Protein production in differentiating stem cells is more complex than previously thought

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Tweaks in the sequence of messenger RNAs (mRNAs) can influence their rate of protein production, A*STAR researchers have shown. This process is important for how embryonic stems cells (ESC) differentiate into other tissue types.

ESCs are cells in an embryo that can develop into any tissue in the body. Their differentiation into other cell types is controlled by protein production through regulating the expression of the genes that encode the proteins.

Ribosomes are molecular machines that translate mRNA sequences into proteins. A single gene can produce many different mRNA variants through an editing process called RNA 'splicing'. Many of these mRNA variants produce similar but different protein variants. mRNAs contain a coding region that has an 'untranslated region' (UTR) on either end that regulates protein synthesis.

"We set out to determine how changes in the mRNA UTR sequences after splicing influence the rate at which mRNA variants are translated into proteins," explains Leah Vardy from the A*STAR Institute of Medical Biology.

By comparing the rate at which mRNA splice variants were translated into proteins in ESCs and neural precursor cells (NPCs), a cell type into which ESCs can differentiate, Vardy's team found that small changes in the mRNA sequence generated during splicing influence the rate of

protein production of these variants. This made a big difference to their respective protein levels.

"We already knew that UTRs controlled the rate of translation, but have now shown that different splice variants within the same cell can also be translationally regulated through variations in their UTRs," says Vardy.

The researchers used RNA sequencing to determine the translation rates of different variants based on the numbers of ribosomes attached to mRNAs. Those with a high load of ribosomes were considered more highly translated.

The team found, for example, 31 different genes that showed variant-specific changes in translation rates in ESCs and NPCs. They also found that, in ESCs, 10 per cent of mRNAs with multiple variants had different translation rates for each variant. The different translation rates correlated with differences in the UTR sequences, which the researchers believe are behind the variation in translation rates.

"These findings confirm an added level of complexity where different splice variants from the same gene can be translated into proteins at very different rates within the same cell," says Vardy. "This shows that splicing also controls the rate of protein production from specific variants, and not just protein sequence."

The team next plans to identify some of the key regulatory sequences within UTRs to determine how they regulate the translation rate.

More information: Queenie Wing-Lei Wong et al. Embryonic Stem Cells Exhibit mRNA Isoform Specific Translational Regulation, *PLOS ONE* (2016). DOI: 10.1371/journal.pone.0143235