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MicroRNAs as Potential Biomarkers and Innovative Therapeutic Targets in Retinal Degenerations

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The human retina, as a part of the central nervous system, is distinctively designated to the initiation of the visual processing. In accordance with its complex anatomy and physiology, a broad number of coding and noncoding regions of the genome have been implicated in the heterogeneous pathogenesis of several retinal degenerative diseases, i.e., monogenic disorders, such as the various Mendelian-inherited forms of retinitis pigmentosa (RP), and multifactorial polygenic/environmental disorders, such as age-related macular degeneration (AMD) and pathologic myopia (PM). Both occurrence and progression of these chronic vision-threatening diseases can be influenced by genetic and epigenetic factors, affecting different retinal and sub-retinal structures: the neural retina (NR), composed by the inner neurosensory layer with its vascular capillary nets and the outer photoreceptor cells (PRCs) layer with the underlying retinal pigment epithelium (RPE), which is separated from choriocapillaris by a modified basement stratum named Bruch's membrane (BM), while the supporting glial Müller cells span the NR from external to inner limiting membranes sealing the axonal fibers of the retinal ganglion cells from the vitreous. The diverse retinal degenerations primarily involve a specific target-structure: (i) RP phenotypes are primary caused by damages of PRCs; (ii) AMD lesions depend on degenerative RPE modifications; (iii) PM-related scleral expansion irreversibly modifies the RPE-BM complex. Both health and function of the human retina rely on a collaborative interaction among diverse classes of molecular regulators.

Starting from 1993, small non-coding endogenous RNAs of approximately 21-25 nucleotides in length, named microRNAs (miRNAs), have been recognized as key factors of posttranscriptional gene regulation in mammalian genomes. At present, our knowledge about either origin or functions of circulating exosomal miRNAs is going to be implemented, and there are several investigative methods that allow the identification of miRNAs contribution to heterogeneous disorders. The perceived opportunity appears especially large in neoplastic diseases [1-6], even if the evaluation of diagnostic specificity and reproducibility of miRNAs assessment remains a work in progress [7,8]. In the last years, transcriptome analyses have documented the presence of several miRNAs expressed in the human adult retina, indicating the pivotal role of miRNAs as regulators for homeostasis, function and survival of the differentiated cell types at the level of mature retinal and sub-retinal tissues [9,10]. The demanding physiologic tasks of the retina postulate the action of a continuous gene regulation to render its perennial post-mitotic cells less vulnerable to premature damage or death secondary to the most frequent causes of irreversible low-vision and blindness, i.e., AMD, PM, and RP [11,12]. Moreover, because miRNAs are involved in transferring inflammatory signals among cells, they may have a crucial prognostic value in the above-mentioned diseases, whose modalities of onset and/or progression are invariably related to complex para-inflammatory processes [13-22]. Particularly, in Alzheimer's disease and AMD, a group of five miRNAs (miRNA-9, -34a, -125b, -146a and -155) has been found up-regulated during several independent experimental tests, indicating the presence of progressive inflammatory damages in both pathologic patterns of these age-related neurodegenerative disorders [23].

In an all-embracing view, this scenario highlights the potential relevance of miRNAs to advance the clinical management of the most severe retinal diseases. Notionally, the pathogenic mechanisms of each different retinal disorder express specific miRNA-genes inside pathologic cells. Part of these expressed miRNAs are then secreted by exosomes and become circulating miRNAs, which can be detected in patients' serum samples as biomarkers of vision-threatening diseases. It has been shown that altered miRNA expression patterns in the human fluids might be the result of various eye disorders. Recent studies are beginning to document the possible role of circulating miRNAs as biomarkers for both pathologic conditions and severity of disease progression. It is very challenging to approach the question whether each cell type of the retinal complex has its own miRNA phenotype, since one miRNA can target different gene products that might be expressed in different microstructures. Although some patterns of miRNAs expression have been tentatively labeled as distinctive signatures of specific retinal cell types [24-30], no unequivocal data have been hitherto obtained in patients on the correlations between dysregulated miRNA profiles and pathologic retinal phenotypes, i.e., AMD [31-33], PM [34], and RP [35,36]. The miRNAs identified in human serum and plasma is known to be relatively stable, as they have been found to be resistant to RNAase degradation, even in stored samples. This remarkable extracellular stability has made miRNAs desirable candidates for epidemiological and clinical studies, indicating their potential role as non- or minimal-invasive biomarkers particularly because small serum or plasma samples are needed for miRNAs profiling. However, despite a multitude of investigations of basic research, there are only few independent validation studies on blood-born miRNAs as disease biomarkers. Toward clinical applications in ophthalmology numerous obstacles still need to be overcome, starting from the lack of data resulting from trials conducted on homogeneous study groups. Because no study has been hitherto conducted in patients with retinal degenerative disorders to assess the degree of

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intra-individual consistency in correlating the clinical changes in diseases' expressivity with putative modifications of miRNAs profile, this comparative approach of investigation should be recommended to advance our levels of knowledge and to provide concrete answers about the translational potentialities of miRNAs, as recently advocated by Andreas Keller and Eckart Meese emphasizing a very challenging question: "Can circulating miRNAs live up to the promise of being minimal invasive biomarkers in clinical settings?" [8].

Circulating miRNAs vary in their expression and concentration in serum samples, and these variations indicate the potential role of miRNAs as biomarkers of pathologic status vs. health condition. Indeed, several investigations have been recently conducted on patients suffering from cancers, infections, cardiovascular, metabolic, neurodegenerative or genetic diseases, in which miRNAs were found variably dysregulated compared to those detected in healthy controls [23,37-55]. Expression of circulating miRNAs may change in the course of the pathologies exemplified above and/or their complications. In this context, it is important to note that, during the period of illness, circulating miRNAs can be modified either at the level of their panel expression or at the single-miRNA concentration. The detection of dysregulated circulating miRNAs could have application in early diagnosis and progression of retinal degenerations, as already shown for other degenerative disorders of the central nervous system [23,50-52]. Just for example, starting from the available knowledge about a multifactorial degenerative disease characterized by both environmental and gene-related pathogenetic mechanisms such as AMD [14-16,18], the future steps for translational miRNAs application might be focused on the ability of correlating differences in miRNAs profiles to: (i) status of AMD patient versus matched healthy control; (ii) morpho-functional deteriorations of RPE cells and/or PRCs layers characterizing the dry AMD forms; (iii) occurrence of choroidal neovascularization complicating the wet AMD forms. Considering both technology and cost of the analyses, the miRNAs detection in serum samples of patients with disorders of neural ocular structures has the potential to become an affordable approach. It may be especially helpful when the eye disease is asymptomatic or paucisymptomatic and/or when it is characterized by critical patterns of heterogeneity. In these cases, the detection of one or more dysregulated circulating miRNAs could be used as a specific parameter to facilitate the phenotypic and/or genotypic interpretation of the disease, and the ophthalmologists may benefit of these new diagnostic parameters/tools. At the same time, miRNAs are now investigated as potential target for innovative therapies. One of the most promising experimental strategies foresees the use of liposome-like structures loaded with anti-sense miRNAs when a specific miRNA is over-expressed. On the other hand, the same strategy with liposomes loaded with miRNAs can be used when a specific miRNA is down-expressed, with the aim to re-establish the normal level of miRNAs. It is noteworthy to recall that miRNAs play an important role during the expression process of different genes. It has been shown that more than 2,000 genes encode for miRNAs which, in turn, recognize distinct and multiple mRNAs as targets. This biological process is crucial for the cell because the protein production is affected by the amount of mRNA, which is translated at the ribosomes level. In this context, the protein concentration and bioavailability into the cell is determined by the accessible amount of the specific mRNA. More recently, it has been shown that miRNAs can be "secreted" by cells with exosomes, which are liposome-like particles filled of specific miRNAs and circulating into the blood stream. This loop resembles the so-called autocrine and paracrine loops, employed by the cells for their cell-to-cell talks with growth/differentiation factors. It represents one the main mechanism used by a living cell to control its development and functions, as well as to maintain its homeostasis. Similarly, miRNAs are released by cells with exosomes to reach new cells, in distant or near tissues, using the blood/serum/plasma as a vehicle. This mechanism ensures a sort of equilibrium mediated, at distance, by miRNAs. In case of altered equilibrium, a specific pathology may occur. This alteration can be used to recognize a serum miRNA as parameter/biomarker for diagnostic and/or prognostic purposes. Indeed, by improving our understanding about the pathogenesis of AMD, PM and RP, together with the clinical laboratory-based screening and the forthcoming development of new therapeutic strategies, it will be possible to ameliorate the clinical management of numerous patients at high risk of low-vision and blindness. In the near future, new miRNA-based assays, which are highly sensitive and specific, might be able to attain a "customized" classification of the different eye diseases. The study of miRNA biomarkers implicating in pathogenesis, diagnosis and prognosis of retinal degenerations represents a translational topic of increased research interest, especially because miRNAs themselves might be considered as therapeutic targets or even therapeutic agents as anti-miRNAs. In view of these elements of miRNA-related exploratory context, additional studies will help us in assessing miRNAs potential as upstream regulators and/or downstream targets of the common vision-disabling diseases.

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Conflicts of Interest

The authors declare no conflict of interest.

References

1. Simpson RJ, Lim JW, Moritz RL, Mathivanan S (2009) Exosomes: proteomic insights and diagnostic potential. Expert Rev Proteomics 6: 267-283.
2. Balatti V, Maniero S, Ferracin M, Veronese A, Negrini M, et al. (2011) MicroRNAs dysregulation in human malignant pleural mesothelioma. J Thorac Oncol 6: 844-851.
3. Novello C, Pazzaglia L, Cingolani C, Conti A, Quattrini I, et al. (2013) miRNA expression profile in human osteosarcoma: role of miR-1 and miR-133b in proliferation and cell cycle control. Int J Oncol 42: 667-675.
4. Sheinerman KS, Umansky S (2015) Universal screening test based on analysis of circulating organ-enriched microRNAs: a novel approach to diagnostic screening. Expert Rev Mol Diagn 15: 329-338.
5. Qiu X, Zhang H, Yu H, Jiang T, Luo Y (2015) Duplex-specific nuclease-mediated bioanalysis. Trends Biotechnol 33: 180-188.
6. Pimentel F, Bonilla P, Ravishankar YG, Contag A, Gopal N, et al. (2015) Technology in microRNA profiling: circulating microRNAs as noninvasive cancer biomarkers in breast cancer. J Lab Autom 20: 574-588.
7. Witwer KW (2015) Circulating microRNA biomarker studies: pitfalls and potential solutions. Clin Chem 61: 56-63.
8. Keller A, Meese E (2016) Can circulating miRNAs live up to the promise of being minimal invasive biomarkers in clinical settings? Wiley Interdiscip Rev RNA 7: 148-156.
9. Andreeva K, Cooper NG (2014) MicroRNAs in the Neural Retina. Int J Genomics 2014: 165897.
10. Sundermeier TR, Palczewski K (2016) The impact of microRNA gene regulation on the survival and function of mature cell types in the eye. FASEB J 30: 23-33.
11. Chizzolini M, Galan A, Milan E, Sebastiani A, Costagliola C, et al. (2011) Good epidemiologic practice in retinitis pigmentosa: from phenotyping to biobanking. Curr Genomics 12: 260-266.
12. Bourne RR, Stevens GA, White RA, Smith JL, Flaxman SR, et al. (2013) Causes of vision loss worldwide, 1990-2010: a systematic analysis. Lancet Glob Health 1: e339-349.

13. Xu H, Chen M, Forrester JV (2009) Para-inflammation in the aging retina. Prog Retin Eye Res 28: 348-368.

14. Campa C, Costagliola C, Incorvaia C, Sheridan C, Semeraro F, et al. (2010) Inflammatory mediators and angiogenic factors in choroidal neovascularization: pathogenetic interactions and therapeutic implications. Mediators Inflamm 2010: 1-14.

15. Parmeggiani F, Romano MR, Costagliola C, Semeraro F, Incorvaia C, et al. (2012) Mechanism of inflammation in age-related macular degeneration. Mediators Inflamm 2012.

16. Parmeggiani F, Sorrentino FS, Romano MR, Costagliola C, Semeraro F, et al. (2013) Mechanism of inflammation in age-related macular degeneration: an up-to-date on genetic landmarks. Mediators Inflamm 2013: 435607.

17. Yoshida N, Ikeda Y, Notomi S, Ishikawa K, Murakami Y, et al. (2013) Clinical evidence of sustained chronic inflammatory reaction in retinitis pigmentosa. Ophthalmology 120: 100-105.

18. Gallenga CE, Parmeggiani F, Costagliola C, Sebastiani A, Gallenga PE (2014) Inflammaging: should this term be suitable for age related macular degeneration too? Inflamm Res 63: 105-107.

19. Yamamoto Y, Miyazaki D, Sasaki S, Miyake K, Kaneda S, et al. (2015) Associations of inflammatory cytokines with choroidal neovascularization in highly myopic eyes. Retina 35: 344-350.

20. Murakami Y, Yoshida N, Ikeda Y, Nakatake S, Fujiwara K, et al. (2015) Relationship between aqueous flare and visual function in retinitis pigmentosa. Am J Ophthalmol 159: 958-963.

21. Karlstetter M, Scholz R, Rutar M, Wong WT, Provis JM, et al. (2015) Retinal microglia: just bystander or target for therapy? Prog Retin Eye Res 45: 30-57.

22. Ma W, Wong WT (2016) Aging Changes in Retinal Microglia and their Relevance to Age-related Retinal Disease. Adv Exp Med Biol 854: 73-78.

23. Hill JM, Pogue AI, Lukiw WJ (2015) Pathogenic microRNAs common to brain and retinal degeneration; recent observations in Alzheimer's disease and age-related macular degeneration. Front Neurol 6: 232.

24. Zhu Q, Sun W, Okano K, Chen Y, Zhang N, et al. (2011) Sponge transgenic mouse model reveals important roles for the microRNA-183 (miR-183)/96/182 cluster in postmitotic photoreceptors of the retina. J Biol Chem 286: 31749-31760.

25. Karali M, Manfredi A, Puppo A, Marrocco E, Gargiulo A, et al. (2011) MicroRNA-restricted transgene expression in the retina. PLoS One 6: e22166.

26. Silva VAO, Polesskaya A, Sousa TA, Corrêa VM, André ND, et al. (2011) Expression and cellular localization of microRNA-29b and RAX, an activator of the RNA-dependent protein kinase (PKR), in the retina of streptozotocin-induced diabetic rats. Mol Vis 17: 2228-2240.

27. Lin H, Qian J, Castillo AC, Long B, Keyes KT, et al. (2011) Effect of miR-23 on oxidant-induced injury in human retinal pigment epithelial cells. Invest Ophthalmol Vis Sci 52: 6308-6314.

28. Li Y, Li C, Chen Z, He J, Tao Z, et al. (2012) A microRNA, mir133b, suppresses melanopsin expression mediated by failure dopaminergic amacrine cells in RCS rats. Cell Signal 24: 685-698.

29. Hu G, Huang K, Yu J, Gopalakrishna-Pillai S, Kong J, et al. (2012) Identification of miRNA signatures during the differentiation of hESCs into retinal pigment epithelial cells. PLoS One 7: e37224.

30. Lumayag S, Haldin CE, Corbett NJ, Wahlin KJ, Cowan C, et al. (2013) Inactivation of the microRNA-183/96/182 cluster results in syndromic retinal degeneration. Proc Natl Acad Sci U S A 110: E507-516.

31. Ertekin S, Yıldırım O, Dinç E, Ayaz L, Fidancı SB, et al. (2014) Evaluation of circulating miRNAs in wet age-related macular degeneration. Mol Vis 20: 1057-1066.

32. Grassmann F, Schoenberger PG, Brandl C, Schick T, Hasler D, et al. (2014) A circulating microrna profile is associated with late-stage neovascular age-related macular degeneration. PLoS One 9: e107461.

33. Szemraj M, Bielecka-Kowalska A, Oszajca K, Krajewska M, Goś R, et al. (2015) Serum MicroRNAs as Potential Biomarkers of AMD. Med Sci Monit 21: 2734-2742.

34. Lechner J, Bae HA, Guduric-Fuchs J, Rice A, Govindarajan G, et al. (2013) Mutational analysis of MIR184 in sporadic keratoconus and myopia. Invest Ophthalmol Vis Sci 54: 5266-5272.

35. Huang XF, Huang F, Wu KC, Wu J, Chen J, et al. (2015) Genotype-phenotype correlation and mutation spectrum in a large cohort of patients with inherited retinal dystrophy revealed by next-generation sequencing. Genet Med 17: 271-278.

36. Conte I, Hadfield KD, Barbato S, Carrella S, Pizzo M, et al. (2015) MiR-204 is responsible for inherited retinal dystrophy associated with ocular coloboma. Proc Natl Acad Sci U S A 112: E3236-3245.

37. Du M, Liu S, Gu D, Wang Q, Zhu L, et al. (2014) Clinical potential role of circulating microRNAs in early diagnosis of colorectal cancer patients. Carcinogenesis 35: 2723-2730.

38. Wang J, Ye H, Zhang D, Hu Y, Yu X, et al. (2016) MicroRNA-410-5p as a potential serum biomarker for the diagnosis of prostate cancer. Cancer Cell Int 16: 12.

39. Shimomura A, Shiino S, Kawauchi J, Takizawa S, et al. (2016) A novel combination of serum microRNAs for detecting breast cancer in the early stage. Cancer Sci .

40. Jin BX, Zhang YH, Jin WJ, Sun XY, Qiao GF, et al. (2015) MicroRNA panels as disease biomarkers distinguishing hepatitis B virus infection caused hepatitis and liver cirrhosis. Sci Rep 5: 15026.

41. Peng F, He J, Loo JF, Yao J, Shi L, et al. (2016) Identification of microRNAs in Throat Swab as the Biomarkers for Diagnosis of Influenza. Int J Med Sci 13: 77-84.

42. Benz F, Roy S, Trautwein C, Roderburg C, Luedde T (2016) Circulating MicroRNAs as Biomarkers for Sepsis. Int J Mol Sci 17.

43. Ninomiya M, Kondo Y, Kimura O, Funayama R, et al. (2016) The expression of miR-125b-5p is increased in the serum of patients with chronic hepatitis B infection and inhibits the detection of hepatitis B virus surface antigen. J Viral Hepat .

44. Han Z, Zhang L, Yuan L, Liu X, Chen X, et al. (2015) Change of plasma microRNA-208 level in acute myocardial infarction patients and its clinical significance. Ann Transl Med 3: 307.

45. Li C, Chen X, Huang J, Sun Q, Wang L (2015) Clinical impact of circulating miR-26a, miR-191, and miR-208b in plasma of patients with acute myocardial infarction. Eur J Med Res 20: 58.

46. Wang KJ, Zhao X, Liu YZ, Zeng QT, Mao XB, et al. (2016) Circulating MiR-19b-3p, MiR-134-5p and MiR-186-5p are Promising Novel Biomarkers for Early Diagnosis of Acute Myocardial Infarction. Cell Physiol Biochem 38: 1015-1029.

47. Xiao J, Shen B, Li J, Lv D, Zhao Y, et al. (2014) Serum microRNA-499 and microRNA-208a as biomarkers of acute myocardial infarction. Int J Clin Exp Med 7: 136-141.

48. Ding L, Ai D, Wu R, et al. (2016) Identification of the differential expression of serum microRNA in type 2 diabetes. Biosci Biotechnol Biochem 80: 461-465.

49. Wang C, Wan S, Yang T, et al. (2016) Increased serum microRNAs are closely associated with the presence of microvascular complications in type 2 diabetes mellitus. Sci Rep 6: 20032.

50. Burgos K, Malenica I, Metpally R, Courtright A, Rakela B, et al. (2014) Profiles of extracellular miRNA in cerebrospinal fluid and serum from patients with Alzheimer's and Parkinson's diseases correlate with disease status and features of pathology. PLoS One 9: e94839.

51. Tan L, Yu JT, Liu QY, Tan MS, Zhang W, et al. (2014) Circulating miR-125b as a biomarker of Alzheimer's disease. J Neurol Sci 336: 52-56.

52. Ding H, Huang Z, Chen M, Wang C, Chen X, et al. (2016) Identification of a panel of five serum miRNAs as a biomarker for Parkinson's disease. Parkinsonism Relat Disord 22: 68-73.

53. Cook NL, Pereira TN, Lewindon PJ, Shepherd RW, Ramm GA (2015) Circulating microRNAs as noninvasive diagnostic biomarkers of liver disease in children with cystic fibrosis. J Pediatr Gastroenterol Nutr 60: 247-254.

54. Kubiczkova Besse L, Sedlarikova L, Kryukov F, Nekvindova J, Radova L, et al. (2015) Combination of serum microRNA-320a and microRNA-320b as a marker for Waldenström macroglobulinemia. Am J Hematol 90: E51-52.

55. Wang W, Zhang Y, Zhu B, Duan T, et al. (2015) Plasma microRNA expression profiles in Chinese patients with rheumatoid arthritis. Oncotarget 6: 42557-42568.