CCLG: The Children & Young People's Cancer Association research:

Investigating the shape of fusion genes in rhabdomyosarcoma

Project title: Investigating the RNA structurome of fusion-positive rhabdomyosarcoma

Project stage: Ongoing (started September 2024, planned end September 2027)

Funded by: CCLG and CCLG Special Named Funds including Pass The Smile For Ben, Be More Ruby, Just George, Team Jake, Jacob's Join, Hattie's Rainbow of Hope, Cohen's Fight and The Jenni Clarke Fund

Led by: Dr Darrell Green, University of East Anglia

About the project

Around 55 children are diagnosed with rhabdomyosarcoma each year in the UK. But unlike adult cancers, which are caused by an accumulation of genetic errors (DNA) acquired over decades, some types of rhabdomyosarcoma are caused by a single genetic fault.

Around 25% of patients with rhabdomyosarcoma have a genetic error where two normal genes have fused together to become one abnormal gene. This fusion causes the cancer. This is known as the 'fusion-positive' subtype and has the worst survival rates. Fusion-positive rhabdomyosarcoma patients have one of two fusion genes, PAX3::FOX01 or PAX7::FOX01.

These fusion gene errors make abnormal instructions for proteins. More than just sequences of the genetic code, these instructions (called mRNA) also fold into complex 3D shapes. The correct shapes are critical for producing the protein.

Dr Darrell Green at the University of East Anglia has recently discovered that the 3D shapes of fusion gene mRNA are a central driver of fusion-positive rhabdomyosarcoma. He believes this could be critical in understanding how the cancer develops, spreads around the body, and responds to treatment. In the future, he hopes to create targeted medicines that can affect the 3D mRNA so that it can no longer produce the cancer-causing protein.

In this project, Dr Green hopes to confirm the importance of 3D shape and discover what changes between different fusion genes and in different patients. His research team will:

1. Create the world's first 3D computer models of the shape of the two fusion genes.
2. Compare the tumours of each variant in lab models and patient samples to see how the mRNA's 3D shape affects the cancer's spread around the body.
3. Look at whether shape-modifying medicines can stop the tumours from spreading.

The 3D models will be invaluable for companies developing and testing new shape-modifying drugs to treat gene mutations. Because the drugs would target fusion genes, which only the cancer cells have, Dr Green hopes that there would be no damage to healthy cells. The long-term goal for this project is to deliver a Phase 1 clinical trial of a new fusion gene targeting drug within five years.

Progress

Researchers used a special mapping method to look at the shapes the PAX3::FOX01 fusion gene's mRNA. They discovered that the fusion gene is unusual because the mRNA folds multiple times and binds to itself – which the researchers didn't find in other cancer fusion proteins. This suggests that cancer cells produce the mRNA in a number of different forms/shapes, which could impact cancer survival and spread differently. Simply reducing the amount of the fusion protein might therefore not have the intended effect (improving survival) as it might only reduce the amount of less dangerous forms. The team believe that this means any new treatments targeting the fusion gene needs to entirely wipe it out, not just reduce the levels.

The team are now using genetic engineering techniques to modify rhabdomyosarcoma cells so that they lack the key enzymes they need to build the folded PAX3::FOX01 3D mRNAs. This should show whether a treatment that knocks out all fusion gene mRNA shapes would be a viable treatment for further research.

What's next?

The next step is to test the modified cancer cells that can't build PAX3::FOX01 3D mRNAs. The team believe that the loss of the enzyme will lead to predict that the mRNA structure 'unravelling', so the cell will no longer be able to produce the cancer-promoting protein.

The researchers have faced some delays, so have currently only investigated one form of the PAX3::FOX01 gene. They also hope to investigate the other form of PAX3::FOXO1, plus the forms of PAX7::FOX01, in the near future.

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