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FIRST STEP IN TREATING SOME NEURODEGENERATIVE DISORDERS

Relevant for: Science & Technology | Topic: Biotechnology, Genetics & Health related developments

Naked: Unlike other structures in the cell, the RNA granules are not covered and confined by a membrane.

Dive into the cytoplasm of any cell and one comes across structures made of messenger RNA (mRNA) and proteins known as RNA granules, in general. Unlike other structures in the cell (such as mitochondria), the RNA granules are not covered and confined by a membrane. This makes them highly dynamic in nature, thereby allowing them to constantly exchange components with the surrounding.

RNA granules are present in the cytoplasm at low numbers under normal conditions but increase in number and size under stressful conditions including diseases.

A defining feature which does not change from one organism to another (conserved) of the RNA granule protein components is the presence of stretches containing repeats of certain amino acids.

Such stretches are referred to as low complexity regions. Repeats of arginine (R), glycine (G) and glycine (G) — known as RGG — are an example of low complexity sequence.

Messenger RNAs are converted to proteins (building blocks of the cell) by the process of translation. RNA granules determine messenger RNA (mRNA) fate by deciding when and how much protein would be produced from mRNA. Protein synthesis is a multi-step and energy expensive process.

Therefore, a common strategy used by cells when it encounters unfavorable conditions is to shut down protein production and conserve energy to deal with the stressful situation. RNA granules help in the process of shutting down protein production.

Some RNA granule types (such as Processing bodies or P-bodies) not only regulate protein production but also accomplish degradation and elimination of the mRNAs, which in turn helps in reducing protein production.

In recent years, a strong link has emerged between RNA granules and neurodegenerative disorders such as Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD). The proteins implicated in these diseases such as ewing sarcoma breakpoint region 1 (EWSR1) and fused in sarcoma (FUS) are RNA binding proteins that can reside in RNA granules.

These above-mentioned proteins also contain low complexity sequences (repeats of amino acids) that are important for their movement into RNA granules.

In fact, these proteins are deposited as insoluble granules/aggregates in the neurons of ALS and FTD patients which are believed to contribute to the pathophysiology of these diseases. Finding ways of solubilising these aggregates could provide a breakthrough in treating these diseases.

Our group studies how RNA granules form and subsequently fall apart. A recent work from our lab published in *Nature Communications* has identified a protein (Sbp1) as a factor that

dissolves the RNA granules (P-bodies).

This work, led by a PhD student Raju Roy, makes a surprising yet insightful conclusion that low complexity sequences (containing repeats of arginine (R) and glycine (G) amino acids — RGG) which normally promote granule formation, in this case promote the disintegration of RNA granules in yeast cells.

Mr. Roy further observed that the identified protein Sbp1 is specific for dissolving P-bodies and not stress granules which are related RNA granule type also present in the cytoplasm.

We predict that our observation is the tip of the iceberg and there are likely to be several such factors in the cell which may dissolve specific granule types.

Often insightful results pertaining to fundamental cellular processes obtained using elegant yet simple model systems such as yeast are not given the importance they deserve. This is because of the popular notion that these studies may not be relevant enough for ‘complex’ humans.

We focused on using yeast for our studies because it is a simple model organism that is easy to work with and genetically manipulate in the laboratory. Importantly, many seminal discoveries pertaining to several cellular processes were made in yeast and subsequently found to be true in humans as well. This indicates that knowledge obtained from yeast is very often applicable to humans.

The next step was, therefore, to investigate whether our finding was relevant for human proteins. Gitartha Das, a co-author of the study wondered if Sbp1 (which could dissolve P-bodies) could help in reducing the aggregates of human proteins involved in neurodegenerative disorders. EWSR1 protein aggregates have been implicated in diseases such as ALS and FTD. We expressed human EWSR1 protein in yeast cells and observed that it formed aggregates.

Further experiments indicated that Sbp1 protein was important for reducing these EWSR1 aggregates, indicating that what we learned using yeast is likely to be true in the context of humans. This study has highlighted the potential of amino acid repeats (RGG) as a therapeutic intervention. We are excited about this possibility and are gearing up to experimentally test the effect of repeat sequences in genetically engineered mice that accumulate insoluble pathological aggregates in brain cells.

At the onset, the aim of this study was not to look for possible interventions for neurodegenerative disorders. Instead, the study was driven by our quest for answering a simple but powerful fundamental question about how RNA granules fall apart. An important and satisfying take-home message from this study is that asking and addressing fundamental questions in science is equally important as doing ‘applied’ research.

(Purusharth I. Rajyaguru is Associate Professor, Department of Biochemistry at IISc Bangalore)

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