

HORIZON
2020

Mechanistic analysis of DNA damage signaling and bypass upon replication of damaged DNA template in human cells.

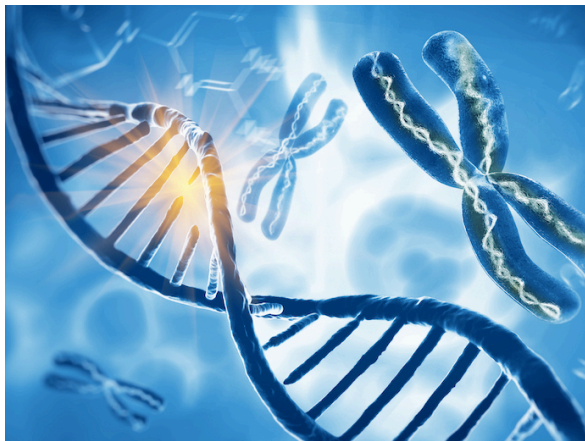
Results in Brief

Understanding how the human body works to keep cancer in check


New research highlights how the body develops checkpoints that sense and repair damaged DNA, thus serving as an important anticancer barrier.




HEALTH




© Giovanni Cancemi, Shutterstock


Deoxyribonucleic acid, better known as [DNA](#) , is no ordinary molecule. That's because within its double helix structure is all the genetic instructions our cells need to develop, function, grow and reproduce. Needless to say, any damage to the DNA can have a significant impact on cellular production and sometimes results in critical diseases like cancer.

To protect our [genome](#)  from internal and external sources of damage, our bodies have developed checkpoints. Sensing the presence of damaged DNA, these checkpoints block cell production until the damage is fully repaired, thus acting as an important anticancer barrier.




Although we know that these checkpoints exist, we don't know how they react against particular problems. "One particularly serious problem is when the replication machinery, or the system that copies the genetic information, encounters lesions on



the DNA template that cause it to generate replicative stress,” says Néstor García-Rodríguez, a researcher at the [Andalusian Molecular Biology and Regenerative Medicine Centre](#) .

With the support of the EU-funded DNACheck project, García-Rodríguez is providing new insight into how human cells sense, and deal with, the replicative stress that can result in cancer and other diseases.

This research was undertaken with the support of the [Marie Skłodowska-Curie Actions](#) .

Finding out where ssDNA comes from

In [prior research conducted in budding yeast](#) , García-Rodríguez concluded that when replicative stress occurs, the checkpoint response is activated by the accumulation of [single-stranded DNA](#)  (ssDNA) behind the [replication forks](#) . In this project, he aimed to find out where the ssDNA comes from in human cells.

“It has been assumed that ssDNA accumulates at stalled replication forks and is caused by an uncoupling of the replicative [helicase](#)  and [polymerase](#)  movement,” he explains.

“However, increasing evidence suggests that replication forks do not permanently stall when they encounter DNA lesions but instead restart, leaving ssDNA gaps downstream from the lesions.”

During this project, researchers successfully identified a remarkable mechanism that promotes the robust activation of the replication checkpoint in human cell lines.

“This process involves action by different nucleases at the ssDNA gaps generated behind the replication forks and in the presence of lesions on the DNA template,” adds García-Rodríguez.

A groundbreaking discovery

The DNACheck project succeeded in confronting the textbook model of replication forks being the origin of the checkpoint signal during replication stress and instead shifted the focus to the relevance of ssDNA gaps.

“The fact that we found that the checkpoint activation mechanism is conserved in human cells is a groundbreaking discovery and one that allowed me to open my own line of research in biomedicine,” concludes García-Rodríguez.

García-Rodríguez is currently focusing his attention on better understanding the dynamic of ssDNA gap processing and filling, including identifying putative new factors involved in such processes.

He also plans to study how interfering with ssDNA processing could be used to selectively kill cancer cells. If successful, this work may open the door to new therapeutic approaches to treating cancer patients.

Keywords

DNAcheck, cancer, DNA, ssDNA, single-stranded DNA, genome, replicative stress, biomedicine

Discover other articles in the same domain of application



Are there really bacteria in the womb?



Pitting bacteria against bacteria in the fight against lung infections





Shedding light on the HIV life cycle



Mapping gene expression in two colours



Project Information

DNAcheck

Grant agreement ID: 794054

[Project website](#)

DOI

[10.3030/794054](https://doi.org/10.3030/794054)

Project closed

EC signature date

15 March 2018

Start date

1 October 2018

End date

30 September 2020

Funded under

EXCELLENT SCIENCE - Marie Skłodowska-Curie Actions

Total cost

€ 170 121,60

EU contribution

€ 170 121,60

Coordinated by

UNIVERSIDAD DE SEVILLA



Spain

Last update: 12 February 2021

Permalink: <https://cordis.europa.eu/article/id/429016-understanding-how-the-human-body-works-to-keep-cancer-in-check>

European Union, 2025

