

REVIEW

Aging and systemic hormonal status affects the circulating miR-21, miR-146a and FasL levels

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MicroRNAs are small molecules, found in all cell types and body fluids, which most commonly affect negatively to gene expressions by translational repression. Their role in various physiological conditions and diseases has been emphasized during the last twenty years. In our recent studies with postmenopausal monozygotic twin sisters (n=11), we have investigated how different systemic hormonal status affects the levels of specific circulating microRNAs and other molecules related to inflammation and apoptosis, both processes associated with aging. Our results have shown that the systemic levels of miR-21, miR-146a and Fas ligand are lower within the postmenopausal women who are using estrogen-based hormonal replacement (HRT), compared to their non-using co-twins (p=0.018, p=0.039, p=0.021, respectively). To get further knowledge about the aging effect, we also measured the same markers from the premenopausal control women (n=8), with natural hormonal status, and found out that the inflammatory profile was healthier among the young women and that the serum miR-21 profile was more similar with the HRT users than non-users, and miR-146 and FasL profile more similar to non-users. These findings demonstrate that HRT has effects on the circulating inflammation related regulatory molecules. Whether we can state that the effects are clearly positive or negative, needs further investigations and understanding of the regulatory system.

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Aging is a process influenced by the combination of genetics and environmental factors. During the last decades, epigenetics, including microRNA (miR) regulation, has revolutionized our understanding of how our genes are being switched on and off. It is known that a single miR can regulate several biological processes as well as a group of miRs are affecting the expression of a single gene. To make it more complex, it is not only about how miRs regulate different processes: In addition, also miRs themselves are regulated by various molecules such as sex steroid hormones. Interest towards the interplay between hormonal regulation and different stages of miR maturation and targeting has emerged among many research groups in the recent years^[1]. The studies have shown that the regulatory system among these molecules is bi-directional, meaning both hormonal

signaling and miR biogenesis and function are affecting each other. It has also been stated that miRs deliver their messages similarly to hormones themselves. In our recent study we demonstrated that circulating miR-21 (onco-miR) and miR-146a (inflamma-miR) levels differ between postmenopausal monozygotic twin sisters whose hormonal status differs from each other, especially what comes to systemic estrogen concentrations^[2]. We have also shown with the same data, that HRT enhances the IGF-1 signaling by lowering the levels of miR-223 and miR-182 in the skeletal muscle^[3]. In addition, we have reported that the HRT users possess better muscle quality properties than the non-user twin sisters^[4]. Nothnick *et al*^[5] have also studied the interplay of hormones and miR regulation within the uterus of ovariectomized mice by demonstrating that steroid

hormones not only affect the miR expression at the transcription level but also the expression of the molecules, Exportin-5 and Dicer1, involved in miR maturation process. Several studies are focusing on the associations with miR levels and cancers associated with tissues sensitive to estrogens and androgens^[6-8].

One of the most intriguing questions in miR research is whether we should consider a change in a single miR level significant or should we examine the miR profile from a specific tissue as a whole. Many studies have shown that changes in specific miR levels are characteristics to certain diseases such as various cancers, autoimmune disorders and neurological diseases^[9]. Another set of studies has shown changes in miR profiles in different conditions^[10]. As we showed in our recent twin paper, the levels of specific circulating miRs are partly genetically regulated (miR-21: $r=0.66$, miR-146a: $r=0.38$)^[2]. Due to that, setting common reference values for normal and abnormal miR levels for the clinical use, might be challenging.

In our ongoing studies we are focusing on the serum levels of the specific miRs and FasL in another longitudinal data set consisting of aged male sprint athletes^[11]. It seems like an aging effect can be detected in this unique study population what comes to the studied molecules. In addition, our miR work continues with the already discussed twin data, in order to get a better picture of the entire miR profile of the serum samples.

Overall, it is not so obvious, whether we express certain inherited properties or not, it is all about the interplay between the genes and the environment and the bunch of molecules working in between. MicroRNAs seem to be one of the sensitive mechanisms affecting the fine-tuning of the gene expression. Due to their already detected variation in different conditions and diseases and high stability in the biological samples, miRs are promising tools to be used in diagnostics and therapeutics. However, in order to generalize and take the miR analysis into official clinical use, the methods need to be standardized.

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