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SHORT COMMENTARY

Forgotten Circadian Aspect in miRNAs Oriented Research

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INTRODUCTION

Until today several tens of classes of small non-coding RNAs have been discovered. Among them a class of miRNAs represents one of the most abundant (and still growing) groups with thousands of members. miRNAs are expressed in a tissue specific manner, play a number of regulatory roles in the cell and can be excreted by the cell to the extracellular space and/or circulation (Hammond, 2015; Voglova et al, 2016). miRNAs have attracted a growing interest with notable acceleration after 2005. Moreover, according to Scopus, March, 2017, there are more than 39,000 registered patents or submitted patent applications focused on miRNA. miRNA oriented research is so intensive mainly because of a robust influence of miRNA on transcriptome regulation. This knowledge opens a possibility to manipulate miRNA regulated expression in order to achieve desired changes via artificially developed oligos. The above mentioned technology is known as RNA interference (RNAi). This approach has already resulted in first clinical studies (Lam et al, 2015). The second line of investigation is aimed at mechanisms determining which miRNAs are excreted into the extracellular space, whether they can play a role as signaling molecules and how specific their composition is in regards to tissue and/or cell state (Lu et al, 2005). Recently, it seems to be accepted that miRNA spectrum in plasma corresponds well with many specific diseases and commercial pharmacological companies are already developing panels of miRNAs to be tested in medical practice (Zampetaki et al, 2012).

Activities of pharmacological companies are promising but still, there are many aspects that did not obtain deserved attention. One of the most important missing lines of investigation involves the influence of the circadian system on miRNA expression. RNAi oriented research struggles with several issues that need to be addressed. Among them stability, efficiency, off targeting and toxicity are the most important problems (Lam et al, 2015; Voglova et al, 2016). We believe that knowledge about a role of the circadian system in regulation of miRNAs and their targets expression can substantially increase efficiency, targeting and even tolerability of RNAi based drugs.

The circadian system represents genetically encoded way how to improve adaptation to cycling environmental conditions such as ligh:dark cycle. Molecular mechanism of the circadian system functioning is based on clock gene expression creating a feed-back loop present in all human cells. Expression of clock genes per (homologues 1, 2 and 3) and *cry* (homologues 1 and 2) is induced by heterodimer BMAl1/CLOCK via regulatory region E-box. Protein products of *per* and *cry* genes, after generation of a complex and translocation into the nucleus, inhibit BMAl1/CLOCK induced transcription of their own mRNA. Oscillations are conveyed to the whole transcriptome via several regulatory domains including widespread E-box. As a result of this, hundreds of genes are rhythmically expressed in a tissue specific manner (Panda et al, 2002).

It is estimated that in humans, 50% of miRNA is located within gene sequences and they are usually regulated by their host gene promoter (Rodriguez et al, 2004; Baskerville and Bartel, 2005). Therefore, it is very likely that rhythmically expressed transcriptome will be will lead to rhythmic expression of miRNAs. This is supported by experimental evidence demonstrating that expression of more than 1000 of non-coding RNAs shows a rhythmic pattern (Zhang et al, 2014). In the mouse liver 57 miRNA primary transcripts were proven to be directly under the circadian control (Wang et al, 2016). Rhythm in their expression was described for many miRNAs, e.g. miR-263a, miR-263a, miR-16, miR-181, miR-96, miR-182, miR-20a and miR-141 (Voglova et al, 2016). Moreover, it was shown that 26 of 79 (one third) measurable miRNAs in human healthy volunteers show a daily rhythm (Heegaard et al, 2016). This finding points out the importance of knowledge about miRNA rhythmicity for their use as potential biomarkers and indicates a necessity of more precise guidelines for their sampling. However, the issue is more complex. Knowledge about miRNA and mRNA can influence also RNAi efficiency and off targeting. We suppose that a promising way how to administer RNAi based drug is to time their administration according to highest target mRNA and lowest off target mRNA expressions (or to determine the most optimal ratio of target/off target rhythmic acrophases). Information about rhythmic expression

of coding and non-coding RNAs is growing exponentially. In combination with efficient tools for miRNA targets prediction *in silico* approach allows easy designing of experiments which would include also circadian regulation.

Another problem of RNAi based drugs, where biological rhythms oriented research can "give a hand", is RNAi toxicity. Several decades ago pharmacology developed a new branch called chronopharmacology. The most important aspect of chronopharmacology is administering of drugs at times during which they are best tolerated (Dallmann et al, 2004). Perhaps the most substantial amount of epidemiological evidence supporting beneficial effect of chronomodulated therapy has been accumulated in oncology (Liao et al, 2010). According to Lam et al. RNAi based therapeutics have already been tested in several types of solid tumors and advanced cancer. There were 14 clinical trials registered at clinicaltrials.gov in 2015 focused on cancer treatment by siRNA or miRNA. Optimization of RNAi use in cancer treatment can benefit from knowledge acquired during trials focused on chronomodulated chemotherapy. There are several meta-analyses demonstrating that chronomodulated chemotherapy significantly improved the overall survival in comparison with conventional chemotherapy (Liao et al, 2010). Recent knowledge implicates that chronomodulation of cancer treatment can be even more personalized as there are gender-dependent differences in efficiency of chemotherapy between men and women with better survival of men (Levi et al, 2017). Gender-dependent differences were described recently also in miRNA expression and this aspect will probably have to be addressed also in biomarker oriented research (Guo et al, 2016).

We assume that successfully and dynamically growing pharmacological field focused on RNAi based drugs and miRNA biomarkers has gathered such a substantial amount of information that a more complex analysis can be performed. At this point circadian regulation of miRNA occurrence in tissues and circulation should be considered as RNAi based drugs might show better efficiency and/or tolerability when chronotype and gender is taken into consideration. Supported by APVV-14-0318.

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