Role of miR-200c in oxidative stress-induced pathologies

Physiological levels of reactive oxygen species (ROS) play an important role as second messengers; however, increased ROS production or insufficient scavenging compromises many biological processes, including endothelial function. ROS play a causal role in various pathophysiological conditions, including ischemia, atherosclerosis, diabetes and aging.

We have shown that ROS increase the expression of miR-200c, which induces apoptosis and senescence in endothelial cells (EC) through the downregulation of its target, the transcription factor ZEB1. Next, we analysed the role of miR-200c on three closely related proteins that modulate EC function and ROS production: sirtuin 1 (SIRT1), endothelial nitric oxide synthase (eNOS) and forkhead box 1 (FOXO1). Our studies showed that miR-200c directly targets SIRT1, eNOS and FOXO1; through this mechanism, miR-200c decreases nitric oxide (NO) and increases the acetylation of SIRT1 targets, namely FOXO1 and p53. FOXO1 acetylation inhibits its transcriptional activity on target genes, namely SIRT1 and the scavengers of ROS, catalase and manganese superoxide dismutase. P53 acetylation increases its transcriptional activity on miR-200c promoter, further increasing its expression. In addition, miR-200c increased ROS production and induces p66Shc phosphorylation in Ser-36; this mechanism induces a further increase in ROS and inhibits FOXO1 transcription, strengthening this molecular circuit.

These in vitro results were validated in three in vivo models of oxidative stress, namely skin fibroblasts from young and old donors, femoral arteries from old mice and a mouse model of hind limb ischemia. In all cases, miR-200c levels were higher than controls and its targets i.e. ZEB1, SIRT1, eNOS and FOXO1, were decreased. In the mouse hind limb ischemia model, treatment with anti-miR-200c restored the expression of its targets and improved limb perfusion.

In conclusion, miR-200c destroys the auto-regulatory loop existing among SIRT1/FOXO1/eNOS. This causes an increase in ROS and a reduction in NO, contributing to endothelial dysfunction in conditions of increased oxidative stress such as aging and ischemia.

Other pathologies associated with an increase of ROS in which we have found and investigated the miR-200c up-regulation are the following:

- miR-200c increases in diabetic and ischemic patients in the skin biopsies, both in fibroblast and keratinocytes of diabetic foot ulcer patients and the treatment with anti-miR-200c is very promising in diabetic ulcer healing (On this project an Italian Ministry of health grant RF-2016-02362708 was obtained: Co-PI of the project and UO3 PI Dr Magenta).

- In atherosclerotic plaques, an example of endothelial dysfunction, miR-200c increases even more in unstable than stable plaques and in the plasma of patients with atherosclerosis compared to healthy patients.

- In psoriasis, miR-200c increases in the lesional skin of psoriatic patients compared to non lesional skin and in plasma of patients with psoriasis and correlates with the determinants of cardiovascular risk (There is an ongoing collaboration with Dr. Luisa Bracci Laudiero of IFT-CNR on p75NTR role in psoriasis and the possible link with miR-200c).
Following Doxorubicin (Doxo) treatment, which is known to induce cardiotoxicity there is an increase of miR-200c in the left ventricle of mice in which cardiotoxicity was induced by administration of Doxo.

In muscular dystrophy miR-200c is induced in different muscles in mdx mice and we are currently studying whether its inhibition can improve muscle regeneration (There is an AFM project on this topic, PI Dr Magenta in collaboration with Dr Francesca De Santa of IBCN-CNR Rome, and Dr Alessio Torcinaro with an AFM Fellowship on this topic).

In familial hypercholesterolemia where miR-200c increases in the plasma of children affected by this disease and correlates with miR-33 which are the modulators of cholesterol homeostasis.

In conclusion, miR-200c is a sensor of the cellular redox state and its increase determines oxidative stress causing the deleterious effects associated with all the pathophysiological conditions associated with an increase in ROS such as: aging, ischemia, atherosclerosis, muscular dystrophy, diabetes, psoriasis and familial hypercholesterolemia.

References:

ORCID: 0000-0002-9054-337x


Keywords: microRNA, oxidative stress, endothelial dysfunction, oxidative stress-associated diseases
Contacts: ale.magenta@gmail.com; alessandra.magenta@ift.cnr.it; a.magenta@idi.it
Website(s):
Other: