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New Molecules Precisely Target Mutant Disease Gene: Weizmann Institute of Science

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These molecules may prevent only some of a crucial gene's activities without affecting others

When Weizmann Institute of Science's Prof. Rivka Dikstein set out to study a gene regulating inflammation, she had no idea she'd find a promising route to developing a drug for Huntington's disease.

Dikstein's team, in the Biomolecular Sciences Department, focused on a gene called Spt5, which regulates transcription, or the copying of DNA for manufacturing proteins. The scientists discovered that Spt5 plays a key role in inflammation: Unlike other inflammatory genes that take hours or even days to produce their effects, this gene triggers a rapid inflammatory response within minutes.

At around the time of these studies at Weizmann, scientists elsewhere uncovered yet another function of Spt5: the role it plays in Huntington's disease, a devastating inherited disorder caused by an excessive repetition of a DNA segment in the gene called "huntingtin."

Expression of the mutant huntingtin gene leads to the manufacture of an abnormal protein that gradually damages the brain, causing progressive neurological decline and ultimately death. Spt5 was found to bind to a partner protein, which, in turn, promotes the expression of the mutated form of the huntingtin gene. Dikstein had the idea that administering drugs that block the activity of Spt5 might prevent the mutated gene from being expressed – possibly providing a previously unexplored approach to treating Huntington's.

In their latest research published in Molecular Cell, Dr. Anat Bahat, a staff scientist in Dikstein's team, searched for small molecules that could stop Spt5 activity. They screened about 100,000 small molecules and identified 18 that bind to Spt5 directly. The Spt5 gene encodes a large protein with numerous binding sites, and these 18 molecules bound to the protein in different ways. Several of these molecules inhibited all known Spt5 activities, but interestingly, a few selectively affected only individual ones. In particular, two of the molecules blocked the expression of the mutated huntingtin gene without affecting either the normal huntingtin gene or the inflammatory genes Spt5 regulates.

This blockage has presently been demonstrated in experiments performed on mouse neurons in laboratory dishes. If these findings are further supported by studies in animals and later in humans, they may lead to the development of a drug that will help to treat or even prevent Huntington’s disease.

Dikstein said, “Selective biological effects of the small molecules may help us target certain aspects of Spt5 activity without affecting others. These molecules may help develop drugs against inflammation and against Huntington’s disease, and they can serve as tools for further studying Spt5’s function.”

Indeed, using these molecules, Dikstein’s team has already discovered additional, previously unknown regulatory functions of Spt5. It turns out that this gene is involved in controlling cellular proliferation, and that it regulates a metabolic hormone that controls appetite and body weight. These findings open up new directions of research with potential future applications.

The research team included Or Lahav of Biomolecular Sciences Department, Dr. Alexander Plotnikov of the Nancy and Stephen Grand Israel National Center for Personalized Medicine and Dr. Dena Leshkowitz of Weizmann’s Life Sciences Core Facilities Department.

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