NEUROLOGIC DISORDERS NEWS ARTICLE

TDP-43 screen identifies potential therapeutics for ALS and frontotemporal dementia

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Investigators at the University of California San Diego reported in *Neuron* on the development of a chemical screen that identified small molecules from a set of mostly at least FDA phase I-approved therapeutics that could prevent the clumping of TDP-43 without toxic effects in amyotrophic lateral sclerosis (ALS) cells.

As post-mitotic cells that for the most part never divide from youth to death, neurons are particularly vulnerable to the accumulation of misfolded persistent protein aggregates that can ultimately cause a variety of tissue-particular neurodegenerative diseases, like ALS and frontotemporal dementia (FTD).

Other cells like the liver or the muscle continually divide, and so they can remove and take out the trash, but most neurons are the same throughout the course of a lifetime.

Mutations in proteins such as FUS, HNRNPA2B1 or TDP-43 are implicated in hereditary forms of ALS and FTD, both of which are fatal diseases characterized by progressive degeneration of cortical and motor neurons for which there is no cure or treatment.

Researchers performed cell-based assays targeting TDP-43 clumps since ALS is characterized by the accumulation of TDP-43 associated with RNA in protein clumps or aggregates.

Principal investigator Eugene Yeo told *BioWorld Science*, "We have elucidated a vulnerability in the process of protein RNA sequestration in these cells and motor neurons of ALS patients. So we have found a point of vulnerability that we can leverage to achieve a potential therapeutic strategy to be able to develop small molecule compounds that may have benefit to ALS and FTD patients."

Yeo, who is a professor of cellular and molecular medicine at the University of California at San Diego, and his team have been working for more than a decade on studying RNA processing in human cells. Their goal is to understand the roles of proteins that interact with RNA play in normal development and how they go awry to lead to many forms of genetic and sporadic diseases. They have studied the basics of how RNA molecules are processed, stabilized,

modified, spliced or transported in cells and particularly in neurons as a way to leverage their basic understanding of these processes to develop new therapeutic approaches.

As post-mitotic cells, meaning that they're not dividing, neurons are particularly sensitive to fluctuations in RNA defects or processing defects and Yeo thinks this a major reason why these pathogenic protein accumulations are so distinctly neuronal as contrasted against other tissues, such as muscle or liver. Yeo emphasized that neuronal cells by and large are no longer dividing, so neurons do not have any real opportunity to discard persistent aggregates just by dividing.

Yeo emphasized that because most neurons live as long as their owners, they accumulate damage and environmental issues that can lead to changes, particularly in the RNA content that then produces toxic proteins.

During aging, neurons lose the ability to deal with these toxicities in robust ways and that can lead to dysfunction of neurons, neuroinflammation, and many other issues.

By passing phase I trials, these molecules the team used in their screening have passed. During the screen they did not select for compounds that kill the cells and when the researchers validated the compounds in secondary assays, they treated the cells with compounds for a very long time, so the ones that are toxic are also discarded. Next they will perform in vivo evaluations starting with flies and mice models. There is a lot of chemistry that can be done to make these compounds so that they are even safer and are more bioavailable, Yeo said.

In principle, this serves as an initial platform for next-gen compounds that can target this vulnerability in this accumulation and persistence. Most importantly this is a conceptual framework for which Fang and co-investigators are proposing and showing proof of concept that protein:RNA aggregates can be used as an assay for finding new therapeutic entities, according to Yeo. Also, Yeo pointed out they can leverage this to find compounds that can be a good starting point for medicinal chemistry efforts.

The compounds Yeo and his team have identified enhanced survival of mouse neurons in a dish that express aberrant protein and they seem to retain an ability to function as if they were normal at least in a dish according to Yeo.

Next, the researchers are moving ahead to proof-of-concept studies in mouse models of neurological disease. They also plan additional medicinal chemistry to look at making more palatable forms of these compounds and are looking to get more funding from the NIH and maybe commercial sources to be able to continue to do this work with patients.

(Fang, M.Y. et al. Neuron 2019, Advanced publication).