

# Smurf2 Regulates DNA Repair and Packaging to Prevent Tumors

The blueprint for a cell's functions is written in the genetic code of DNA sequences as well as in the landscape of DNA and in histone modifications. DNA is wrapped around histones to package it into chromatin, which is stored in the nucleus. It is important to maintain the integrity of the chromatin structure to ensure that the cell continues to behave appropriately. Recently, Ying Zhang, Ph.D., in CCR's Laboratory of Cellular and Molecular Biology, and her colleagues showed that alterations in the organization of DNA can lead to tumor growth in a variety of tissues. This study appeared in the February 2012 issue of *Nature Medicine*.

To understand how cancer cells might acquire changes in the chromatin landscape, Michael Blank, Ph.D., a Postdoctoral Fellow in Zhang's lab, investigated the role of the protein Smurf2. Previous studies have demonstrated that Smurf2 functions as an enzyme that adds a tag, called ubiquitin, to proteins to signal their destruction, but there is only scant information about whether Smurf2 has any role in cancer.

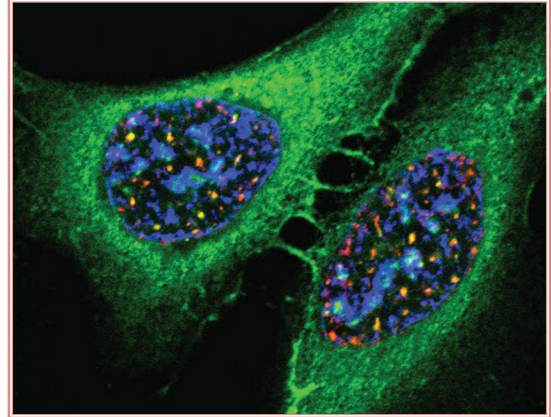
The researchers generated a mouse model in which they prevented Smurf2 expression (*Smurf2*<sup>-/-</sup>). *Smurf2*<sup>-/-</sup> mice develop normally and have no obvious physical problems early on. However, tumors begin to grow in a variety of tissues as the mice age, suggesting that Smurf2 may play a role in preventing tumor formation.

Therefore, the researchers studied cells from normal mice and from *Smurf2*<sup>-/-</sup> mice. Over time, the *Smurf2*<sup>-/-</sup> cells began to grow faster and expressed genes distinct from the normal cells. *Smurf2*<sup>-/-</sup> cells

also formed tumors when injected into mice. Re-expressing Smurf2 in the *Smurf2*<sup>-/-</sup> cells did not correct their altered growth and indicated that changes in the cells' DNA may have already occurred. Other studies indicated that Smurf2 plays a role in regulating the DNA damage response and the packaging of DNA.

The addition of certain molecules to histones allows DNA to wrap more or less tightly around histone proteins. The researchers found that certain histone modifications were increased in *Smurf2*<sup>-/-</sup> cells and that Smurf2 can directly target the protein RNF20 for destruction by adding ubiquitin. Decreasing the levels of RNF20 in *Smurf2*<sup>-/-</sup> cells decreased the histone modification, increased DNA packaging, and decreased cell growth. Expressing RNF20 in normal cells increased their growth rate. The researchers also found that Smurf2 and RNF20 move to sites of DNA damage where Smurf2 decreases the level of RNF20. These results show that Smurf2 plays an important role in tumor formation in the mouse by regulating RNF20, which controls the DNA damage response and DNA packaging. But is the same pathway important in human tumors?

To address this question, the researchers examined a number of human tumor cell lines. Similar to mouse cells, they found that removing Smurf2 resulted in increased RNF20 levels and its associated histone



(Image: M. Blank, CCR)

Following DNA damage, Smurf2, labeled in green, moves to sites of double-stranded DNA breaks, shown in red. Because Smurf2 regulates a cell's response to DNA damage at these sites as well as the organization of the DNA in the nucleus, loss of Smurf2 may promote tumor formation.

modification, while loss of RNF20 increased DNA packaging. In a panel of 40 breast tumors, the investigators found that 32 tumors expressed high levels of RNF20 protein. A set of 55 lymphomas showed similar elevated levels of RNF20.

This research has shown that human DNA is sensitive to the levels of Smurf2 and RNF20 and that loss of Smurf2 function may contribute to human tumor formation via changes in the DNA damage response and chromosomal organization. Future studies will need to investigate whether inhibiting RNF20 activity or reactivating Smurf2 can prevent tumor formation in human cells.

To learn more about Dr. Zhang's research, please visit her CCR Web site at <http://ccr.cancer.gov/staff/staff.asp?name=yzhang>.