

A Closer Look: the FA Pathway

What is the FA pathway and why does it matter?

The “FA pathway” is a complex, multi-step cascade of genes that protects our cells from chromosomal damage. More than 22 healthy FA genes are required for this pathway to function. When any one of these genes is defective, the pathway fails and the consequence is disease.

At the 2017 Scientific Symposium, 15 presentations were dedicated to the FA pathway (almost a third of all presentations), as well as 19 poster presentations (over a quarter of all posters). This reflects the interest in and importance of understanding the pathway. Every time scientists learn more about the FA pathway, or other pathways that affect FA, we learn more about how the disease operates. This knowledge opens the door for the development of specific, targeted therapies that may one day turn FA into a very manageable condition.

What pathway-related work are scientists carrying out?

Dr. Jung Eun Yeo of South Korea is studying how two different FA genes that were thought to work together to promote DNA interstrand crosslink (ICL) repair actually share some roles and operate separately for others. These experiments used CRISPR/Cas9 gene editing techniques to knock out specific genes whose functions these scientists wanted to examine. They discovered that FANCD2 and FANCI act in concert during DNA ICL repair, but they function separately to accomplish other important tasks. This kind of information shows that FA patients of complementation groups FA-D2 and FA-I may have different responses to current treatments. Understanding better the roles of these and other FA

proteins will be crucial to developing personalized strategies in the treatment of FA.

Sylvie van Twest, working with Dr. Andrew Deans at St. Vincent’s Institute of Medical Research in Australia, developed a biochemical system that can analyze the functional impact of any FA mutation. Their analyses may one day be able to predict the severity of symptoms and, once again, develop more effective personalized treatments.

Dr. Anna Motnenko of the United Kingdom explained how her work in Dr. Martin Cohn’s lab has identified a particular protein, UHRF2, which is a sensor for interstrand crosslink repair. This protein is necessary for recruitment of FANCD2 at sites of DNA damage. Thus it is important for activation of the FA pathway. This study illustrates one of the many links between FA and cancer, in that the protein they have identified is frequently deregulated in various cancers. When FA scientists study it, their discoveries may wind up pushing

the boundaries of cancer research and helping cancer patients worldwide.

In addition to the FA pathway, FA scientists are discovering that other pathways may also repair interstrand crosslinks. Dr. Dan Semlow of Harvard described the discovery of one such pathway, which operates before and instead of the FA pathway, with the FA pathway serving as back up. Dr. Puck Knipscheer of the Netherlands described a possible third pathway. This new information about additional pathways for DNA repair is extremely important and suggests novel approaches for developing new FA therapies.

Therapeutic applications are on the horizon. Dr. Lauren van Wassenhove of Stanford described how certain small molecule activators of an enzyme that detoxifies aldehydes might be able to prevent or delay bone marrow failure, leukemia, and other cancers in people with FA.

The bottom line is that these studies of the FA pathway and other pathways acting in concert hold great promise in the development of personalized treatments that may be able to reverse or prevent the DNA damage that is at the heart of FA. At FARF we are pushing hard to accelerate this research that is happening all over the world, and to promote the development of the therapies suggested by these discoveries. ■

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