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Tiny molecule could help diagnose and treat mental disorders

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According the World Health Organization, such mood disorders as depression affect some 10% of the world's population and are associated with a heavy burden of disease. That is why numerous scientists around the world have invested a great deal of effort in understanding these diseases. Yet the molecular and cellular mechanisms that underlie these problems are still only partly understood.

The existing anti-depressants are not good enough: Some 60-70% of patients get no relief from them. For the other 30-40%, that relief is often incomplete, and they must take the drugs for a long period before feeling any effects. In addition, there are many side effects associated with the drugs. New and better drugs are clearly needed, an undertaking that requires, first and foremost, a better understanding of the processes and causes underlying the disorders.

The Weizmann Institute's Prof. Alon Chen, together with his then PhD student Dr. Orna Issler, investigated the molecular mechanisms of the brain's serotonin system, which, when misregulated, is involved in depression and anxiety disorders. Chen and his colleagues researched the role of microRNA molecules (small, non-coding RNA molecules that regulate various cellular activities) in the nerve cells that produce serotonin. They succeeded in identifying, for the first time, the unique "fingerprints" of a microRNA molecule that acts on the serotonin-producing nerve cells. Combining bioinformatics methods with experiments, the researchers found a connection between this particular microRNA, (miR135), and two proteins that play a key role in serotonin

production and the regulation of its activities. The findings appeared today in *Neuron*.

The scientists noted that in the area of the brain containing the serotonin-producing nerve cells, miR135 levels increased when antidepressant compounds were introduced. Mice that were genetically engineered to produce higher-than-average amounts of the microRNA were more resistant to constant stress: They did not develop any of the behaviors associated with chronic stress, such as anxiety or depression, which would normally appear. In contrast, mice that expressed low levels of miR135 exhibited more of these behaviors; in addition, their response to antidepressants was weaker. In other words, the brain needs the proper miR135 levels – low enough to enable a healthy stress response and high enough to avoid depression or anxiety disorders and to respond to serotonin-boosting antidepressants. When this idea was tested on human blood samples, the researchers found that subjects who suffered from depression had unusually low miR135 levels in their blood. On closer inspection, the scientists discovered that the three genes involved in producing miR135 are located in areas of the genome that are known to be associated with risk factors for bipolar mood disorders.

These findings suggest that miR135 could be a useful therapeutic molecule – both as a blood test for depression and related disorders, and as a target whose levels might be raised in patients. Yeda Research and Development Co. Ltd., the technology transfer arm of the Weizmann Institute, has applied for a patent connected to these findings and recently licensed the rights to miCure Therapeutics to develop a drug and diagnostic method. After completing preclinical trials, the company hopes to begin clinical trials in humans.

Prof. Alon Chen is the Head of the Max Planck Society - Weizmann Institute of Science Laboratory for Experimental Neuropsychiatry and Behavioral Neurogenetics.

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The Weizmann Institute of Science in Rehovot, Israel, is one of the world's top-ranking multidisciplinary research institutions. Noted for its wide-ranging exploration of the natural and exact sciences, the Institute is home to scientists, students, technicians and supporting staff. Institute research efforts include the search for new ways of fighting disease and hunger, examining leading questions in mathematics and computer science, probing the physics of matter and the universe, creating novel materials and developing new strategies for protecting the environment.

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