Free Radical Biology and Medicine ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

Free Radical Biology and Medicine

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

Review Article

Regulation of cardiac and renal ischemia–reperfusion injury by microRNAs

Johan M. Lorenzen [a,b,*], Sandor Batkai [a], Thomas Thum [a,c,**]

[a] Institute of Molecular and Translational Therapeutic Strategies, Germany
[b] Department of Nephrology, Hannover Medical School, 30625 Hannover, Germany
[c] National Heart and Lung Institute, Imperial College London, United Kingdom

ARTICLE INFO

Keywords:
MicroRNAs
Ischemia–reperfusion injury
Kidney
Heart
Free radicals

ABSTRACT

Tissue damage caused by ischemia–reperfusion (I/R) injury represents a serious event, which often leads to deterioration or even loss of organ function. I/R injury is associated with transient tissue oxygen deprivation due to vessel occlusion and a subsequent reperfusion period following restoration of blood flow. Initial tissue damage inflicted by ischemia is aggravated in the reperfusion period through mechanisms such as burst of reactive oxygen and nitrogen species and inflammatory reactions. I/R injury occurs during surgical interventions, organ transplantation, diseases such as myocardial infarction, circulatory shock, and toxic insults. Recently, microRNAs have come into focus as powerful regulators of gene expression and potential diagnostic tools during I/R injury. These small noncoding ribonucleotides (~22 nucleotides in length) posttranscriptionally target mRNAs, culminating in suppression of protein synthesis or increase in mRNA degradation, thus fundamentally influencing organ function. This review highlights the latest developments regarding the role of microRNAs in cardiac and renal I/R injury.

Contents

Introduction . . . 1
MicroRNA functions . . . 2
MicroRNAs during renal I/R injury . . . 2
MicroRNAs during cardiac I/R injury . . . 3
MicroRNAs as I/R biomarkers . . . 4
Acknowledgments . . . 6
References . . . 6

Introduction

Oxygen deprivation (ischemia) induced by transient disruption of blood supply followed by reopening of the occluded vessel (reperfusion) is a pivotal mechanism of organ injury during various medical conditions. Ischemia–reperfusion (I/R) injury is a central mechanism in myocardial infarction, circulatory shock, various toxic insults, surgical interventions, or organ transplantation; it arises after a complex cascade of events [1,2]. During ischemia, the tissue undergoes damage that is further exacerbated by a massive burst of reactive oxygen (ROS) and nitrogen species during reperfusion [3]. The hypoxia and the following oxidative/nitrative stress result in protein modifications, lipid oxidations, and DNA breakage, triggering a chain of deleterious responses that affect all major extra- and

Abbreviations: CaMKII, calmodulin kinase II; DRP1, dynamin-related protein-1; EPC, endothelial progenitor cell; FGFR2, fibroblast growth factor receptor 2; Hsp20, heat shock protein 20; HIF-1α, hypoxia-inducible factor 1α; I/R, ischemia–reperfusion; KIF3B, kinesin family member 3B; LIF, leukemia inhibitory factor; MV, microvesicle; PIO, pioglitazone; PTEN, phosphatase and tensin homologue; PDCD4, programmed cell death protein 4; ROS, reactive oxygen species; ROCK1, Rho-associated protein kinase 1; RISC, RNA-induced silencing complex; Sirt1, sirtuin 1; Ncx1, sodium/calcium exchanger 1.

* Corresponding author at: Institute for Molecular and Translational Therapeutic Strategies, Germany.
** Corresponding author. Fax: +49 511 532 5274.
E-mail addresses: Lorenzen.Johan@mh-hannover.de (J.M. Lorenzen), Thum.Thomas@mh-hannover.de (T. Thum).

0891-5849/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.freeradbiomed.2013.06.044

intracellular tissue components: endothelial dysfunction, neutrophil adherence to endothelium and *trans*-endothelial migration, the release of inflammatory mediators, cellular calcium overload, and eventually cell death [4]. These events are the underlying mechanism of acute I/R organ damage and dysfunction in the heart and kidney.

In the "Era of Reperfusion" [5] and by use of advanced organ protection during surgery the ischemic time and associated organ damage and mortality have been significantly reduced. Although acute complications of I/R injury are still a major medical concern, the therapeutic advances led to a shift in focus on chronic complications such as organ failure. After I/R, the surviving tissue initiates an adaptive process to maintain adequate organ function, called remodeling. However, the remodeling process might eventually evolve into abnormal changes, with ensuing dysfunction and subsequent organ failure. Novel therapeutic strategies have been recently developed to target the critical event of the remodeling process. Despite the recent advances, the underlying molecular signaling between cellular components, extracellular matrix, and tissue vascularization during chronic cardiac or renal remodeling associated with I/R injury are far from being completely understood.

MicroRNAs have been implicated as transcriptional regulators in a wide range of biological processes determining cell fate, stress response, proliferation, or death [6]. The ensuing immense research effort has identified many associations between disease processes and specific microRNAs. In particular, a multitude of studies demonstrated the role of microRNAs in chronic cardiovascular or renal disease processes [7–12].

This review provides an overview of the role of microRNAs in the development and consequences of I/R injury in the heart and kidney. Also, advances in microRNA-based biomarker and therapeutic approaches that might be important in preventing or treating I/R injury are discussed.

MicroRNA functions

MicroRNAs, short endogenous noncoding RNAs, are important regulators of target messenger RNA translation by binding mainly to complementary sequences of the 3′ untranslated region of target messenger RNA transcripts thereby leading to RNA degradation and/or inhibition of protein synthesis [13]. MicroRNAs are evolutionarily well conserved and are abundant in all human cells; the estimated number of microRNA genes that the human genome encodes is well above 1000, and they regulate the activity of at least 50% of the genome [14]. Biogenesis and maturation of microRNAs have been extensively studied and were recently summarized [15]. Transcription of the primary microRNAs by RNA polymerase II results in a hairpin structure, called precursor microRNA. The precursor microRNA associates with exportin 5 and Ran-GTP and is transported into the cytoplasm, cleaved by Dicer, and processed into a double-stranded product consisting of 22 nucleotides. The guide strand of the mature microRNA is incorporated into the RNA-induced silencing complex (RISC). The RISC–microRNA complex specifically targets mRNAs and leads to suppression of protein synthesis or mRNA degradation [6]. The central aspect of microRNA transcriptional regulation is the fact that each individual microRNA affects a comprehensive set of genes, regulating thereby cellular pathways and biological functions.

In recent years, many associations between disease mechanisms and specific microRNAs have been identified and confirmed using large-scale microarray expression analyses and genetic approaches [15]. As a pharmacological approach, modified RNA oligonucleotides that are complementary to specific microRNAs have been developed [16]. The fundamental role of microRNAs in the progression and regulation of diseases, and recent innovation in oligonucleotide chemistry, put microRNAs in the forefront of novel innovative therapeutic targets, particularly in the cardiovascular field.

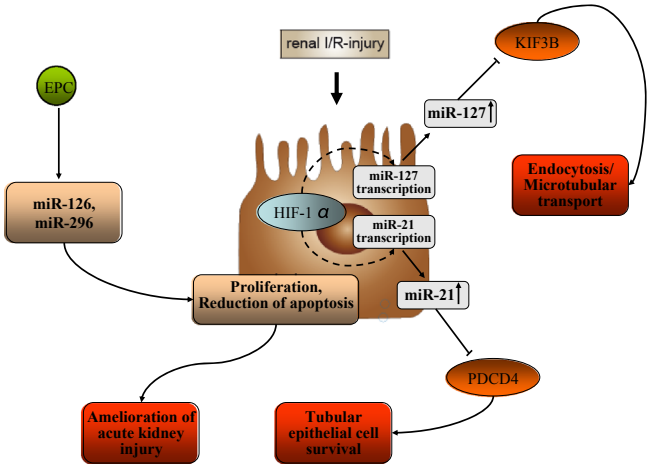

Fig. 1. MicroRNA deregulation with respect to the tubular epithelial cell is shown during renal I/R injury (see text). EPC, endothelial progenitor cell; HIF-1α, hypoxia-inducible factor 1α; KIF3B, kinesin family member 3B; PDCD4, programmed cell death protein 4.

MicroRNAs during renal I/R injury

Targeted deletion of Dicer from the proximal tubular epithelium protects from I/R-induced renal injury (preserved renal function, less tissue damage and tubular apoptosis, survival benefit) and is associated with changes in the expression of distinct microRNAs (e.g., miR-132, -362, and -379; see Fig. 1) [17]. After unilateral warm ischemia in a murine model, nine microRNAs were shown to be differentially regulated compared to control animals (miR-21, miR-20a, miR-146a, miR-199a-3p, miR-214, miR-192, miR-187, miR-805, and miR-194) [18]. The same signature could be repeated in immunodeficient RAG-2/common γ-chain double-knockout mice, suggesting that the microRNA expression is independent of influx of inflammatory cells. MiR-21 expression was shown to be increased in proliferating tubular epithelial cells, whereas knockdown of miR-21 in these cells resulted in enhanced apoptosis. In a subsequent study the same group bioinformatically highlighted the usefulness of this distinct microRNA expression pattern in I/R injury versus sham controls as a distinguishing biomarker using principal component analysis [19]. Another group identified miR-127 to be consistently deregulated during ischemia/reperfusion in vitro and in vivo in a rat model. MiR-127 was found to be regulated by hypoxia-inducible factor 1α (HIF-1α) bioinformatically and to target kinesin family member 3B (KIF3B) [20]. However, the regulation of miR-127 by HIF-1α could not be confirmed experimentally in this study. MiR-127 modulation in vitro was associated with changes in cell adhesion and cytoskeleton structure. Regulation of its target KIF3B resulted in modulation of endocytosis and microtubular transport in NRK-52E cells (rat renal proximal tubular cell line).

MicroRNA-enriched microvesicles (MVs) secreted by endothelial progenitor cells (EPCs) were shown to ameliorate ischemia/reperfusion injury in the murine kidney [21]. MiRNA array analysis showed the presence of 131 miRNAs shared by EPCs and EPC-derived MVs and 26 microRNAs specifically concentrated in MVs, including proangiogenic and antiapoptotic miR-126 and miR-296. RNase treatment of MVs led to a loss of these miRs. Moreover, they were shown to be absent in MVs derived from Dicer-silenced or antagomiR-treated EPCs. In a rat model of ischemia/reperfusion

Please cite this article as: Lorenzen, JM; et al. Regulation of cardiac and renal ischemia–reperfusion injury by microRNAs. *Free Radic. Biol. Med.* (2013), http://dx.doi.org/10.1016/j.freeradbiomed.2013.06.044