FONDAZIONE ISTITUTO FIRC
DI ONCOLOGIA MOLECOLARE

PRESS RELEASE

Antitumor Therapies: even more selective if they work on DNA "packaging"

A study carried out at IFOM in Milan opens a new therapeutic prospective on fighting tumours: induction of tumour cell death by opening up the DNA "packaging" that blocks the cellular response to DNA damage. The hypothesis was tested by administering a class of antitumor drugs already in clinical use: inhibitors of HDACs, cellular factors that modulate chromatin structure, i.e. genome "packaging". Although achieved in the field of basic research, these results open a new and interesting therapeutic prospective for the treatment of those tumours whose highly compacted chromatin make them less sensitive to radio- and chemo-therapies. These findings come from the research efforts of scientist Fabrizio d'Adda di Fagagna at IFOM in Milan with the collaboration of an international team of investigators. The study will appear online today in the prestigious journal Nature Cell Biology.

When a cell accumulates mutations in DNA, a tumour often arises due to activation of one or more oncogenes. These mutated genes are capable of inducing uncontrolled cell growth, resulting in neoplasia.

Luckily our cells have mechanisms for arresting uncontrolled proliferation. One of these is a form of premature cell aging or senescence.

This phenomenon occurs when a large amount of DNA is damaged. Normally DNA damage causes cell death, however in cells that have become senescent due to activation of an oncogene, such damage may be hidden by the dense compacting of their chromatin, i.e. the "packaging" of their DNA.

Until now, activation of the chromatin compacting mechanism was considered to be synonymous with cellular senescence and to have a positive effect by arresting tumour cell proliferation.

The study carried out by Fabrizio d'Adda di Fagagna, group leader of the research unit on telomeres and cell senescence at IFOM (FIRC Institute of Molecular Oncology) Foundation in Milan, and published today in the prestigious journal Nature Cell Biology, reveals instead that this

mechanism is unexpectedly found also in fully proliferating tumour cells. Thus its presence would represent a survival mechanism for the tumour cells since it attenuates the DNA damage response signal.

The scientist explains that “acting on ‘chromatin packaging’ could be the key to fighting tumours in which this cellular mechanism is operating, opening promising therapeutic prospectives”. In fact, the observation that cells expressing an oncogene are damaged but they survive due to exaggerated chromatin compacting led the team of scientists directed by d’Adda di Fagagna to try to “unpack” chromatin in human cells leverei in vitro dato che abbiamo fatto exps sia in vivo che vitroby administering therapeutic agents already used in oncology to inhibit chromatin compacting enzymes, *histone deacetylases* (HDACs).

Since this class of drugs seems to be useful specifically for cells that express an oncogene, the research performed by the team of d’Adda di Fagagna shows that compacting of chromatin is present not only when a cellular senescence mechanism is active but also during proliferation of a tumour cell, meaning that this phenomenon is associated with a large number of tumours. “What we were able to observe” explains Gabriele Sulli, one of the main authors of the study, “is that cells treated with HDAC inhibitors were able to ‘sense’ the damaged DNA and send an alarm response, activating apoptosis, i.e. programmed cell death”. But that is not all: “surprisingly”, adds Raffaella Di Micco, a young co-author of the study, now continuing her research career at New York University, “this only occurs in cells that have an activated oncogene, while healthy cells are spared”. Thus, unlike the administration of chemo- and radio-therapeutic agents, this treatment would target tumour cells in which the DNA is damaged due to the presence of an oncogene, without compromising the survival of healthy cells.

Many clinical trials already envision the use of HDAC inhibitors as anticancer therapy but currently only a fraction of patients respond to treatment. What makes this study extraordinary is that it identifies cells with highly compacted chromatin as the ones that may respond positively to HDAC inhibitors. “A very important result that allows us to target current antitumor therapies more precisely, selecting the tumours most suitable for treatment with this class of drugs” claims Saverio Minucci, director of the Research Unit on chromatin alterations during tumorigenesis in the Department of Experimental Oncology at the IEO, professor in the Biomolecular Sciences and Biotechnology Department at the University of Milan, expert on HDACs and collaborator on the study that identified this new molecular mechanism of action.

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