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Review Article

MicroRNAs and toxicology: A love marriage

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ABSTRACT

With the dawn of personalized medicine, secreted microRNAs (miRNAs) have come into the very focus of biomarker development for various diseases. MiRNAs fulfil key requirements of diagnostic tools such as i) non or minimally invasive accessibility, ii) robust, standardized and non-expensive quantitative analysis, iii) rapid turnaround of the test result and iv) most importantly because they provide a comprehensive snapshot of the ongoing physiologic processes in cells and tissues that package and release miRNAs into cell-free space. These characteristics have also established circulating miRNAs as promising biomarker candidates for toxicological studies, where they are used as biomarkers of drug-, or chemical-induced tissue injury for safety assessment. The tissue-specificity and early release of circulating miRNAs upon tissue injury, when damage is still reversible, are main factors for their clinical utility in toxicology. Here we summarize in brief, current knowledge of this field.

1. Introduction

The extracellular presence of miRNAs was described for the first time in 2008, in plasma of patients with lymphoma [1]. By now, detection of circulating miRNAs was reported in 12 different biofluids, among them plasma, serum, cerebrospinal fluid, saliva, and urine [2]. They are remarkably stable, due to the fact that they are either encapsulated in extracellular vesicles (EV) or associated with proteins, mainly Ago2 or apolipoproteins [3]. Environmental epigenetic studies have provided evidence that miRNAs regulate gene activity upon environmental changes or after exposure to toxic substances [4]. Toxicant-induced changes in miRNA expression are informative markers for the evaluation of toxic effects on multiple tissues and organs. Therefore, miRNAs are considered to be predictive biomarkers or indicators of tissue injury due to toxicant exposure [4]. Since miRNAs regulate mRNA expression, their altered transcription profiles are helpful to elucidate and define adverse outcome pathways of specific toxicants [5].

A wide range of toxicants alter miRNA levels in target organs (Fig. 1). These changes can be detected in a non- or minimally invasive fashion using liquid biopsies, for example serum/plasma or urine.

2. MicroRNAs in liver toxicity

Standard biomarkers of drug induced liver injury (DILI) include alanine aminotransferase and aspartate aminotransferase (AST). However, both the specificity and sensitivity of these markers are limited since there is lack of correlation of liver enzyme changes and observable histopathological damage [6]. Moreover, elevated serum level of alanine aminotransferase (ALT) also a commonly used biomarker of hepatocellular injury, also reflect muscle injury. Therefore, more sensitive and specific biomarkers are needed for better prediction of liver toxicity. Circulating miRNAs, e.g. miR-122-5p and miR-192-5p, are both highly enriched in the liver tissue and exhibit dose and exposure duration-dependent changes in the plasma that are parallel to the serum aminotransferase levels and the histopathology of liver degeneration [7]. Moreover, miR-103a-3p was reported as an appropriate biomarker among the circulating miRNAs identified in rats with acetaminophen-induced hepatotoxicity [8]. Furthermore, a study in human and mouse models suggested that circulating miR-122-5p can be used as a potential novel early, predictive and reliable blood marker for viral-, alcohol-, and chemical-induced liver injury [9].

3. MicroRNAs in neurotoxicity

In the nervous system, miRNA regulation contributes to the development, differentiation, function, and pathogenesis of neurodegenerative diseases. Several nervous system–enriched or nervous system-specific miRNAs have been reported [10]. Recently it was investigated, that circulating nervous system–enriched miR-9-3p and hippocampus-enriched miR-384-5p could be indicators for trimethyltin-induced of neurotoxicity in serum [11]. As far as neurotoxicity is concerned,

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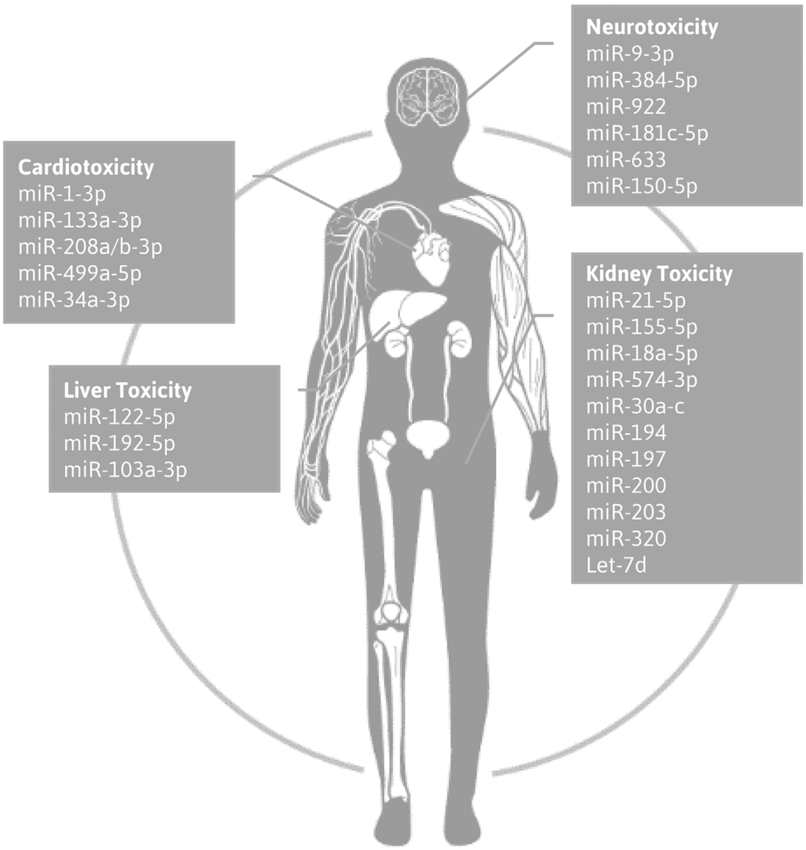

Fig. 1. MicroRNAs altered by toxicants in target organs. Changes can be detected in a non- or minimally invasive fashion using liquid biopsies, for example serum/plasma or urine.

biomarkers present in the cerebrospinal fluid (CSF) can be particularly valuable because of the co-localization of CSF with the target tissues and the relative inaccessibility of CSF to biomarkers indicative of changes in other tissues. MiRNAs in CSF have not been widely studied yet. One study has identified miR-922, miR-181c-5p and miR-633 as differently expressed in multiple sclerosis (MS) patients [12]. A second more recent study of miRNAs in the CSF of people with MS has identified miR-150-5p as a novel candidate biomarker for MS [13].

4. MicroRNAs in kidney toxicity

Kidney injury is currently quantified by serum creatinine. However, patients with acute kidney injury (AKI) are not in steady-state with regard to kidney function and serum creatinine is slow to report cellular damage. Serum creatinine also lacks specificity, becoming elevated by non-renal pathologies such as dehydration and muscle injury [14]. New biomarkers are needed to report drug-induced kidney injury with enhanced sensitivity and specificity. Recently it was shown, that miR-21-5p miR-155-5p and miR-18a-5p were among the highest upregulated miRNAs in the kidney after injury. Moreover this upregulation was observed in multiple models of AKI but not following liver damage, which confirms the robustness, reproducibility and specificity of the miRNA response. And finally, the excretory profile of miR-21-5p and miR-155-5p in urine could successfully distinguish patients with and without AKI [15]. Factors such as IL-19 have been identified to be secreted by human RPTECs, the secretion levels in urine samples can be used as a marker for kidney toxicity. This concept can certainly be translated to secreted miRNAs [16], and this is indeed the case for miR-574-3p, miR-30a, miR-30c, miR-194, miR-197 and miR-200 [17] miR-203, miR-320, let-7d [18]. Interestingly, small non-coding RNAs are not only potential biomarkers of kidney toxicity, because when used as therapeutics small RNAs are suggested to be specifically toxic to the kidney. In order to assess the adverse effects and identify non-toxic RNAi chemistries, in vitro-models using renal epithelial cell line RPTEC/TERT1 have been established [19].

5. MicroRNAs in cardiotoxicity

Cardiotoxicity is one of the major safety concerns in drug development. Muscle-specific miRNAs, so-called myomiRs (miR-1-3p, miR133a-3p, miR-208a-3p/b-3p, and miR-499a-5p) are abundantly expressed in the myocardium [20]. They play a central role in cardiogenesis, heart function and pathology. While miR-1-3p and miR-133a-3p predominantly control early stages of cardiogenesis supporting commitment of cardiac-specific muscle lineage from embryonic stem cells and mesodermal precursors, miR-208a-3p and miR-499a-5p are involved in the late cardiogenic stages mediating differentiation of cardioblasts to cardiomyocytes and fast/slow muscle fiber specification [21]. In acute myocardial infarction (MI) circulating levels of cardiac miRNAs are significantly elevated making them to be a promising biomarker for early diagnosis of acute MI [21]. In doxorubicin induced cardiotoxicity circulating levels of miR-34a-3p [22] and miR-208a-3p [23] were enhanced. Moreover, it was shown that miR-133a-3p/b, specific markers of muscle toxicity, in combination with miR-208a-3p can be used to differentiate cardiac from skeletal muscle toxicity [24].

6. Conclusion and future perspective

The clinical utility of circulating miRNAs in body fluids as toxicological biomarkers, and the link between miRNA-related pharmacogenomics and adverse drug reactions is a matter of current and future investigations. Due to the strategies and challenges associated with the risk management of toxicants and the relationship between toxicity and disease states, the analysis of miRNA expression changes, as informative markers for toxic effects on the tissue level, will become extremely useful. The presented examples might be extended as different adverse outcome pathways might also lead to differential secretion of MicroRNAs.

References

[1] C.H. Lawrie, S. Gal, H.M. Dunlop, B. Pushkaran, A.P. Liggins, K. Pulford, A.H. Banham, F. Pezzella, J. Boultwood, J.S. Wainscoat, C.S.R. Hatton, A.L. Harris, Detection of elevated levels of tumour-associated microRNAs in serum of patients with diffuse large B-cell lymphoma, Br. J. Haematol. 141 (2008) 672–675, http://dx.doi.org/10.1111/j.1365-2141.2008.07077.x.

[2] J.A. Weber, D.H. Baxter, S. Zhang, D.Y. Huang, K.H. Huang, M.J. Lee, D.J. Galas, K. Wang, The microRNA spectrum in 12 body fluids, Clin. Chem. 56 (2010) 1733–1741, http://dx.doi.org/10.1373/clinchem.2010.147405.

[3] A. Keller, E. Meese, Can circulating miRNAs live up to the promise of being minimal invasive biomarkers in clinical settings? Wiley Interdiscip. Rev. RNA 7 (2016), http://dx.doi.org/10.1002/wrna.1320.

[4] H.W. Yu, W.C. Cho, The role of microRNAs in toxicology, Arch. Toxicol. (2015), http://dx.doi.org/10.1007/s00204-014-1440-2.

[5] J. Krauskopf, T.M. de Kok, D.G. Hebels, I.A. Bergdahl, A. Johansson, F. Spaeth, H. Kiviranta, P. Rantakokko, S.A. Kyrtopoulos, J.C. Kleinjans, MicroRNA profile for health risk assessment: environmental exposure to persistent organic pollutants strongly afects the human blood microRNA machinery, Sci. Rep. (2017) 9262, http://dx.doi.org/10.1038/s41598-017-10167-7.

[6] S. Campion, J. Aubrecht, K. Boekelheide, D.W. Brewster, V.S. Vaidya, L. Anderson, D. Burt, E. Dere, K. Hwang, S. Pacheco, J. Saikumar, S. Schomaker, M. Sigman, F. Goodsaid, The current status of biomarkers for predicting toxicity, Expert Opin. Drug Metab. Toxicol. 9 (2013) 1391–1408, http://dx.doi.org/10.1517/17425255.2013.827170.

[7] K. Wang, S. Zhang, B. Marzolf, P. Troisch, A. Brightman, Z. Hu, L.E. Hood, D.J. Galas, Circulating microRNAs, potential biomarkers for drug-induced liver injury, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 4402–4407, http://dx.doi.org/10.1073/pnas.0813371106.

[8] T. Yokoi, M. Nakajima, microRNAs as mediators of drug toxicity, Annu. Rev. Pharmacol. Toxicol. 53 (2013) 377–400, http://dx.doi.org/10.1146/annurev-pharmtox-011112-140250.

[9] Y. Zhang, Y. Jia, R. Zheng, Y. Guo, Y. Wang, H. Guo, M. Fei, S. Sun, Plasma microRNA-122 as a biomarker for viral-, alcohol-, and chemical-related hepatic diseases, Clin. Chem. 56 (2010) 1830–1838, http://dx.doi.org/10.1373/clinchem.2010.147850.

[10] G.M. Schratt, F. Tuebing, E.a Nigh, C.G. Kane, M.E. Sabatini, M. Kiebler, M.E. Greenberg, A brain-specific microRNA regulates dendritic spine development, Nature 439 (2006) 283–289, http://dx.doi.org/10.1038/nature04909.

[11] K. Ogata, K. Sumida, K. Miyata, M. Kushida, M. Kuwamura, J. Yamate, Circulating miR-9* and miR-384-5p as potential indicators for trimethyltin-induced neurotoxicity, Toxicol. Pathol. 43 (2015) 198–208, http://dx.doi.org/10.1177/0192623314530533.

[12] A. Haghikia, A. Haghikia, K. Hellwig, A. Baraniskin, A. Holzmann, B.F. Décard, T. Thum, R. Gold, Regulated microRNAs in the CSF of patients with multiple sclerosis: a case-control study, Neurology 79 (2012) 2166–2170, http://dx.doi.org/10.1212/WNL.0b013e3182759621.

[13] P. Bergman, E. Piket, M. Khademi, T. James, L. Brundin, T. Olsson, F. Piehl, M. Jagodic, Circulating miR-150 in CSF is a novel candidate biomarker for multiple sclerosis, Neurol. Neuroimmunol. Neuroinflamm. 3 (2016) e219, http://dx.doi.org/10.1212/nxi.0000000000000219.

[14] A.D.B. Vliegenthart, J.M. Shaffer, J.I. Clarke, L.E.J. Peeters, A. Caporali, D.N. Bateman, D.M. Wood, P.I. Dargan, D.G. Craig, J.K. Moore, A.I. Thompson, N.C. Henderson, D.J. Webb, J. Sharkey, D.J. Antoine, B.K. Park, M.A. Bailey, E. Lader, K.J. Simpson, J.W. Dear, Comprehensive microRNA profiling in acetaminophen toxicity identifies novel circulating biomarkers for human liver and kidney injury, Sci. Rep. 5 (2015) 15501, http://dx.doi.org/10.1038/srep15501.

[15] J. Saikumar, D. Hoffmann, T.M. Kim, V.R. Gonzalez, Q. Zhang, P.L. Goering, R.P. Brown, V. Bijol, P.J. Park, S.S. Waikar, V.S. Vaidya, Expression, circulation, and excretion profile of microRNA-21, −155, and −18a following acute kidney injury, Toxicol. Sci. 129 (2012) 256–267, http://dx.doi.org/10.1093/toxsci/kfs210.

[16] P. Jennings, D. Crean, L. Aschauer, A. Limonciel, K. Moenks, G. Kern, P. Hewitt, K. Lhotta, A. Lukas, A. Wilmes, M.O. Leonard, Interleukin-19 as a translational indicator of renal injury, Arch. Toxicol. 89 (2015) 101–106, http://dx.doi.org/10.1007/s00204-014-1237-3.

[17] R. Nassirpour, B.L. Homer, S. Mathur, Y. Li, Z. Li, T. Brown, D. Carraher, J. Warneke, S. Bailey, K. Percival, S.P. O'Neil, L.O. Whiteley, Identification of promising urinary microRNA biomarkers in two rat models of glomerular injury, Toxicol. Sci. 148 (2015) 35–47, http://dx.doi.org/10.1093/toxsci/kfv167.

[18] R. Nassirpour, S. Mathur, M.M. Gosink, Y. Li, A.M. Shoieb, J. Wood, S.P. O'Neil, B.L. Homer, L.O. Whiteley, Identification of tubular injury microRNA biomarkers in urine: comparison of next-generation sequencing and qPCR-based profiling platforms, BMC Genomics 15 (2014) 485, http://dx.doi.org/10.1186/1471-2164-15-485.

[19] A. Moisan, M. Gubler, J.D. Zhang, Y. Tessier, K. Dumong Erichsen, S. Sewing, R. Gérard, B. Avignon, S. Huber, F. Benmansour, X. Chen, R. Villaseñor, A. Braendli-Baiocco, M. Festag, A. Maunz, T. Singer, F. Schuler, A.B. Roth, Inhibition of EGF uptake by nephrotoxic antisense drugs In vitro and implications for preclinical safety profiling, Mol. Ther. − Nucleic Acids 6 (2017) 89–105, http://dx.doi.org/10.1016/j.omtn.2016.11.006.

[20] S. Yan, K. Jiao, Functions of miRNAs during mammalian heart development, Int. J. Mol. Sci. 17 (2016), http://dx.doi.org/10.3390/ijms17050789.

[21] D.A. Chistiakov, A.N. Orekhov, Y.V. Bobryshev, Cardiac-specific miRNA in cardiogenesis, heart function, and cardiac pathology (with focus on myocardial infarction), J. Mol. Cell Cardiol. 94 (2016) 107–121, http://dx.doi.org/10.1016/j.yjmcc.2016.03.015.

[22] E. Piegari, R. Russo, D. Cappetta, G. Esposito, K. Urbanek, C. Dell'Aversana, L. Altucci, L. Berrino, F. Rossi, A. De Angelis, MicroRNA-34a regulates doxorubicin-induced cardiotoxicity in rat, Oncotarget 7 (2016) 62312–62326, http://dx.doi.org/10.18632/oncotarget.11468.

[23] Y. Nishimura, C. Kondo, Y. Morikawa, Y. Tonomura, M. Torii, J. Yamate, T. Uehara, Plasma miR-208 as a useful biomarker for drug-induced cardiotoxicity in rats, J. Appl. Toxicol. 35 (2015) 173–180, http://dx.doi.org/10.1002/jat.3044.

[24] J. Calvano, W. Achanzar, B. Murphy, J. DiPiero, C. Hixson, C. Parrula, H. Burr, R. Mangipudy, M. Tirmenstein, Evaluation of microRNAs-208 and 133a/b as differential biomarkers of acute cardiac and skeletal muscle toxicity in rats, Toxicol. Appl. Pharmacol. 312 (2015) 53–60, http://dx.doi.org/10.1016/j.taap.2015.11.015.