A DNA lesion alarm system: A formidable protection system for the cell, but some do without.

In the brain, a type of cell was discovered that does not activate the molecular alarms normally sounded when the genome is damaged. They are the astrocytes, named for their spectacular cellular shape reminiscent of a star. When their differentiation is completed and their maximum functional specialisation attained, astrocytes turn off the genes that are responsible for triggering alarms in the presence of such damage and consequently no longer activate a series of responses related to it. For example they do not undergo programmed cell death if exposed to ionizing radiation, as other cells do. This surprising discovery was made by a group of scientists at IFOM in Milan, led by Fabrizio d'Adda di Fagagna, and is published online today in the authoritative scientific journal Cell Death and Differentiation.

Every cell contains about 2 metres of DNA: this very long thread of genetic heritage is kept in a chest of treasures – the cell - which is at least several million times smaller.
Maintaining this thread intact is extremely complicated. Breaks induced by a variety of agents and situations inside and outside of the cell and the organism are the order of the day.
Cellular destiny (normal or tumour) is played out in the arena of DNA stability and integrity.

Most organisms respond to the insult by activating a series of molecular alarms, proteins that find the damaged DNA and set off a cascade of reactions that lead essentially to two objectives: one is the activation of a **molecular taskforce to decide on** and coordinate the cellular events necessary for resolving the problem, and the other is the mobilisation of repair enzymes, true DNA mechanics, that go to the lesion site and repair the damage.

The reaction is known as the "*DNA Damage Response*" or DDR.
This formidable protection system is based on the actions of diverse proteins, essentially organised into a command centre that decides what to do, and an operative centre with more technical functions.
Regarding this system, it appears that evolution has followed the "never change a winning team" rule. In fact, the fundamental functions of the DDR are conserved, practically unchanged, in cells from organisms as simple as unicellular brewer's yeast to those of complex organisms like humans.

Yet there are some that live and perform their functions while dispensing with the precious molecular alarms of the DDR. In fact, the study conducted by Fabrizio d'Adda di Fagagna, scientist and director of the "Telomeres and senescence" research program at IFOM (Istituto FIRC di Oncologia Molecolare) reveals a particular type of cell that surprisingly shows exactly such behaviour. They are the astrocytes of the central nervous system.

Astrocytes are the most numerous cell type in the mammalian brain. They extend a network of increasingly complex and articulated tentacles around themselves, giving them their star-like appearance. Through these fine branchings, they make intimate contacts with millions of synapses, influencing their formation, maintenance and plasticity. Astrocytes are members of a class of cells known as glia, which perform a variety of functions essential to the development, support and functioning of the nervous system.
The IFOM scientists coordinated by d'Adda di Fagagna made this discovery while studying the cellular response of neuronal stem cells to DNA damage.

«When DNA breaks occur, we know that most cells active the DDR» explains d'Adda di Fagagna, whose research group has long studied the molecular mechanisms underlying the cellular response to such insults. «We found this capacity to respond to lesions - continues the scientist - for example, also in neuronal stem cells, a type of stem cell that in the nervous system gives rise to neurons and two types of glial cells, the so-called oligodendrocytes and the astrocytes. However, this last type of cell, to our great surprise, does not sound the characteristic alarms and activate all of those proteins that constitute the central command nucleus of the DDR».

Coordinated by d'Adda di Fagagna, the researchers Leonid Schneider and Marzia Fumagalli discovered this anomaly while subjecting various types of cells to ionizing radiation and, while neuronal stem cells, as well as neurons themselves, reacted as expected by activating all of the elements of the DDR, on the contrary, the astrocytes inactivated the genes necessary for triggering their molecular alarms.

«Nevertheless, astrocytes are capable of repairing damaged DNA» specifies d'Adda di Fagagna. «These cells – continues the scientist – do not have the alarm systems but they maintain expression of the enzymes that carry out the repairs, those that rejoin the ends of the broken DNA, re-establishing its continuity. The signalling and alarm functions of the DDR are like the officers on the bridge of a ship, from where they survey the situation and decide the route to follow. Instead, the repair enzymes are more like carpenters that repair the leaks. In the astrocytes the ones who make the repairs are present, but the higher ranking response functions are missing».

What does all of this mean? In general, when a cell finds too many DNA lesions and the DDR alarms inside are activated excessively or for too long, to avoid catastrophic accumulation of mutations it may even decide to commit suicide by initiating a programmed cell death process known as apoptosis. This happens, for example, when DNA breaks are induced by ionising radiation (which is often used as a research instrument, but also forms that basis of radiotherapy for tumours).
Under these conditions, instead of choosing a destiny of death, astrocytes survive. This behaviour might be explained by the fact that astrocytes do not sound molecular DDR alarms.

Astrocytes are cells that have reached their maximum level of specialization and no longer proliferate. Their main objective is to support the neurons in performing their functions and this may also be the reason why it is essential that they remain active, even in the presence of DNA damage.
This is only one of the hypotheses to explore regarding the peculiar behaviour of astrocytes confronted with genome damage, and research will continue toward understanding the details of this phenomenon.

The discovery by d'Adda di Fagagna and collaborators has particularly significant implications also for cancer research.

In general, knowledge of the molecular mechanisms by which cells protect their genomes is fundamental for understanding and then stopping cellular transformation and tumour development.
The results published today in the journal *Cell Death and Differentiation*, however, open new research prospectives, in particular for astrocytomas, brain tumours derived from astrocytes.
Regarding this d'Adda di Fagagna concludes: «It could be interesting to study this type of tumour now, in light of this discovery, analysing in more detail whether the various elements of the DDR are functioning and determine the specific responses to therapies based on radiotherapeutic or chemotherapeutic agents capable of causing DNA damage. On one hand this may lead to better molecular characterisation of the disease and on the other, to new potential therapeutic targets».

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