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MicroRNAs and drug-induced kidney injury

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ABSTRACT

Drug-induced kidney injury (DIKI) is a severe complication in hospitalized patients associated with higher probabilities of developing progressive chronic kidney disease or end-stage renal diseases. Furthermore, DIKI is a problem during preclinical and clinical phases of drug development leading to high rates of project terminations. Understanding the molecular perturbations caused by DIKI would pave the way for a new class of therapeutics to mitigate the damage. Yet, another approach to ameliorate DIKI is identifying sensitive and specific translational biomarkers that outperform the current diagnostic analytes like serum creatinine and facilitate early diagnosis. MicroRNAs (miRNAs), a class of non-coding RNAs, are increasingly being recognized to have a two-pronged approach toward DIKI management: 1) miRNAs have a regulatory role in gene expression and signaling pathways thereby making them novel interventional targets and 2) miRNAs enable diagnosis and prognosis of DIKI because of their stable presence in biofluids. In this review, apart from summarizing the literature on miRNAs in DIKI, we report small RNA sequencing results showing miRNA expression profiles at baseline in normal kidney samples from mice and humans. Additionally, we also compared the miRNA expression in biopsies of normal human kidneys to patients with acute tubular necrosis, and found 76 miRNAs significantly downregulated and 47 miRNAs upregulated (FDR adjusted $p < 0.05$, +/−2-fold change).
In summary, we highlight the transformative potential of miRNAs in therapeutics and translational medicine with a focus on drug-induced kidney damage.

Contents

1. Introduction

1.1. Drug-induced kidney injury

The high susceptibility of the kidney to toxicity is mainly due to its function of eliminating endogenous waste products as well as xenobiotics. These substances can induce toxic responses due to a high local concentration and/or transformation into reactive metabolites (Kahl et al., 2010). Commonly prescribed drugs (Table 1) are known to cause acute kidney injury (AKI) that is a severe condition associated with high probabilities of developing progressive chronic kidney

Abbreviations: AKI, Acute kidney injury; ATN, Acute tubular necrosis; DIKI, Drug-induced kidney injury; EMT, Epithelial to mesenchymal transition; FDR, False discovery rate; I/R, Ischemia/reperfusion; miRNA, MicroRNA; qRT-PCR, Quantitative real time PCR.

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Table 1
Commonly used drugs with nephrotoxic side effects.

Name	Pharmacological class	Name	Pharmacological class
Capreomycin	Aminoglycosides antibiotics	5-Fluorouracil	Antineoplastic
Gentamicin	Aminoglycosides antibiotics	Arsenic trioxide	Antineoplastic
Kanamycin	Aminoglycosides antibiotics	Camptothecin	Antineoplastic
Neomycin	Aminoglycosides antibiotics	Carmustine	Antineoplastic
Streptomycin	Aminoglycosides antibiotics	Cisplatin	Antineoplastic
Tobramycin	Aminoglycosides antibiotics	Doxorubicin	Antineoplastic
Acetaminophen	Analgesic	Idarubicin	Antineoplastic
Bacitracin	Antibiotics	Mitomycin C	Antineoplastic
Ciprofloxacin	Antibiotics	Paclitaxel	Antineoplastic
Demeclocycline	Antibiotics	Puromycin	Antineoplastic
Imipenem	Antibiotics	Aldesleukin	Antineoplastic, immunomudulating
Methoxyflurane	Analgesic	Ifosfamide	Antineoplastic, immunosuppressive
Polymyxins	Antibiotics	Methotrexate	Antineoplastic, antimetabolite, Immunosuppressant
Rifampicin	Antibiotics	Pentamidine	Antiprotozoal
Streptozocin	Antibiotics	Acyclovir	Antiviral
Sulfamethoxazole	Antibiotics	Cidofovir	Antiviral
Tetracyclines	Antibiotics	Foscarnet	Antiviral
Trimethoprim	Antibiotics	Tenofovir	Antiviral
Vancomycin	Antibiotics	Deferoxamine	Chelating agent
Sulfonamides	Antibiotics, anti-diabetics, diuretics	EDTA	Chelating agent
Pentamidine isethionate	Antifungal	Sodium Aurothiomalat	Immunosuppressive, anti-rheumatic
Amphotericin B	Antifungal, antiprotozoal	Cyclosporine A	Immunosuppressive
Chlorpropamide	Anti-hyperglycemic	Penicillamine	Immunosuppressive
Gallium nitrate	Anti-hypercalcemia	Tacrolimus	Immunosuppressive
Pamidronate	Anti-hypercalcemia	Lithium	Psychiatric medication
Aspirin	Anti-inflammatory, analgesic, Antipyretic	Diatrizoate	Radiocontrast
Ibuprofen	Anti-inflammatory, analgesic, Antipyretic	Iodipamide	Radiocontrast

disease or end-stage renal diseases, thus leading to high mortality rates (Chawla et al., 2014). In fact, the incidence of dialysis-requiring AKI increased from 222 to 533 cases per million person-years from 2000 to 2009 in the USA (Hsu et al., 2013). Epidemiological studies show that drugs are the cause of 18%–27% of hospitalizations and 19% of intensive care unit patients within the group of AKI patients (Uchino et al., 2005; Taber & Pasko, 2008). Taking into account that treating patients with end stage renal diseases accounted for over $40 billion in public and private US funds in 2009 (niddk.nih.gov, 2016), drug-induced AKI (DIKI) is a major public health concern. Additionally, DIKI accounts for approximately 10% of the failures in the preclinical and clinical stages (Cook et al., 2015) thus having a high relevance and a significant economic impact in drug development.

Kidney injury in humans is measured using functional biomarkers like blood urea nitrogen and/or serum creatinine. Although theses biomarkers are considered to be the standard diagnostic analytes in routine care, they are known to be modified by nutrition, muscle mass, age, sex, muscle injury, and aggressive fluid resuscitation (Waikar et al., 2012). Furthermore, they increase only when the glomerular filtration rate decreases by more than 50% and they do not reflect dynamic changes in filtration rates (Uchino, 2010). Novel sensitive and specific biomarkers are urgently needed to provide for cost-effective and non-invasive methods of detecting and treating early stage kidney injury. Early diagnostic and predictive biomarkers would also allow for stratification of patients that may be susceptible to develop AKI thereby facilitating clinical trials. Currently, in the absence of any therapeutics for AKI, renal replacement therapy remains the only option (Bellomo, 2015) for severe AKI, leading to an indispensable need for improved kidney injury management, i.e. detection as well as improved therapy.

In the last two decades, due to significant advances in understanding the molecular pathogenesis of AKI using state-of-the-art genome sequencing technologies, microRNAs (miRNAS) have emerged as novel therapeutic targets as well as biomarker candidates for AKI.

1.2. MicroRNA biogenesis, function and extracellular features

MiRNAs are approximately 20–25 nucleotides long, non-coding and evolutionary conserved small RNAs. MiRNAs were first discovered in *Caenorhabditis elegans* (Lee et al., 1993; Wightman et al., 1993) followed by the recognition of their conservation in a wide range of species (Pasquinelli et al., 2000), leading to the current status of 788 known miRNAs in rats, 1899 in mice and 2585 in humans (miRBase, 2014).

In the cell, miRNAs regulate gene expression at the post-transcriptional level. As part of a ribonucleoprotein complex called miRISC (miRNA-induced silencing complex) they bind to complementary sequences in the 3′-untranslated regions of target mRNAs thus inhibiting mRNA translation. The process of miRNA maturation, miRISC incorporation and subsequent mRNA binding is relatively well explored and reviewed in detail in several review articles (Krol et al., 2010; Garcia-Lopez et al., 2013; Desvignes et al., 2015). The complementarity between miRNA and mRNA does not have to be perfect for translational inhibition, therefore one miRNA regulates several hundred mRNAs and likewise, one mRNA is regulated by several miRNAs (Filipowicz et al., 2008). In fact, it is estimated that over 50% of all protein-coding genes are regulated by miRNAs in mammals (Krol et al., 2010) revealing their overall involvement in diverse physiological as well as pathological processes (Wiemer, 2007; Visone & Croce, 2009; Wang & Lee, 2009; Ceman & Saugstad, 2011; T. Li et al., 2011; Szabo & Bala, 2013). Many miRNAs are found to be highly enriched in particular organs or at a particular stage of development or disease progression in human body (Landgraf et al., 2007; Kriegel et al., 2013)—for instance the liver specific miR-122 (Lagos-Quintana et al., 2002), kidney cortex enriched miR-192 (Tian et al., 2008), skeletal muscle enriched miR-133a and -b (Sempere et al., 2004), or the cardiomyocyte specific miR-208a (van Rooij et al., 2007). The expression of the miR-17~92 cluster, consisting of miR-17, -18a, -19a, -20a, -19b1 and -92a1, seems to be essential for normal nephrogenesis since ablation of the cluster in a mouse model resulted in reduced numbers of nephrons (Marrone et al., 2014). Furthermore, miR-21 and miR-150 were found highly enriched in kidney cysts of patients with polycystic kidney disease and kidney biopsies from patients with lupus nephritis, respectively (Zhou et al., 2013; Lakhia et al., 2015).

Outside the cell, miRNAs were discovered for the first time in serum/plasma from cancer patients (Chen et al., 2008; Mitchell et al., 2008) and afterward in other body fluids like urine, breast milk, saliva and cerebral fluid (Weber et al., 2010). Extracellular miRNAs are very stable and