *in vivo* with caution in cross-interaction with other molecules involved in signaling pathways especially those affecting microRNAs, performing a role in molecular modulation of cardiovascular cells.

AUTHOR BIOSKETCH



Professor G. Pavon-Djavid obtained her PhD degree in chemistry in 1992 and her HDR degree in 2013 from Paris 13 University, Paris, France. She is a member of the LVTS Laboratory for Vascular Translational Science U1148 INSERM Paris 13 University. As a member of Cardiovascular Bioengineering Institute, Dr. Pavon-Djavid aims to integrate chemistry and biology towards development of new effective diagnostic and therapeutic modalities.

Cardiovascular disease (CVD) is the leading cause of death for people with modern lifestyle. Oxidative stress induced by reactive oxygen species (ROS) and inflammation plays an important role in the etiology of CVD.[1] Hence, natural antioxidant carotenoids could have a significant role in the prevention of CVD. Both prospective and retrospective epidemiological studies have consistently and clearly shown that increased intake of fruits and vegetables rich in carotenoids is associated with a decreased risk of CVD.[2]

Despite the determined positive role of antioxidants in cellular and animal studies, literature data are conflicting. Many antioxidant supplements such as vitamin E and β-carotene are ineffective even disappointing in reducing cardiovascular morbidity and mortality in clinical trials.[3] In a study, β-carotene was applied for prevention of low-density lipoprotein (LDL) oxidation in atherosclerotic processing, but it showed an inverse association between serum β-carotene levels and coronary heart disease risk. In a view, the epidemiologic evidence does generally support the idea that a diet high in carotenoid- rich foods is associated with a reduced risk of heart disease. What is the possible confounding factor between the trials and epidemiologic evidence? Why do not agree the trials and epidemiologic studies?

It seems our knowledge around the molecular mechanism of carotenoids is at the toddling stage yet. According to the cardiovascular studies, results from intervention trials indicate that supplemental β-carotene enhances the risk of developing lung cancer and in turn mortality among smokers.[4] A feasible mechanism which can explain the contrastive role of carotenoids either as beneficial or harmful agents in cancer is that their excess or deficiency may trigger changes in molecular pathways involved in cell stress signaling.[5] Their ability to modify the expression of transcription factors depends on several factors such as carotenoid concentration, determined action of multiple micronutrients, cell type, and redox status. Nevertheless, numerous gaps still exist in our comprehension of the role of carotenoids as modulators of cell signaling.

Improved knowledge of the role of carotenoids in signaling pathway *in vitro* and *in vivo* will assist us in understanding their prospective role in health and disease. Then, search for a new class of antioxidants targeting the specific subcellular locales, and the phenotype-genotype association analysis for oxidative stress will likely be avenues for future research in this realm.[6] Therefore, the search for novel effective antioxidant therapies in

***Corresponding author:** Graciela Pavon-Djavid, Email: graciela.pavon@univ-paris13.fr

mainstream medicine is possible and promising, however it demands significant advances in basic molecular cell biology, pharmacology, and nutrigenomics as well as clinical bioanalysis.

Reliable evidence indicate that carotenoids, and their metabolites, might modulate molecular pathways related with cell proliferation, acting at Akt, tyrosine kinases, mitogen activated protein kinase (MAP kinase) and growth factor signaling cascades.[7] With emerging evidence, it is now obvious that carotenoids confer their activities by regulating the expression of genes and microRNAs.[8] MicroRNAs have granted a new aspect to cardiovascular disease. They modulate the expression of batch of messenger RNA targets that often have associated functions; thereby ruling intricate biological processes. MicroRNA-21 (miR-21) is a highly expressed microRNA (miRNA) in cardiovascular system, but there are no evidence of *in vivo* and *in vitro* carotenoids in microRNA expression. Recent studies have shown that expression of miR-21 is deregulated in heart and vasculature under cardiovascular disease conditions such as proliferative vascular disease, cardiac hypertrophy and heart failure, as well as ischemic heart disease.[9]

Another important microRNA, namely miR 712, is knows as a potential biomarker for atherosclerosis which is a cardiovascular disease of the arterial wall bound up with lipid retention and inflammation.[10] In cancer for instance, several different miRNAs operate as mediators of pathogenic stress-related signaling pathways in settings of cardiovascular disease.[11] Or for example, cardiac stress commonly leads to fibrosis as a result of excessive extracellular matrix (ECM) production and collagen deposition, causing the stiffening of ventricular chambers and cardiac arrhythmias.[12] Under conditions of cardiovascular disease, miR-29 is down regulated in association with fibrosis and excessive ECM production.[13]

As a brief concluding remark, a clear understanding of the mechanisms of action of carotenoids, both as redox agents as well as modulators of cell signaling and the influence of this metabolism on these properties is key factor required in the evaluation of these biomolecules as cardioprotective agents.[7]

Acknowledgements

This work was supported by Center for International Scientific Studies and Collaboration (CISSC) and the cultural cooperation section of the French embassy in Iran (SCAC) under grant No. N355677.

Ethical issues

There is none to be declared.

Competing interests

There is none to be disclosed.

References

1. Carrera-Bastos P, Fontes-Villalba M, O'Keefe JH, Lindeberg S, Cordain L. The western diet and lifestyle and diseases of civilization. *Res Rep Clin Cardiol* **2011**; 2: 15-35. doi: 10.2147/RRCC.S16919
2. Voutilainen S, Nurmi T, Mursu J, Rissanen TH. Carotenoids and cardiovascular health. *Am J Clin Nutr* **2006**; 83: 1265-71.
3. Kritchevsky SB. beta-Carotene, carotenoids and the prevention of coronary heart disease. *J Nutr* **1999**; 129: 5-8.
4. Leppala JM, Virtamo J, Fogelholm R, Huttunen JK, Albanes D, Taylor PR, et al. Controlled trial of alpha-tocopherol and beta-carotene supplements on stroke incidence and mortality in male smokers. *Arterioscler Thromb Vasc Biol* **2000**; 20: 230-5. doi: 10.1161/01.ATV.20.1.230
5. Palozza P, Serini S, Di Nicuolo F, Calviello G. Modulation of apoptotic signalling by carotenoids in cancer cells. *Arch Biochem Biophys* **2004**; 430: 104-9. doi: 10.1016/j.abb.2004.02.038
6. Madamanchi NR, Vendrov A, Runge MS. Oxidative stress and vascular disease. *Arterioscler Thromb Vasc Biol* **2005**; 25: 29-38. doi: 10.1161/01.ATV.0000150649.39934.13
7. Palozza P, Serini S, Calviello G. Carotenoids as modulators of intracellular signaling pathways. *Curr Signal Transd Ther* **2006**; 1: 325-35. doi: 10.2174/157436206778226950
8. Srivastava SK, Arora S, Singh S, Singh AP. Phytochemicals, microRNAs, and Cancer: Implications for Cancer Prevention and Therapy. *Mitochondria as Targets for Phytochemicals in Cancer Prevention and Therapy*: Springer; **2013**. p. 187-206. doi: 10.1007/978-1-4614-9326-6_9
9. Cheng Y, Zhang C. MicroRNA-21 in cardiovascular disease. *J Cardiovasc Transl Res* **2010**; 3: 251-5. doi: 10.1007/s12265-010-9169-7
10. Son DJ, Kumar S, Takabe W, Kim CW, Ni CW, Alberts-Grill N, et al. The atypical mechanosensitive microRNA-712 derived from pre-ribosomal RNA induces endothelial inflammation and atherosclerosis. *Nat Commun* **2013**; 4: 3000. doi: 10.1038/ncomms4000
11. Mendell JT, Olson EN. MicroRNAs in stress signaling and human disease. *Cell* **2012**; 148: 1172-87. doi: 10.1016/j.cell.2012.02.005
12. Wang S, Aurora AB, Johnson BA, Qi X, McAnally J, Hill JA, et al. The endothelial-specific microRNA miR-126 governs vascular integrity and angiogenesis. *Dev Cell* **2008**; 15: 261-71. doi: 10.1016/j.devcel.2008.07.002
13. Fichtlscherer S, Zeiher AM, Dimmeler S. Circulating microRNAs: biomarkers or mediators of cardiovascular diseases? *Arterioscler Thromb Vasc Biol* **2011**; 31: 2383-90. doi: 10.1161/ATVBAHA.111.226696