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NEW YORK (GenomeWeb News) – Researchers from Italy and Japan have identified a set of small, non-coding RNA needed for the effective function of a signaling pathway that's activated in response to DNA damage.

As they reported in *Nature* this week, the investigators got wind of the new non-coding RNA function when they began meddling with the function of two well-known RNA processing enzymes — DICER and DROSHA — in cells with DNA damage caused by cellular processes such as oncogene-related senescence or external factors such as ionizing radiation.

Through a series of related cell line experiments — coupled with Illumina HiSeq and GAIIx RNA sequencing experiments on mouse cells that could be prompted to undergo restriction enzyme-induced DNA damage — the group defined a new set of 22-23 nucleotide-long, double-stranded RNAs that are produced by DICER and DROSHA but have different functional roles than other small RNAs that these enzymes make.

The newly identified non-coding RNAs, dubbed DDRNAs, share sequences with those found at sites of DNA damage, they reported. And rather than going on to participate in RNA interference, these DDRNAs seem to contribute to DDR pathway function in human, mouse, and zebrafish cells through a mechanism that's independent of RNAi.

"All of the RNAs described so far … contribute at multiple levels to regulate the functional organization and expression of the genome," senior author Fabrizio d'Adda di Fagagna, a researcher with Milan's FIRC Institute of Molecular Oncology, or IFOM, and head of that institute's telomere and senescence research program, said in a statement.

"The DDRNA are unique because they safeguard genome integrity," added d'Adda di Fagagna, who is also affiliated with the National Research Council in Pavia. "For an RNA, it is a novel task that broadens the spectrum of the functional versatility so far proven for this type of molecules."

In the absence of these DDRNAs, he and his team reported, the DNA damage response pathway could not perform its characteristic duties — namely, arresting the cell cycle and clustering DNA repair factors around the damaged genetic material in so-called DDR foci following DNA damage. On the other hand, the researchers could reactivate this pathway by adding back DDRNAs or allowing cells to make their own.

The DDRNAs involvement in DNA damage response seems to be distinct from previously characterized RNA interference pathways, which also rely on small, non-coding RNAs produced by DICER and DROSHA, the study's authors explained.

The small RNA role in this process is also intriguing because all of the other DDR pathways components characterized so far have been proteins, the researchers noted. But results of the new study indicate that RNAs in the form of DDRNAs contribute to foci formation by the DDR through interactions with a DNA repair complex containing proteins encoded by MRE11, RAD50, and NBS1.

Those involved in the study say the findings may have implications for understanding genomic stability in the context of both cancer- and normal cellular aging and senescence-related processes.

"This new class of RNA opens a completely new perspective for interpreting the processes of aging and mechanisms of transformation and of tumor progression linked to the generation of DNA damage," d'Adda di Fagagna explained in a statement.

"[W]e will now investigate if the mechanisms of synthesis of these DDRNAs are altered in cancer and the impact that these changes may have on the onset and development of tumors," he added, noting the collaboration between the IFOM in Milan and Pavia's CNR will take advantage of a laboratory based at CNR that was established to specifically study processes related to maintaining genomic stability in the cell.