Scientists “Fingerprint” A Culprit In Depression, Anxiety, & Other Disorders That Could Lead To Treatment Breakthroughs

According to the World Health Organization (WHO), such mood disorders as depression affect some 10% of the world’s population and are associated with a heavy burden of disease. In fact, the WHO recently reported that depression is the leading cause of disability worldwide. That’s 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 antidepressants 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. Ora 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 recently in the journal 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.

This is just the latest in a new line of research aimed at developing more effective, rapid-acting antidepressants. In April, researchers at the University of Texas Southwestern Medical Center uncovered an important mechanism by which ghrelin — a natural antidepressant hormone — works inside the brain. The researchers found that the hormone can trigger the formation of new neurons, known as neurogenesis, in the hippocampus — the brain region that regulates mood, memory and complex eating behaviors. Furthermore, they found that this process is imperative to reduce the severity of depression after prolonged stress exposure. The research team also uncovered a neuroprotective drug that they say has the potential to be a powerful treatment for depression.

In another exciting breakthrough, also from UT Southwestern Medical Center, researchers found that by blocking NMDA receptors with the drug ketamine, they could elicit rapid antidepressant effects in patients with treatment-resistant depression. Developing rapid-acting antidepressant medications would have enormous implications for those suffering from depression. Current drug treatments for depression can take up to 8 weeks to reach full effect, which is clearly inadequate for those at immediate risk of suicide. Furthermore, many people with severe depression must try several different types of antidepressants before they find the type that works for them. This process can take many months — even years in some cases. That's why researchers are excited about recent findings indicating that ketamine and similar medications — like memantine — could be used for immediate alleviation of depression symptoms.