by treating human and mouse cells with DNA-damaging doxorubicin. Mendell’s team focused on NORAD because, unlike many IncRNAs, it was abundant in many tissues, and its sequence was highly conserved between mouse and human.

To probe NORAD function, the researchers inactivated the IncRNA in a human colon cancer cell line and nontransformed human fibroblasts, revealing a surprising phenotype. “All the cells that lose this RNA exhibit a chromosomal instability phenotype, meaning that they have a high frequency of chromosome gain or loss during mitosis,” says Mendell.

The researchers went on to show that NORAD is a major binding partner for PUMILIO proteins, an ancient and highly conserved family of cytoplasmic proteins that repress translation of mRNAs. One molecule of NORAD can bind 15 PUMILIO molecules, resulting in inactivation of PUMILIO.

After DNA damage, NORAD levels are sufficient to sequester most of the cell’s PUMILIO proteins, allowing beneficial expression of target genes involved in DNA replication, repair, and mitosis. In the NORAD knockout cells, increased repression of target genes by PUMILIO proteins leads to mistakes in chromosome handling and aneuploidy.

The work is the first to implicate an IncRNA as well as PUMILIO proteins in the maintenance of chromosome integrity. Whether they play a role in cancer remains to be seen, says Mendell. “We’re interested in whether this pathway is perturbed in cancer, and whether it can influence cancer phenotypes,” he says.

Some clues may lie in already-existing expression data from large-scale tumor genetic projects like TCGA, and his team plans to look at that, Mendell says.

The work “opens a new area of understanding of where chromosome handling might go awry,” says Maxwell Krem, MD, PhD, of the University of Louisville School of Medicine in Kentucky, who was not involved in the new study. Chromosomal instability is associated with disease prognosis and response to treatment, and attacking pathways that regulate genomic stability could become an important addition to standard chemotherapy in the future, he says. –Pat McCaffrey

**Pathway to Chromosomal Instability Revealed**

A recently published study reveals an unexpected role for a long noncoding RNA (lncRNA) in maintaining the proper number of chromosomes in cells (Cell 2016;164:69–80).

Larger cousins of microRNAs, IncRNAs are transcripts of more than 200 nucleotides with no detectable open reading frames, often with unknown function. The new work shows that one IncRNA, dubbed NORAD (noncoding RNA activated by DNA damage) preserves genome stability by promoting expression of genes involved in DNA repair, replication, and mitosis. Loss of NORAD in human cells results in altered chromosome number, a hallmark of cancer cells.

Lead investigator Joshua Mendell, MD, PhD, and colleagues at the University of Texas Southwestern Medical Center in Dallas, set out to identify IncRNAs that regulate the response of cells to DNA damage. They first spotted NORAD among IncRNAs induced by treating human and mouse cells with DNA-damaging doxorubicin. Mendell’s team focused on NORAD because, unlike many IncRNAs, it was abundant in many tissues, and its sequence was highly conserved between mouse and human.

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**Vaccinating against HPV: A Call to Action**

All 69 NCI-designated cancer centers issued a joint statement at the end of January urging health care providers to encourage vaccination against human papillomavirus (HPV).

HPV causes the majority of cervical, anal, vaginal, penile, vulvar, and oropharyngeal cancers. According to the Centers for Disease Control and Prevention (CDC), approximately 79 million people in the U.S. are currently infected with HPV. The FDA has approved three safe and effective HPV vaccines to ward off most HPV-related cancers. However, the vaccination rate in the United States stands at about 30% (40% for girls and 21% for boys), which is not only significantly lower than many other countries—including Australia (75%), the United Kingdom (84% to 92%), and Rwanda (93%)—but falls well short of 80%, the goal set by the Healthy People 2020 initiative (www.healthypeople.gov).

The focus has been on “the virus being sexually transmitted, rather than HPV vaccines preventing cancer,” says Lisa Richardson, MD, director of the CDC’s division of cancer prevention and control. Meanwhile, this stigma has resulted in “a reluctance among many primary care providers to provide a clear, simple recommendation: ‘Now’s the time for your young adolescent to get vaccinated,’” says Robert Croyle, PhD, director of the NCI’s division of cancer control and population sciences.

The vaccine’s efficacy increases the earlier it is given — “it works best in those who haven’t been infected with the virus, which essentially means people who aren’t yet sexually active,” says Gary Gilliland, MD, PhD, president and director of Fred Hutchinson Cancer Research Center in Seattle, WA. As such, children should be vaccinated by age 17, and ideally before they turn 13. However, young men and women up to ages 21 and 26, respectively (who weren’t vaccinated as adolescents), can still protect themselves against infection by completing the three-dose series.

“We’re often asked, ‘When are we going to find a cure for cancer?’” observes Patrick Loehrer Sr., MD, director of Indiana University’s Simon Cancer Center in Indianapolis. “The truth is that the...
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