

Cellular watchdog sniffs out cancer

IMBA researchers explore relationship between cellular stress and carcinogenesis

Noxious, mutagenic and carcinogenic substances are stress factors for cells, and the damage they cause to genetic material can trigger the development of cancer. However, the cells put up stiff resistance against malignant transformation. Scientists at the Institute of Molecular Biotechnology (IMBA) in Vienna studying two of the most widespread types of cancer, lung cancer and breast cancer, recently made an extremely significant discovery: the cells have their own „watchdog“ that sniffs out oncogenic stress and counteracts carcinogenesis.

Cancer is one of the most frequent causes of death in the developed world. One in eight European and North American women will be diagnosed with breast cancer during her lifetime. Incidences of lung cancer have also risen sharply in recent years. The cause is often mutagens, such as radioactive radiation or the chemical substances found in exhausts and tobacco smoke. The latter is responsible for some 90% of all new cases of lung cancer.

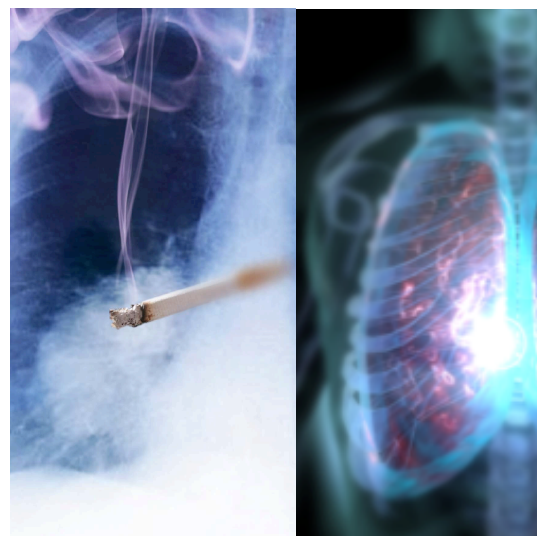
Fortunately, not every exposure to mutagens results immediately in cancer. The human body possesses an ingenious defence mechanism that protects its cells against malignant transformation. Daniel Schramek, a doctoral candidate working in the laboratory of Josef Penninger at the IMBA, has now discovered an essential constituent of this system.

The enzyme MKK7, a stress kinase, acts as a watchdog in the cells. It registers the stress caused by exposure to mutagenic substances or oncogenes – genes with the potential to cause cancer – and recognises that the cells are in danger of transforming into cancer cells. MKK7 immediately switches on the JNK signal pathway, which activates the tumour suppressor protein p53 by transforming it into a stable form. The active tumour suppressor protein subsequently halts the division of this cell until its genetic material has been repaired. If the DNA can no longer be repaired, the cell's death is triggered.

Absence of MKK7 causes earlier, more malignant tumours

Researchers made this discovery by examining mice lacking the MKK7 enzyme. The lung and breast cancers detected in these mice were distinctly more malignant and lethal than the corresponding cancers found in the MKK7-positive control group. This is prompted by the fact that cells without MKK7 no longer realise that they are turning into cancer cells – and consequently fail to take countermeasures such as activating the tumour suppressors. Similar results have been reproduced in human cell lines. The relationship between MKK7 and tumour malignancy has even been demonstrated in tissue specimens from lung cancer patients.

“We have known for some time that activated oncogenes trigger cellular stress,” explains Daniel Schramek, first author of the study. “But we had not identified the system that detects this stress and consequently protects the cells – and as a result the human body – against cancer.” This same MKK7 system also pinpoints cellular stress attributable to external factors such as environmental influences or radioactive radiation. Josef Penninger, the last author of the paper, says: “The really interesting aspect of this paper is that we have now opened the door to a better understanding of the relationships between stress, the environment and carcinogenesis on the molecular level. This is important since cells that have lost the ability to recognise oncogenic stress are powerless to halt uncontrolled cell division.”



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IMBA Press Release

The IMBA scientists published their findings on 13 February 2011 in the scientific journal Nature Genetics. This paper was written in cooperation with scientists in Athens, Sydney, Madrid and Turin and at the Otto Wagner Hospital in Vienna.

The original publication, "The stress kinase MKK7 couples oncogenic stress to p53 stability and tumour suppression" (Schramek et al.), appeared on 13 February 2011 in Nature Genetics (advanced publication online).



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