DNA Repair in Mammal Embryos Is a Matter of Timing

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Investigators at St. Jude Children's Research Hospital have discovered that the cells of the developing nervous system of the mammalian embryo have an exquisite sense of timing when it comes to fixing broken chromosomes: the cells use one type of repair mechanism during the first half of development and another during the second half.

The team also showed that blocking a repair pathway causes the cell to commit suicide, a process called apoptosis; and that preventing this attempt at apoptosis keeps the damaged cell alive and able to become cancerous. Moreover, the type of cancer that develops depends on which repair pathway was originally disrupted.

These findings reflect the meticulous timing of an important aspect of embryo development and help to explain the origin of a variety of cancers from muscle tumors to brain tumors, researchers said. A report on these results appears in the online prepublication issue of *Proceedings of the National Academy of Science*.

Specifically, the St. Jude researchers showed that the DNA repair pathway called homologous recombination (HR) works primarily during the first half of embryo development, when many cells are dividing inside the growing body. In contrast, the pathway called non-homologous end joining (NHEJ) becomes an important repair mechanism midway through development, when cells begin to assume their final form and take on specific roles.

HR and NHEJ repair a type of DNA damage called a double-strand break (DSB), which cuts completely through the DNA. DNA exists as two individual strands that associate to form its double-stranded, twisted-ladder—shaped structure.

The researchers also discovered that a protein called ATM is required for apoptosis that is triggered by blocking NHEJ. However, apoptosis triggered by blocking HR does not require this protein. ATM is a critical DNA damage-signaling factor that is required to prevent a severe human neurodegenerative syndrome called ataxia telangiectasia. This new work points to the specific DNA repair pathway that ATM is required to monitor in order to prevent neurodegeneration.

The HR pathway fixes a broken chromosome by using that chromosome's exact "twin" as a blueprint to guide the repair job, according to Peter McKinnon, Ph.D., an associate member of Genetics and Tumor Cell Biology at St. Jude and senior author of the PNAS paper. However, such twins only exist in cells that are preparing to divide into two new cells, a process called mitosis, he noted. Then, as the cell starts to divide, each member of the sister chromatid pair moves into a different new cell.

Because HR is active only during the first half of embryo development, it is the critical repair pathway for the rapidly multiplying precursor and stem cells—cells that populate the body during early development with "daughter" cells—that later take on specific roles, according to researchers.

"Therefore, if HR-related apoptosis is blocked during the early part of embryo development, precursor and stem cells are affected. And since those cells give rise to many different types of cells and tissues, many different types of cancers can arise, such as skin cancer and sarcomas (cancers of bone, cartilage, fat, muscle or blood vessels)," McKinnon

said.

But as cells acquire specialized structures and functions, they stop dividing and no longer produce sister chromatids. “When cells begin assuming specific roles in the brain, they stow away most of their chromosomes into tightly wrapped strings of DNA and use only those genes required to survive and allow them to perform these roles,” McKinnon explained. “In the absence of sister chromatids to use as blueprints, the NHEJ repair pathway uses various chemical means to join the broken ends of DNA strands.”

Since the cell uses NHEJ only when many cells are becoming specialized, cancers that arise in the absence of this pathway are more specific, such as cancer of a type of cell that produces only immune cells called B lymphocytes. The wide variety of cancers that can form represents the fact that HR and NHEJ are important throughout the developing body, and not just in the developing nervous system.

An intriguing exception to the timing of HR and NHEJ during nervous system development is the development of medulloblastoma, a tumor in children that arises in the lower part of the brain called the cerebellum, McKinnon said. The infant cerebellum is still undergoing both rapid growth in the number of cells as well as specialization of many cells, he noted. “That means this part of the brain uses both HR and NHEJ to repair broken chromosomes, so disruption of either mechanism can cause cancer in this area of the brain.”

The St. Jude team studied the roles of the two repair pathways using mice that lacked either the gene Xrcc2, which is critical for the HR pathway, or Lig4, which is critical for the NHEJ pathway.

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Source: St. Jude Children's Research Hospital