Cancer Research:

- **Defective cell division process in the eye**
- **New p53 activation mechanism revealed by multiprotein complex**
- **Benefits for innovative cancer therapies**

Errors in the process of cell division (cytokinesis) can lead to the doubling of the genome and thus to the formation of cells with a quadruple chromosome set. This "tetraploid" can lead to an "aneuploid" state (unequal distribution of chromosomes) - a feature of many tumor cells, combined with often poor prognosis and for the team around Andreas Villunger from the Biozentrum Innsbruck at the same time potential attack area for new cancer therapies. In a recent research work, the researchers are investigating a new activation mechanism of the tumor suppressor p53 after defective cytokinesis.

Innsbruck, 31 January 2017: It has been known for many years that the transcription factor p53 is inactivated by mutation in more than half of all tumor patients, which underlines its critical role in the prevention of cancer. In healthy cells, p53 acts as a kind of brake that protects cells against uncontrolled growth after defective cell division or DNA damage. The research team, headed by Andreas Villunger, head of the section for developmental immunology at the Innsbruck biocenter, is also concerned with the mechanisms that lead to the activation of the most important tumor suppressor after defective cytokinesis.

Incomplete cell division in the viewing angle

Cell division is a closely regulated process. As a rule, the constriction and division of a mother into two daughter cells is carried out with the greatest precision after a successful doubling of the genome. If this does not proceed correctly or inaccurately, this process is terminated and a cell with four chromosome sets (tetraploidy) is formed. In order to protect such cells from uncontrolled growth and chromosomal instability, the control function of the protein p53 is required. "This early stage of potential tumor development, its contribution to tumor tumors and those mechanisms that lead to the activation of p53 are currently the focus of our search for new approaches to cancer therapy," said Andreas Villunger, who recently demonstrated with his team , That the enzyme caspase-2, a protease with very diverse properties, can stimulate p53 activation.

P53 activation by multiprotein complex

In the current research published in the prestigious Journal *Genes & Development* , the team, with the first author Luca Fava, examined the p53 activation process in tetraploid cells and investigated the previously unexplored mechanisms leading to p53 activation after DNA duplication and defective cytokinesis to lead. The focus was on a multiprotein complex known as PIDDosom consisting of the proteases PIDD1, RAIDD and Caspase-2. By means of biochemical as well as cell biologic procedures and with the support of further research groups at the site as well as the biocenter in Basel, it was shown for the first time that the protein-cleaving enzyme Caspase-2 cleaves the oncogenic substrate MDM2 and thus eliminates its function as a negative regulator of p53. "The protein p53 is stabilized in this way and can selectively exert its growth-inhibitory effect," explains first author Luca Fava, who returned to Italy after a five-year research project in the Andreas Villunger laboratory with a 1 million $ grant from the Armenian Harvard Foundation , To build up his own laboratory in Trento at the Center for Integrative Biology (CIBIO).

With the first-time description of this mechanism of p53 activation, the Innsbruck researchers will elucidate a further building block in the central process of cell cycle control and provide a new potential approach for the development of innovative cancer therapies against the background of the upcoming World Cancer Day. Ultimately, the transcription factor p53 is to be activated pharmacologically in tumor cells, which have not yet lost it.

Andreas Villunger's team is supported by the FWF and the Partnership in Research (PiR) program of the Christian Doppler Research Society.

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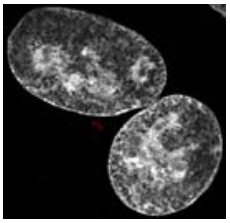
VI: cancer researcher Univ.-Prof. Dr. Andreas Villunger and Mag. Dr. Luca Fava, first author of the new research work.



The image (fluorescence microscope) shows the inside of a cancer cell after defective cytokinesis: two nuclei (white) and four red dots are visible, which mark two centrosomes, each of which is composed of two centrioles. Centrosomes are important organelles, which organize the cytoskeleton in the cell and which occur twice after a cytokinesis defect.

For further information:

Univ.Prof. Mag. Andreas Villunger
Section for Developmental Immunology
Mobile: +43 676 871672380
E-Mail: Andreas.Villunger@i-med.ac.at

Mag.Dr. Luca Fava
Section for Developmental Immunology

Details of the Medical University of Innsbruck

The Medical University of Innsbruck, together with the University of **Innsbruck** , together with the University of Innsbruck, is the largest educational and research institution in Western Austria. It is regarded as a provincial university for Tyrol, Vorarlberg, South Tyrol and Liechtenstein. The following fields of study are offered at the Medical University of Innsbruck: **human medicine and dentistry** as the basis for academic medical training, and **PhD (** doctorate **)** as postgraduate deepening of scientific work. In addition to the study of human or dental medicine, the **PhD** may be connected to the **PhD** .

Since autumn 2011, the Medical University of Innsbruck has been offering the **Bachelor Program** " **Molecular Medicine"** exclusively in Austria **.** From the winter semester 2014/15, the Master's **degree "Molecular Medicine"** can be completed as a further education **.**

The Medical University of Innsbruck is involved in numerous international education and research programs as well as networks. Research focuses on **oncology** , **neurosciences** , **genetics** , **epigenetics** and **genomics** as well as **infectiology** , **immunology and organ and tissue replacement** . The scientific research at the Medical University of Innsbruck is very successful in the highly competitive field of research funding both nationally and internationally.

* Full-time equivalent

Tel .: +43 512 9003 70369
E-mail: Luca.Fava@i-med.ac.at

Media contact:

Mag. A Doris Heidegger
Medical University Innsbruck
Department of Public Relations
Innrain 52, 6020 Innsbruck, Austria
Phone: +43 512 9003 70083, mobile: +43 676 8716 72083
Public-relations@i-med.ac.at , www.i-med.ac.at