FONDAZIONE ISTITUTO FIRC DI ONCOLOGIA MOLECOLARE

# PRESS RELEASE

## RNA: from messenger to guardian of genome integrity

**A new and unexpected role for RNA is identified: the defence of genome integrity and stability. A study published today in the prestigious scientific journal *Nature* shows that an until now unknown class of RNA - the newly christened DDRNA - plays a key role in activation of the molecular alarms necessary to safeguard our genome when DNA damage from internal or external factors occurs. The discovery described in the pages of Nature emerges from a study conducted by Fabrizio d'Adda di Fagagna at IFOM in Milan, in collaboration with the CNR in Pavia, the IIT at the IFOM-IEO in Milan and the Riken Omics Science Center in Yokohama, Japan.**
**Given the importance of the cellular DNA damage response in aging, in the repression and control of tumour development, and in therapeutic treatments for cancer, the discovery could open promising interpretive and potentially therapeutic perspectives.**

For decades the scientific community has attributed a role to RNA that is subordinate to that of DNA: the functional processes of expression of genetic information into proteins.
With some known exceptions, such as the classes of tRNA and rRNA involved in the synthesis of proteins, RNA molecules were considered "fleeting" messengers necessary to carry genetic instructions from the nucleus, site of the genome, to the cytoplasm where proteins, the scaffolding of living organisms, are produced.

In recent years, this simplistic view has given way to an increasingly complex scenario, with the identification of new RNA classes involved in numerous cellular events.

One in particular, however, had never been identified or described to date: it is **DDRNA**, a class of **non protein-coding RNAs** that are generated every time the genome is damaged. They originate from the same sequence of DNA damaged and have the essential task of **launching the molecular alarms** through which the cell detects the problem and resolves it by repairing the damage.
**Therefore, the integrity of the genome depends on DDRNA.**

The discovery emerges from a study published online today in the journal Nature and coordinated by Fabrizio d'Adda di Fagagna, head of the "Telomeres and senescence" research program at IFOM (FIRC Institute of Molecular Oncology) in Milan and a researcher at the CNR in Pavia.

DDRNA (DNA Damage Response RNAs), were named precisely for their ability to trigger the cellular DNA damage response and are not simply a new class of RNA that is added to other previously found.

"**All of the RNAs described so far** - says d'Adda di Fagagna - although very different in structure, sequence and mechanism of action, have essentially one thing in common: all contribute, at multiple levels, to **regulate the functional organization and expression of the genome**. The **DDRNA** are unique because they **safeguard genome integrity**. For an RNA, it is a novel task that broadens the spectrum of the **functional versatility** so far proven for this type of molecules."

Therefore, this discovery represents a milestone in the process leading to a significant change in perspective for this area of molecular biology.

Certainly **new sequencing technologies** are contributing to revolutionise the field by unravelling first the genomes of numerous plant and animal species, and then the so-called transcriptome - the entire and specific program of RNA expressed by a cell. The DDRNA described today in *Nature* was identified thanks to the use of advanced genomic technologies, capable of identifying small amounts of RNA, by scientists at IFOM in close collaboration with the team of **Piero Carninci** of the RIKEN Omics Science Center at the RIKEN Yokohama Institute in Japan.

Experiments were conducted at laboratories in Milan and Yokohama that recreated stress conditions capable of generating DNA damage in cultured cells and then the complete set of RNA expressed from the damaged cells was sequenced.

"The results of these analyzes have clearly demonstrated - Carninci comments - that under such circumstances, short RNA molecules are transcribed from the sequence of damaged DNA. This study has very important implications regarding the function of the non-coding RNAs. These RNAs are often considered "genomic rubbish", because in many cases their function is not yet entirely clear. This study demonstrates unequivocally that even short RNA transcripts may play a role in maintaining genome integrity". Further investigations conducted at the IFOM have revealed that cells rely on them to trigger the alarms necessary for the repair of their damaged genomes.

## DDRNA: a barrier against tumour development

The *DNA Damage Response* or **DDR** is the reaction that a cell triggers to maintain its genomic integrity: when a DNA break is detected, the growth and proliferation of damaged cells are temporarily halted, thus avoiding conditions that cause genome rearrangements and mutations that might predispose to cancer or the accumulation of irreparable DNA damage and cause **cellular aging**.

Therefore, this system constitutes a very effective barrier to the uncontrolled cell growth that is typical of tumours.

The experimental journey that led the team of d'Adda di Fagagna at IFOM, composed of Sofia France and Flavia Michelini, to the discovery of DDRNA was inspired by the study of cancer cells: "Analysing these cells - explains Sofia France, first author of this study supported also by the Italian Institute of Technology at the IFOM-IEO Campus in Milan - we realized that when we blocked the production of a specific class of non-coding RNAs, inside the cell nucleus the molecular alarms that signal the presence of DNA damage were extinguished and the DDR mechanism was not activated; consequently, the tumour cells began to proliferate again."

While pursuing research on this never before seen phenomenon, the scientists at IFOM have identified a novel role for RNA as a mediator of the cellular response to DNA damage and, as such, as a suppressor of tumour growth. And not only: the accumulation of DNA damage and persistent activation of the DDR are also associated with cellular senescence and organism aging, processes in which this new class of RNA may play a key role.

Senescence and malignant transformation are in many ways opposite faces of the same coin. For years, d'Adda di Fagagna and his team have been dedicated to studying these two closely linked cellular processes and their association with impaired genome integrity.
Today's discovery reveals another piece of the puzzle that emerges from research conducted by the scientists at IFOM: "This new class of RNA opens a completely new perspective for interpreting the processes of aging and mechanisms of transformation and of tumour progression linked to the generation of DNA damage" says d'Adda di Fagagna. "In particular, we 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 tumours. It is in this direction - continues the scientist - that we will continue our research **in a close collaboration between IFOM and the CNR of Pavia**, where we have recently established a laboratory dedicated to studying the maintenance of genomic stability."

This work was realized with support from, among others, the FIRC (Italian Foundation for Cancer Research), AIRC (Italian Association for Cancer Research), the Human Frontier Science Program and Telethon.

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## The Scientist

Born in Udine in 1966, since 2003 Fabrizio d'Adda di Fagagna has directed the "Telomeres and Senescence" Research Group that he established in Milan at the IFOM (Istituto FIRC di Oncologia Molecolare) upon returning to Italy after 7 years of research activity at the Gurdon Institute in Cambridge, England.
The results of his research – more than 30 – have been published in such prestigious international journals as Science, Nature Genetics and Nature.
In recent years, d'Adda di Fagagna has won several prestigious awards for research results, including the Young Cancer Researcher Award sponsored by the European Association for Cancer Research (EACR), the authoritative international association for cancer research, and the Sapio Prize for Italian Research.
Recently he has also been elected by the European Molecular Biology Organization (EMBO) to its membership, among the few scientists working in Italy to be selected from the international scientific community.
In addition to directing a research group with an international composition at IFOM, in January 2012 d'Adda di Fagagna obtained a position from the National Research Council, to direct a laboratory in Pavia dedicated to studying the maintenance of genomic stability

## The major research previously conducted by the team of Fabrizio d'Adda di Fagagna

***Nature*, 2003:** demonstrating for the first time how the shortening of telomeres - the ends of chromosomes - associated with continuous cell divisions is interpreted by the cell as a DNA damage and triggers a persistent DDR, inducing a non proliferating life state in cells, defined as cellular senescence, to prevent further cell divisions that could compromise the genome integrity.

***Nature*, 2006:** revealing the importance of the DDR in evoking cellular senescence as a mechanism to stop the early stages of tumour transformation.

***Nature Cell Biology*, 2012:** showing that DNA damage accumulates in telomeres with the passage of time due the irreparability of lesions in these chromosome regions.

***Nature,* 2012**: discovery of a new class of short RNAs that can monitor DNA integrity.

## Research on RNA in stages

**1953** The structure of the **DNA double helix** is described by James Watson and Francis Crick and becomes the keystone upon which the nascent molecular biology would rest.

**1961** Francois Jacob and Jacques Monod publish a study on the genetics of bacteria which suggests the existence of a chemical messenger that carries genetic information from the nucleus, site of the DNA, to the cytoplasm where protein synthesis occurs. In the same year, another future Nobel laureate, Sydney Brenner discovers the nature of this intermediate: it is ribonucleic acid and is defined **mRNA** or messenger RNA.

**1993** The discovery of a small non-coding RNA capable of regulating the expression of genes by binding a specific region of their mRNAs. This is the first in a long series of microRNAs or **miRNA**s that regulate hundreds to thousands of protein-coding genes by blocking the translation of their messengers.

**2005 – 2007** the transcriptomes of humans and other species are analyzed, revealing that these genomes are almost entirely transcribed. The more complex an organism, the greater the number not of RNAs coding for proteins, but instead of long or short non-coding RNAs (**lnc** or **snc** RNA).

**2012 DDRNA,** RNA essential for activation of the cellular response to the presence of DNA damage, is described for the first time.