A new study by Islam et al, in this issue of EMBO Molecular Medicine, reports three microRNAs in the blood that are linked to inter-individual differences in cognition, prior to any sign of cognitive decline. The novel miRNA biomarkers may assist in predicting the risk of cognitive decline and later of developing dementia and can contribute to decision strategies about early therapeutic interventions.

EMBO Mol Med (2021) 13: e14997
See also: MR Islam et al (November 2021)

The prevalence of cognitive decline and dementia in the human population is estimated to double every two decades, imposing a growing challenge to society. Mild cognitive impairment (MCI, or mild neurocognitive disorder) is an acquired deficit in cognitive ability that is typically progressive, affecting skills such as learning and problem-solving, memory, and perception. Individuals diagnosed with MCI have an annual risk of ~10% of conversion to dementia, especially to Alzheimer’s disease (AD, Fig 1A).

Minimally invasive laboratory tests that assist the diagnosis of cognitive status are an unmet need. Although brain imaging or measuring the levels of proteins, such as amyloid beta or tau, in the blood or cerebrospinal fluid (CSF) is considered minimally invasive, today’s tests are proven useful only in the advanced stage of dementia (Beach, 2017; Molinuenu et al, 2018). This limits their utility because late in the disease, treatment options are extremely limited. Therefore, it is an important challenge to discover new markers that can be utilized for screening the seemingly healthy population for the earliest signs of cognitive decline.

In this issue of EMBO Molecular Medicine, Islam et al (2021) propose an original approach for screening healthy individuals at risk of cognitive decline. The approach is based on blood drawing and is “minimally invasive” and features the quantification of microRNAs (miRNAs) in the blood.

miRNAs are endogenous small RNAs that post-transcriptionally regulate gene expression. miRNAs play crucial roles in brain maintenance and are essential for neuron survival (Schraat, 2009). miRNAs have been implicated in the pathogenesis of neurodegeneration and can contribute to biomarker development for cognitive impairment and dementia including AD (Cogswell et al, 2008; Kayano et al, 2016; Barbagallo et al, 2020; Dong et al, 2020; Wei et al, 2020; Zhao et al, 2020).

The underlying reasons for using miRNAs as biomarkers is that small RNAs are present in tissues, including blood and brain cells, but are also detectable outside cells. Their expression can inform about tissue and disease status. The mechanism by which miRNAs exit cells is still under extensive research. However, two main working hypotheses stand out: miRNAs may be spilled out of dying cells or may be secreted in a regulated manner in extracellular vesicles. Equally important for biomarker development is the fact that miRNAs can be quantified in a high throughput manner by modern RNA sequencing techniques. Therefore, relatively rapid analysis of hundreds of miRNA species in large cohorts of human samples opened up in recent years a new field of biomarker discovery.

Utilizing such a framework, Islam et al (2021) addressed an intriguing research mission: to identify miRNAs that are informative about the cognitive state in healthy humans. They performed their analysis by correlating miRNA signatures in blood to the score gained by cognitive assessment tests. The authors further proceeded in an original way to combine data gained from humans with a longitudinal analysis of miRNAs in aging mice. This integrative approach, which combines two very different mammal species, enabled prioritization and cross-validation. This certainly increases confidence in the three miRNA hits, namely, miR-181a-5p, miR-146a-5p, and miR-148a-5p (Fig 1B). Furthermore, the authors demonstrated that these three miRNAs together predict cognitive decline in an independent human cohort. Finally, Islam et al (2021) use mice to provide initial proof that the three miRNAs may not only inform about changes in cognitive status but also might contribute to neural homeostasis and may be potentially involved in the molecular mechanism of cognitive decline.

The strategy of Islam et al (2021) prioritizes miRNAs with similar measured patterns across two species. Therefore, miRNAs measured in blood became relevant to the study only if their signal overcame differences associated with comparing human cognition and its mouse counterpart. Accordingly, the same miRNA molecules must be detected in association with a sophisticated neuropsychological assessment in humans and with one key memory function in mice.

Such an integrative approach is valuable because phenomena conserved across species are more likely to be genuine. However, the authors take into account that they overlook human-specific changes and miRNA genes that are present in the Homo sapiens genome but not conserved to the mouse genome. Together, room is given for future research to explore human-specific features and to incorporate longitudinal human data to directly test actual changes in the course of time.

In the same work, the authors went on to further demonstrate that inhibition (knock-down) of the three miRNAs with “anti-miRNA” synthetic oligonucleotides, can
therapeutically mitigate cognitive impairment in aging mice and in a mouse model of Alzheimer’s disease. This part of the work is impactful twofold: First, the anti-miRNA molecules reported, may be developed in the future, into new experimental drugs for cognitive decline and dementia therapy. Of course, follow-up studies will be required to understand how anti-miRNAs work in this context and their pharmacology. Second, the fact that manipulating the levels of the three miRNAs ameliorates deterioration also implicates them in molecular axes of cognitive decline and suggests that the increased levels in the blood are directly, perhaps mechanistically, linked to congestive decline. However, a better understanding of potential causality will require additional studies in animal models and longitudinal studies in human cohorts.

A couple of notable challenges will be addressed in the future by experts in this emerging field: As the analysis of Islam et al (2021) is primarily based on whole blood RNA, where a substantial amount of the RNA is from blood cells, it is currently unknown if the expression of the three microRNAs originated from brain, other organs, or alterations in the composition of white or red blood cells. Measurements of the miRNAs in cerebrospinal fluid might suggest a potential brain origin, and re-analysis of another study’s data implies that the miRNAs could be detected in the blood’s liquid portion. In addition, micro-RNAs in the blood may be derived from extracellular vesicles of the brain origin (Hill, 2019). Therefore, additional research will probably contribute to a better understanding of the miRNAs’ tissue sources and the molecular mechanism that dictates changes in the miRNA levels in the blood.

Finally, major challenges lay ahead toward future point-of-care utilization of biomarkers, including miRNA biomarkers. Simple means for measurements and standardization of blood miRNA levels in the clinic should be developed. Furthermore, the computational development of a robust personalized predictor that can forecast an individual’s risk, based on absolute miRNA values, will also be needed.

Acknowledgements
Hornstein lab research is supported by Nela and Leon Benoziyo Center for Neurological Diseases, research grant from Edward and Janie Moravitz, Weizmann—Brazil Center for Research on Neurodegeneration at Weizmann Institute of Science, Redhill Foundation—Sam and Jean Rothberg Charitable Trust. Additional funding provided by CreAtes consortium and ALSA, RADALA Foundation; AFM Telethon (20576), the Minerva Foundation with funding from the Federal German Ministry for Education and Research, ISF Legacy Heritage Fund 82817; Israel Science Foundation 135/16 and 3497/21; ERA-Net for Research Programmes on Rare Diseases (eRARE FP7) via Israel Ministry of Health; Dr. Sydney Brenner and friends, Yeda-Sela, Yeda-CEO. NSY is supported by the Israeli Council for Higher Education via the Weizmann Data Science Research Center, by a research grant from the Estate of Tully and Michele Plessier and scholarship from Maccabim Foundation. EH is the incumbent Ira & Gail Mondry professorial chair.

References
Barbagallo C, Mostile G, Baglieri G, Giunta F, Luca A, Raciti L, Zappia M, Purrello M, Ragusa M, Nicoletti A (2020) Specific signatures of serum miRNAs as potential biomarkers to discriminate clinically similar neurodegenerative and vascular-related diseases. Cell Mol Neurobiol 40: 531 – 546
Beach TG (2017) A review of biomarkers for neurodegenerative disease: will they swing us across the valley? Neurot Ther 6: 5 – 13
Cogswell JP, Ward J, Taylor IA, Waters M, Shi Y, Cannon B, Kelnar K, Kemppainen J, Brown D, Chen C et al (2008) Identification of miRNA changes in Alzheimer’s disease brain and CSF yields putative biomarkers and insights
Dong X, Zheng D, Nao J (2020) Circulating exosome microRNAs as diagnostic biomarkers of dementia. Front Aging Neurosci 12: 580199

Hill AF (2019) Extracellular vesicles and neurodegenerative diseases. J Neurosci 39: 9269–9273

Islam MR, Kaurani L, Berulava T, Heilbronner U, Budde M, Centeno TP, Elerdashvili V, Zafieriou M, Benito E, Sertel SM et al (2021) A microRNA signature that correlates with cognition and is a target against cognitive decline. EMBO Mol Med 13: e13659

Kayano M, Higaki S, Satoh J-I, Matsumoto K, Matsubara E, Takikawa O, Niida S (2016) Plasma microRNA biomarker detection for mild cognitive impairment using differential correlation analysis. Biomark Res 4: 22

Molinaue J, Ayton S, Batria R, Bednar MM, Bittner T, Cummings J, Fagan AM, Hampel H, Mielke MM, Mikulskis A et al (2018) Current state of Alzheimer’s fluid biomarkers. Acta Neuropathol 136: 821–853

Schratt G (2009) microRNAs at the synapse. Nat Rev Neurosci 10: 842–849

Wei W, Wang Z-Y, Ma L-N, Zhang T-T, Cao Y, Li H (2020) MicroRNAs in Alzheimer’s disease: function and potential applications as diagnostic biomarkers. Front Mol Neurosci 13: 160

Zhao Y, Jaber V, Alexandrov PN, Vergallo A, Lista S, Hampel H, Lukiw WJ (2020) microRNA-based biomarkers in Alzheimer’s disease (AD). Front Neurosci 14: 585432

License: This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.