Researchers dispute widely held ideas about stem cells

August 29 2007

How do adult stem cells protect themselves from accumulating genetic mutations that can lead to cancer? For more than three decades, many scientists have argued that the "immortal strand hypothesis" - which states that adult stem cells segregate their DNA in a non-random manner during cell division -- explains it. And several recent reports have presented evidence backing the idea.

But in this week's issue of the journal *Nature*, University of Michigan stem cell researcher Sean Morrison and his colleagues deal a mortal blow to the immortal strand, at least as far as blood-forming stem cells are concerned.

They labeled DNA in blood-forming mouse stem cells and painstakingly tracked its movement through a series of cell divisions. In the end, they found no evidence that the cells use the immortal-strand mechanism to minimize potentially harmful genetic mutations.

"This immortal strand idea has been floating around for a long time without being tested in stem cells that could be definitively identified. This paper demonstrates that it is not a general property of all stem cells," said Morrison, director of the Center for Stem Cell Biology at the U-M Life Sciences Institute.

It remains possible that stem cells in other tissues use this process.

"We've been able to show that this is not a mechanism by which blood-

forming stem cells reduce their risk of turning into cancer and, presumably, we should be looking elsewhere to understand what those mechanisms really are," he said.

Stem cells generate all of the tissues in the developing human body, and later in life provide replacement cells when adult tissues are damaged or wear out.

Adult stem cells continue to divide throughout a person's life, replenishing the supply of stem cells while generating other cells that develop into specialized tissues – muscles, nerves or blood, for example.

Like most cells in the body, adult stem cells divide through mitosis, the process of duplicating the chromosomes and distributing a complete set to each of two daughter cells.

During mitosis, the double-stranded DNA molecule splits into two complementary ribbons of genetic material. Each of the original strands is then used as a template to build two double helixes.

DNA encodes genetic information using a four-letter alphabet. Each time a new strand is assembled alongside the template strand, there's a chance that an incorrect genetic letter will be inserted in the new strand, causing a mutation that could lead to cancer.

The immortal strand hypothesis, proposed in 1975, suggests that dividing adult stem cells always retain the older, or "immortal," template strand. The new, mutation-prone strand goes to daughter cells that give rise to specific tissues.

This non-random distribution process is known as asymmetric chromosome segregation. Adult stem cells use it to minimize their chances of accumulating harmful mutations, according to the immortal

strand hypothesis.

To test this idea, Morrison's team administered a DNA-labeling substance called BrdU to mice for several days, giving the DNA time to incorporate the label. Then they extracted the blood-forming stem cells to see how many of them retained BrdU.

If the immortal strand hypothesis is right about asymmetric segregation, then under certain experimental conditions the adult stem cells should hold onto the BrdU label.

"What we found is that not many stem cells retained it," said Morrison, a Howard Hughes Medical Institute researcher.

"In fact, what happened with the label was completely consistent with what you'd expect by random chromosome segregation – which is known to be how most cells divide – and was completely inconsistent, in every context we looked, with the immortal strand model."

The experiments also revealed that BrdU is not the general-purpose stem-cell marker many researchers thought it was.

Some scientists have assumed that BrdU-retaining cells found in a variety of tissues are stem cells. But Morrison and his colleagues are the first known to carefully measure stem cell purity among BrdU-retaining cells, and they found it to be "a very insensitive and nonspecific marker."

The Nature paper will be published online Aug 29. The lead author is Mark Kiel of the U-M Life Sciences Institute, the U-M internal medicine department, the U-M Center for Stem Cell Biology, and the Howard Hughes Medical Institute.

"This study suggests that researchers should test BrdU label retention as a marker before assuming it can be used to identify stem cells in other tissues," Kiel said.

Source: University of Michigan