Cell Calcium 60 (2016) 207–217

Contents lists available at ScienceDirect

Cell Calcium

journal homepage: www.elsevier.com/locate/ceca

Review

Oxidative stress, microRNAs and cytosolic calcium homeostasis

Alessandra Magenta*[,1], Elena Dellambra[1], Roberta Ciarapica, Maurizio C. Capogrossi*

Istituto Dermopatico dell'Immacolata-IRCCS, FLMM, Laboratorio di Patologia Vascolare, Via dei Monti di Creta 104, Rome 00167, Italy

ARTICLE INFO

Article history:
Received 11 March 2016
Received in revised form 6 April 2016
Accepted 7 April 2016
Available online 8 April 2016

Keywords:
Reactive oxigen species
Calcium
microRNAs
Skin
Aging
Diseases

ABSTRACT

Reactive oxygen species increase cytosolic [Ca^{2+}], (Ca_i), and also modulate the expression of some microRNAs (miRNAs), however the link among oxidative stress, miRNAs and Ca_i is poorly characterized. In this review we have focused on three groups of miRNAs: (a) miRNAs that are modulated both by ROS and Ca_i: miR-181a and miR-205; (b) miRNAs that are modulated by ROS and have an effect on Ca_i: miR-1, miR-21, miR-24, miR-25, miR-185 and miR-214; (c) miRNAs that modulate both ROS and Ca_i: miR-133; miR-145, miR-495, and we have analyzed their effects on cell signaling and cell function. Finally, in the last section we have examined the role of these miRNAs in the skin, under conditions associated with enhanced oxidative stress, i.e. skin aging, the response to ultraviolet light and two important skin diseases, psoriasis and atopic dermatitis. It is apparent that although some experimental evidence is already available on (a) the role of Ca_i in miRNAs expression and (b) on the ability of some miRNAs to modulate Ca_i-dependent intracellular signaling, these research lines are still largely unexplored and represent important areas of future studies.

Contents

* Corresponding authors.
E-mail addresses: ale.magenta@gmail.com (A. Magenta), capogrossi@idi.it (M.C. Capogrossi).
[1] These authors contributed equally to this work

http://dx.doi.org/10.1016/j.ceca.2016.04.002
0143-4160/

1. Introduction

Reactive Oxygen Species (ROS) are unavoidable products of aerobic metabolism and, at sub-toxic levels, act as signaling molecules in a variety of physiologic conditions including cell proliferation, growth, differentiation and death [1].

Ca^{2+} is a second messenger involved in intra- and extracellular signaling pathways and plays a key role in cell fate. A low cytosolic [Ca^{2+}], (Ca_i), usually in the range of 100 nM under resting conditions, is maintained in spite of a major gradient between the extracellular space and the cytosol through the action of pumps, channels and exchangers in the plasma membrane, and intracellular Ca^{2+} stores such as the endoplasmic reticulum, mitochondria and other buffer systems [2]. Ca^{2+} and ROS signaling mutually interplay: Ca^{2+} can increase ROS production, on the other hand, ROS can significantly affect Ca^{2+} influx into the cell and intracellular Ca^{2+} stores [2].

In addition to physiologic ROS production/levels, a major increase in ROS occurs in virtually all cell types in a variety of pathologic conditions. For instance, skin cells exposed to ultraviolet (UV) light exhibit enhanced oxidative stress [3]; reperfusion following ischemia induces a burst in ROS production [4]; diabetes and aging are also associated with enhanced ROS and oxidative stress [5,6]. Many studies have examined the effects of ROS and cell signaling pathways, in relation to Ca_i. It has been shown that lethal ROS concentrations induce cell death in association to Ca_i overload [7]. However, an increase in Ca_i occurs also in response to sub-lethal concentrations of ROS; this is due to rapid Ca^{2+} release from the endoplasmic reticulum and slower Ca^{2+} entry from the extracellular space [8,9]. Further, ROS decrease cytosolic pH via inhibition of Na^+/H^+ exchange [10] and intracellular acidification enhances Ca_i even in the absence of extracellular Ca^{2+} and following endoplasmic reticulum Ca^{2+} depletion [11]; this is an additional potential mechanism for ROS-induced increase in Ca_i, although it has not been directly tested. Oxidative stress, in addition to its effect on Ca_i, has been recently shown the modulate the expression of some miRNAs [10,11]; whether ROS-induced increase in Ca_i is involved in miRNAs expression remains to be elucidated.

This review examines the interplay among oxidative stress, miRNAs (miRNAs) and Ca_i and the following topics will be discussed: (a) miRNAs that are modulated both by ROS and Ca_i; (b) miRNAs that are modulated by ROS and have an effect on Ca_i; (c) miRNAs that modulate both ROS and Ca_i. Finally, in the last section we have examined in greater detail the functional role of miRNAs that modulate Cai in the skin, a tissue/organ that is exposed to high concentrations of ROS through UV light exposure and in some pathologic conditions. We took the skin as an example of ROS/but a similar approach could be taken for all tissues and organs.

2. miRNAs biogenesis and function

miRNAs are 21–23 nucleotide non-coding RNA molecules, that modulate the stability and/or the translational efficiency of target messenger RNAs. miRNAs are involved in several biological processes, including proliferation, differentiation, development, apoptosis, and aging (for extensive reviews on miRNA regulation and biogenesis see: [12,13]. miRNAs act as negative regulators of gene expression and, rarely, also as enhancers of gene expression [14].

miRNA biogenesis starts from a primary transcript, generally a thousand nucleotides long mRNA, named the pri-miRNA. The pri-miRNA is a stem–loop structure containing the active miRNA; it undergoes nuclear cleavage by the ribonuclease III Drosha, to generate a 70–100 nucleotides hairpin-shaped pre-miRNA. The pre-miRNA is then transported to the cytoplasm and further cleaved by the ribonuclease III Dicer to form the mature 22-nt miRNA:miRNA* duplex. The mature miRNA strand is incorporated into the RNA-Induced Silencing Complex (RISC), whereas, the complementary strand miRNA* is usually degraded.

miRNAs cause translational inhibition and, in some cases, induce mRNA degradation of their target mRNAs. The rules that guide miRNA/mRNA interactions are complex and still under investigation. For miRNA-mRNA mediated inhibition, complete pairing between the 3′UTR region of the mRNA target and the "seed sequence" of miRNA, a region centred on nucleotides 2–7, is required.

Non-canonical miRNA binding can also confer target regulation [15], indeed, few examples of mRNAs targeted by miRNAs through recognition of 5′UTR or within the coding sequences have been described, as well as "seedless" miRNA/mRNA interactions [16–18].

3. miRNAs in ROS and Ca_i homeostasis

3.1. miRNAs modulated by ROS and Ca_i

In this section we will review those miRNAs that are modulated by ROS and either thapsigargin or tunicamycin, i.e. drugs known to release Ca^{2+} from the Endoplasmic Reticulum (ER) (summarized in Table 1). No definitive cause/effect relationship has been established between the increase in Ca_i induced by ROS and the change in the expression of these miRNAs, however this is a possibility that will need to be examined in future studies.

3.1.1. miR-181a

miR-181a has been shown to increase upon 6 h treatment with 600 μM H_2O_2 in rat bone marrow mesenchymal stem cells (MSCs) and this up-regulation induced cell death, via Hexokinase II (HKII) down-regulation. HKII disrupts the mitochondrial membrane potential, and delivery of anti-miR-181a in MSCs improves MSC survival upon H_2O_2 treatment. Therefore, miR-181a neutralization before transplantation in ischemic tissues may be an effective strategy to improve MSC survival [19]. Modulation of miR-181a by 24 h treatment with 200 μM H_2O_2 in rat vascular smooth muscle cells (VSMCs) was also described, although in this case miR-181a together with miR-181b and miR-181c were down-regulated [20].

Interestingly, in mice, reducing miR-181a levels prior to middle cerebral artery occlusion (MCAO) was shown to be protective [21]. In addition, post-ischemic treatment with miR-181a antagomir, significantly reduced infarct size, improved neurological deficits, reduced inflammatory response and improved behavioural outcome. These findings indicate that post-injury treatment with miR-181a antagomir has neuroprotective effects against ischemic neuronal damage and neurological impairment in mice [22].