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> ONE MONTH, ONE PROTEIN <

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on the benefits of disorder

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Like rules, paradigms are liable to be broken. By the beginning of this century, the 'one gene - one protein' paradigm had begun to shift as scientists grasped the realm of mRNA splicing and post-translational modifications. Today, we know that one gene may give rise to several amino-acid sequences which can be further modified on their surface. Each of these events produces a protein with a different function. Another paradigm is the 'structure - function' paradigm, where a protein's function is defined by the fold it adopts in space, itself dictated by the underlying amino-acid sequence. However, early on in 2000, scientists were observing regions on a protein, which seem to adopt no particular 3D conformation at all but, instead, several conformations depending on the environment. These peculiar regions have since been termed 'disordered regions'. As an illustration, disordered regions located in a protein known as YTHDF are involved in the formation of stress granules when a cell is under some kind of pressure.

Kazimir S. Malevich (1879 -1935)

Stress granules are minute bodies that form in a cell's cytosol, much in the way droplets of vinegar form when added to olive oil. They have no membrane but an outer shell formed by proteins – perhaps, even, by YTHDF proteins themselves. Stress granules are dense, and composed of different kinds of protein and messenger RNA (mRNA) which has not been translated, or whose translation has been interrupted for one reason or another. Though the true purpose of stress granules remains to be understood, biologists believe they provide a means of protecting mRNA from harm brought about by heat-shock or oxidative stress for instance. However, they may also form simply to store mRNA, or perhaps to degrade it or even re-initiate it.

What exactly is mRNA? In a nutshell, mRNA holds the information needed to synthesise a protein sequence. It is a copy of a gene, which is a stretch of DNA. Since DNA remains in the cell nucleus so as not to be damaged, and protein synthesis occurs outside the nucleus, the best way to get the information from one side of the nucleus to the other is by way of a messenger: mRNA. This sounds straightforward enough, but just two sentences to express this complex process tarnishes the enthusiasm, excitement and time it took to understand it.

The notion that DNA produces RNA which ultimately leads to proteins was suggested as early as 1947. Scientists knew that ribosomes were loaded with RNA, and hypothesised that the combination formed a physical template on which proteins were moulded. As a consequence, it was thought that each protein had its own ribosome. As knowledge accumulated over the years that followed – with the elucidation of the structure of DNA in the early 1950s and the cracking of the genetic code soon after – the notion of 'biological information' emerged.

Information was somehow travelling from the nucleus to the ribosomes. But how? mRNA turned out to be the answer. mRNA transfers the information from the nucleus to the cytosol, and presents it to ribosomes that read it, as you would a recipe, to synthesise a protein.

Like DNA, mRNA must not undergo damage either. Faulty mRNA can be detrimental to cells and even cause diseases. Stress granules are one way of protecting mRNA, although they do not form as spontaneously as droplets of vinegar do in oil. The proteins which make up stress granules – as too the stretches of mRNA – must be able to recognise each other and then interact to aggregate. These interactions are prompted by specific domains on the protein sequences but also by certain modifications made to the mRNAs. In particular, a type of methylation known as N^6-methyladenosine (m^6A) modification. m^6A modification is an epigenetic modification of great importance; it is the most abundant and conserved modification in eukaryotic RNA and occurs not only on mRNAs but also on transfer RNAs, circular RNAs, ribosomal RNAs and micro RNAs to name four. m^6A modification is used to literally tune different RNAs to play various roles in many essential biological processes such as cell differentiation and tissue development for example. As for mRNA, in particular, multiple m^6A modifications seem to act as a scaffold for YTHDF proteins as the stress granules form.

YTHDF proteins recognise sites of multiple m^6A modifications on mRNAs by way of a domain on their sequence known as the YT521-B homology domain, or YTH domain. As mentioned above, m^6A modifications provide a scaffold for YTHDF proteins. However, you need more than just a scaffold to shape stress granules – and this is where these peculiar parts of a protein sequence known as 'disordered regions' come in. YTH domains are located on one end of YTHDF proteins, while disordered regions are located on the other. As YTHDF proteins cling onto the 'm^6A scaffold' on mRNAs, their disordered regions end up by meeting, to eventually make contact and interact. This leads to what is called 'phase separation' – that is to say the creation of bodies such as stress granules in the cell cytosol. Considering this phenomenon, scientists suggest that m^6A modification may actually provide a means of regulating cytosolic mRNA, and hence gene expression. Besides interacting with mRNA and each other, YTHDF proteins are also expected to interact with other stress granule proteins to produce even more compact stress bodies.

As far as current knowledge goes, stress granules seem to form to protect mRNA by putting it on hold for a while, or perhaps simply to degrade it. Whichever way you look at it, it all has to do with gene expression and its timing. Cells continue to divulge the myriads of ways they have of regulating gene expression, or indeed protecting it; the combination of m^6A modification, YTH domains and disordered regions is just another example. The realm of disordered regions has flung a new perspective on protein structure and function, and constitute a fascinating field of research. Such regions demonstrate Nature's ubiquitous inventiveness and how, over the course of time, she has found ways to multiply a protein's skills as economically as possible. Moreover, there is reason to believe that stress granules, and in particular their dynamics, are associated with neurodegenerative disorders and various cancers for instance – which makes them ideal therapeutical targets.

Cross-references to UniProt

YTH domain-containing family protein 1, *Homo sapiens (*Human*)* : Q9BYJ9
YTH domain-containing family protein 2, *Homo sapiens (*Human*)* : Q9Y5A9
YTH domain-containing family protein 3, *Homo sapiens (*Human*)* : Q7Z739

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