How 'junk DNA' can control cell development

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Researchers from the Gene and Stem Cell Therapy Program at Sydney's Centenary Institute have confirmed that, far from being "junk", the 97 per cent of human DNA that does not encode instructions for making proteins can play a significant role in controlling cell development.

And in doing so, the researchers have unravelled a previously unknown mechanism for regulating the activity of genes, increasing our understanding of the way cells develop and opening the way to new possibilities for therapy.

Using the latest gene sequencing techniques and sophisticated computer analysis, a research group led by Professor John Rasko AO and including Centenary's Head of Bioinformatics, Dr William Ritchie, has shown how particular white blood cells use non-coding DNA to regulate the activity of a group of genes that determines their shape and function. The work is published today in the scientific journal *Cell*.

"This discovery, involving what was previously referred to as "junk", opens up a new level of gene expression control that could also play a role in the development of many other tissue types," Rasko says. "Our observations were quite surprising and they open entirely new avenues for potential treatments in diverse diseases including cancers and leukaemias."

The researchers reached their conclusions through studying introns—non-coding sequences which are located inside genes.

As part of the normal process of generating proteins from DNA, the code for constructing a particular protein is printed off as a strip of genetic material known as messenger RNA (mRNA). It is this strip of mRNA which carries the instructions for making the protein from the gene in the nucleus to the protein factories or ribosomes in the body of the cell.

But these mRNA strips need to be processed before they can be used as protein blueprints. Typically, any non-coding introns must be cut out to produce the final sequence for a functional protein. Many of the introns also include a short sequence—known as the stop codon—which, if left in, stops protein construction altogether. Retention of the intron can also stimulate a cellular mechanism which breaks up the mRNA containing it.

Dr Ritchie was able to develop a computer program to sort out mRNA strips retaining introns from those which did not. Using this technique the lead molecular biologist of the team, Dr Justin Wong, found that mRNA strips from many dozens of genes involved in white blood cell function were prone to intron retention and consequent break down. This was related to the levels of the enzymes needed to chop out the intron. Unless the intron is excised, functional protein products are never produced from these genes. Dr Jeff Holst in the team went a step further to show how this mechanism works in living bone marrow.

So the researchers propose intron retention as an efficient means of controlling the activity of many genes. "In fact, it takes less energy to break up strips of mRNA, than to control gene activity in other ways," says Rasko. "This may well be a previously-overlooked general mechanism for gene regulation with implications for disease causation and possible therapies in the future."

More information: Paper Abstract

Intron retention (IR) is widely recognized as a consequence of mis-splicing that leads to failed excision of intronic sequences from pre-messenger RNAs. Our bioinformatic analyses of transcriptomic and proteomic data of normal white blood cell differentiation reveal IR as a physiological mechanism of gene expression control. IR regulates the expression of 86 functionally related genes, including those that determine the nuclear shape that is unique to granulocytes. Retention of introns in specific genes is associated with downregulation of splicing factors and higher GC content. IR, conserved between human and mouse, led to reduced mRNA and protein levels by triggering the nonsense-mediated decay (NMD) pathway. In contrast to the prevalent view that NMD is limited to mRNAs encoding aberrant proteins, our data establish that IR coupled with NMD is a conserved mechanism in normal granulopoiesis. Physiological IR may provide an energetically favorable level of dynamic gene expression control prior to sustained gene translation.

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