Campus IFOM—IEO

IEO European Institute of Oncology

Press Release

Leukaemic stem cells become immortal by slowing down cell division

Italian scientists from the IFOM-IEO Campus in Milan have discovered a way to eradicate cancer stem cells, which are thought to be responsible for the incurability of cancer. The discovery was recently published in Nature. The team of researchers, led by Pier Giuseppe Pelicci, uncovered how cancer stem cells become immortal: oncogenes (genes that trigger cancer) prevent stem cells from aging and maintain their ability to form new tissues, i.e. tumours. Present day anti-cancer drugs are targeted against the off-spring ("daughter" cells) of cancer stem cells; the discovery paves the way to a new generation of anti-cancer drugs that target directly cancer stem cells (i.e. the "mother" cells). Such drugs have already entered clinical trials and could become available for the treatment of certain types of cancer within the next 5-10 years. The research was performed in collaboration with the University of Milan.

It was already known that, unlike normal tissue stem cells that eventually age and die, **cancer stem cells are immortal** and maintain indefinitely their ability to self-renew and generate new tumour cells. However, how these cells obtain immortality was unknown.
How do **cancer stem cells evade the physiological process of aging and death** to fuel *ad infinitum* the tumour? It was this question that prompted the study published in *Nature*.
The team scientists led by Pelicci (Scientific Director of the Department of Experimental Oncology at the European Institute of Oncology and Professor of General Pathology at the University of Milan) discovered that the genes (oncogenes) that cause a specific type of cancer **– acute myeloid leukaemia** – also render stem cells immortal. This finding was unexpected because cells normally protect themselves against oncogenes by activating premature aging (senescence) or even death (apoptosis). However, researchers observed that these defense mechanisms are not activated in stem cells. Indeed, **stem cells continue to function even in the presence of oncogenes.**
"Normal tissue stem cells – explains Andrea Viale, one of the authors of the paper – accumulate, with time, DNA damage and eventually stop functioning and die. However, in the case of cancer stem cells, oncogenes render them immortal and **increase their ability to repair DNA damage**. As a result, leukaemic stem cells do not age and can continue indefinitely to fuel the leukaemia".
The researchers discovered that oncogenes promote DNA repair (and hence immortality) by activating a gene called p21. p21 slows down the proliferation of stem cells, allowing them more time to repair their damaged DNA. In other words, **leukaemic stem cells do not age because they proliferate slowly**. Incredibly, when Pelicci's team removed the p21 gene, they saw that stem cells proliferated more, accumulated DNA damage and then died (together with the leukaemia!).
These results support a new theory to explain cancer; i.e. cancers develop from rare, slowly proliferating stem cells that give rise to numerous, rapidly proliferating "daughter" cells. This research has great **implications for the treatment of cancer**: existing anti-cancer therapies target rapidly proliferating cells, and, therefore, have little or no effect on cancer stem cells. Hence, new therapies that target directly cancer stem cells are needed. The results of this study suggest possible ways to achieve this.
"Our discovery – comments Pelicci – highlights a way to eradicate cancer stem cells: **block their DNA repair system**. By doing this cancer stem cells should accumulate DNA damage, causing

them to age and die, as normal tissue stem cells do. New drugs that inhibit genome repair are starting to be tested in the clinic. **In the next 5-10 years, we will know how important these drugs will be to the treatment of cancer"**.

The research was carried out at the **European Institute of Oncology (IEO)**, in collaboration with the **University of Milan** (Department of Biomolecular Sciences and Biotechnology and the Department of Medicine, Surgery and Dentistry) and the **University of Perugia** (Department of Clinical and Experimental Medicine, Policlinico Monteluce). This study was made possible thanks to funds from the **Italian Association for Cancer Research (AIRC)**, the **Italian Ministry of Health**, the **Cariplo Foundation** and the **European Community**.

EDITORIAL DETAILS

Publication: Nature 1 January 2009

Original title of paper: ***Cell-cycle restriction limits DNA damage and maintains self renewal of leukaemia stem-cells***

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Milan, 1 January 2009

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