Press Release

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Leibniz Institute for Age Research
Fritz Lipmann Institute (FLI)

Dr. Jekyll & Mr. Hyde: Telomere and Telomerase in Stem Cells

When a human cell divides, its' daughter cells should each receive an identical copy of the mother cell's genome. Occasionally mistakes occur during this process generating mutations that can give rise to cancer. To avoid detrimental outcome for the organism, cells with mutations that generate deviations from normal chromosomal number are eliminated by cellular protection mechanisms. Researchers from Leibniz Institute for Age Research – Fritz Lipmann Institute (Jena, Germany) now identified a crucial role of telomeres, the end structures of chromosomes, for sensing cells with a wrong chromosome number, referred to as aneuploidy. Telomeres respond to aneuploidy by generating stress signals that suppress the proliferation of aneuploid cells. However, telomerase, the enzyme, which can synthesize telomeres, supports the survival of aneuploid cells by alleviating telomere induced stress signals in response to aneuploidy.

Telomeres, the end structures of linear chromosomes, are composed of repetitive DNA sequences (TTAGGG in humans) and specialized telomere binding proteins. They form protective caps at the ends of linear chromosomes to prevent chromosomal instability. For the complete replication of telomeric DNA and the functionality of telomeres, the activity of a telomere-specific DNA polymerase, the telomerase, is required. Studies in the last two decades revealed that telomeres and telomerase have dual functions in suppressing and facilitating tumorigenesis: In the adult human, the activity of telomerase is mostly restricted to the stem cells and is absent from the vast majority of human cells. In the absence of telomerase, telomere shortening limits cellular life span and prevents tumorigenesis. However, cells with too short telomeres can lose capping function leading to a cellular catastrophe and genetic instability: the origin of many cancer types. In this scenario, telomerase activity is protecting from tumor formation that can be initiated by these dysfunctional telomeres.

Researchers from Leibniz Institute for Age Research – Fritz Lipmann Institute (FLI) in Jena, Germany, have now found surprising news on the role that telomeres and telomerase play for the tumorigenic process (published in *The EMBO Journal*). These new findings reveal that long, functional telomeres can sense chromosomal imbalances and suppress the proliferation and growth of cells with aneuploidy. In this context, telomerase activity can have unfavorable effects: "We found that this enzyme allows cells with aneuploidy to bypass the protective function of telomeres. By that, it supports the survival of defective cells which, in the end, can evolve into tumor cells", PD Dr. Cagatay Günes explains. In this scenario, telomerase promotes carcinogenesis instead of preventing it. "It's like Dr. Jekyll suddenly turning into Mr. Hyde", Dr. Günes recapitulates the astonishing findings.

New Approach for Cancer Therapy

„Our findings suggest telomere and telomerase as potential targets for tumor therapy – but in a totally new way", Prof. Dr. Karl-Lenhard Rudolph, Scientific Director of FLI, explains. Up to now, it was assumed that by

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suppressing the telomerase activity, tumor cells might be eliminated due to telomere shortening. However, this treatment would require long treatment periods, as telomeres shorten by small steps over several cell divisions. The new results of this study imply, that the suppression of telomerase activity may immediately stop tumor cell proliferation.

The findings raise also new questions for basic research that demand for future studies: How do telomeres sense imbalances in chromosome number? How does telomerase manage to bypass the protective function of telomeres?

Publication

Meena JK, Cerutti A, Beichler C, Morita Y, Bruhn C, Kumar M, Kraus JM, Speicher MR, Wang ZQ, Kestler HA, d'Adda di Fagagna F, Günes C, Rudolph KL. Telomerase abrogates aneuploidy-induced telomere replication stress, senescence and cell depletion. EMBO J. 2015 Mar 27. pii: e201490070. doi: 10.15252/embj.201490070

Background Information

The **Leibniz Institute for Age Research – Fritz Lipmann Institute (FLI)** is the first German research organization dedicated to biomedical aging research since 2004. More than 330 members from over 30 nations explore the molecular mechanisms underlying aging processes and age-associated diseases. For more information, please visit *www.fli-leibniz.de*.

The **Leibniz Association** connects 89 independent research institutions that range in focus from the natural, engineering and environmental sciences via economics, spatial and social sciences to the humanities. Leibniz Institutes address issues of social, economic and ecological relevance. They conduct knowledge-driven and applied basic research, maintain scientific infrastructure and provide research-based services. The Leibniz Association identifies focus areas for knowledge transfer to policy-makers, academia, business and the public. Leibniz Institutes collaborate intensively with universities – in the form of "WissenschaftsCampi" (thematic partnerships between university and non-university research institutes), for example – as well as with industry and other partners at home and abroad. They are subject to an independent evaluation procedure that is unparalleled in its transparency. Due to the institutes' importance for the country as a whole, they are funded jointly by the Federation and the Länder, employing some 18,100 individuals, including 9,200 researchers. The entire budget of all the institutes is approximately 1.64 billion EUR. See *www.leibniz-association.eu* for more information.

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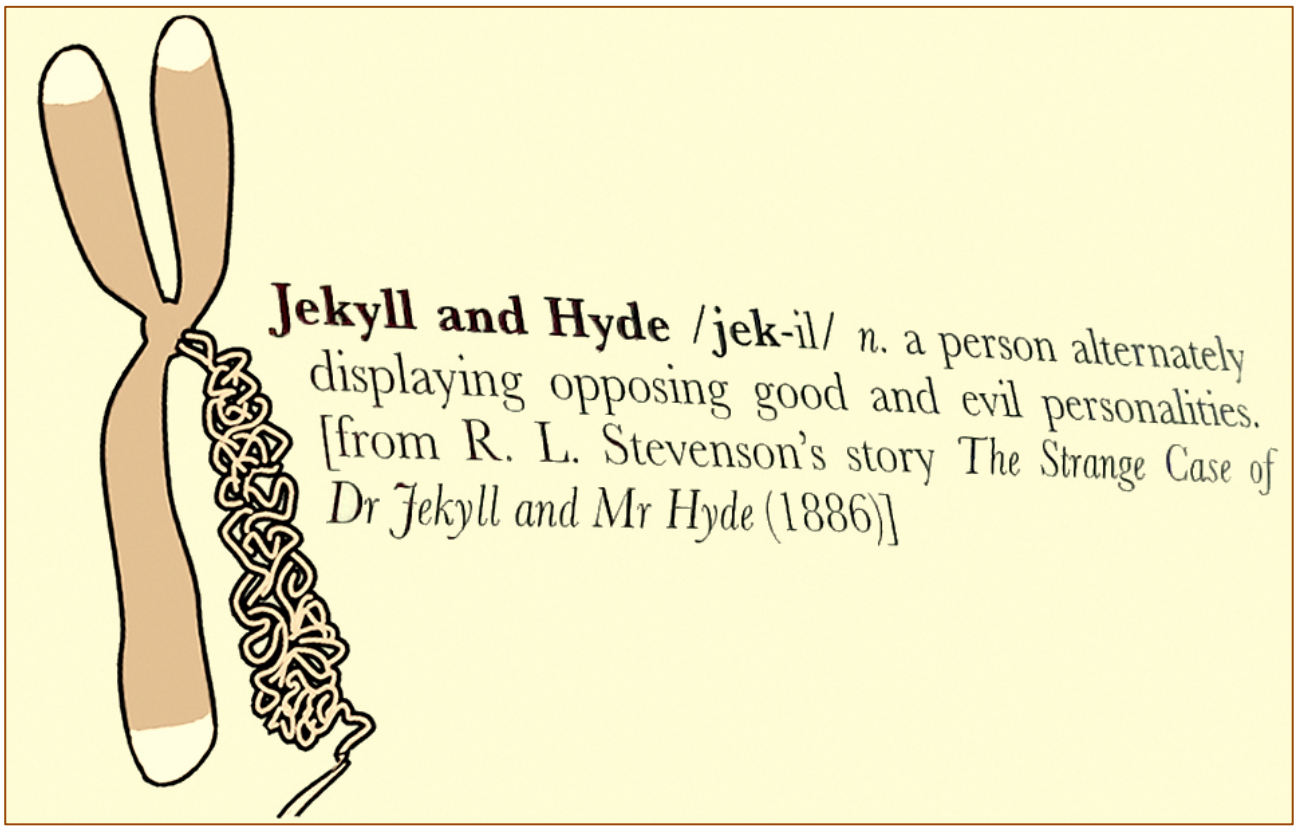

Picture 1

Telomere and telomerase play important roles for proper cellular proliferation but also in the tumorigenic processes: Telomerase activity is required to keep the telomeres intact. In cells that have mutations generating a wrong chromosome number (aneuploidy), intact telomeres help to suppress the proliferation and growth of aneuploid cells, thus preventing genome instability. On the other hand, telomerase activity may allow aneuploid cells to bypass the protective function of telomeres and, by this, support carcinogenesis. It's like telomerase suddenly turning from Dr. Jekyll to Mr. Hyde.

[Picture: Kerstin Wagner/FLI; Source: www.pixabay.com *et al*.]

Note:

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