New mouse model for testing cancer drugs

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Only one in twenty cancer drugs makes its way from the laboratory to become an approved pharmaceutical product. The majority of new agents are only shown to be unsuitable in the later phases of clinical development which would explain the exorbitantly high development costs of 500 to 600 million euros per new cancer drug. In order to recognize at an earlier stage which side effects are associated with the use of new cancer drugs, a research group under the guidance of the Goethe University has developed a new mouse model.

In cooperation with the companies Bayer Schering Pharma AG and Taconic Artemis GmbH, the researchers were the first to simulate drug-induced inhi-bition what is currently one of the most attractive target genes for new cancer drugs. They were able to demonstrate that, as a result of this, the rapid division of cancer cells was prevented while healthy cells were hardly affected. This study has been published in the current issue of the prestigious journal, *Nature Communications*.

The cancer gene, polo-like kinase 1 (Plk1), which is currently the subject of intense investigation, plays a central role in cell division. However, up to now, it has not been possible with classical mouse model to investigate what would happen if this gene were to be silenced in adult animals since the latter is indispensable to embryonic de-velopment. The researchers working together with Prof. Klaus Strebhardt from the Centre for Gynecology and Obstetrics at Frankfurt's University Hospital thus devised a method of silencing the gene at any point during the lifetime of the new transgenic mouse. To this end, they expressed short RNAs with a length of 20 to 22 base pairs in the cells of the mice. These

short RNAs prevent the information which is read by the cancer gene from being converted into proteins. This method known as RNA interference was further developed by the researchers into an inducible system: The design is such that the expression of Plk1-specific RNA and, in turn, the silencing of the gene is only induced by the antibiotic Doxycycline. The mice are therefore able to mature and the relevant gene is not knocked down using Doxycycline until the mice have reached adult age.

The working group supervised by Prof. Strebhardt in cooperation with Bayer Schering Pharma AG and Taconic Artemis GmbH developed the mouse model (Plk1 iKD animals). The mice were subsequently phenotypically characterized. This was done together with the Helmholtz Center in Munich, Munich's two universities as well as the universities of Gießen and Hamburg. "Surprisingly, despite the efficient knock-down of Plk1 in various tissues of the mouse following administration of Doxycycline over a six-week period, no major structural or functional anomalies were identified," reported Strebhardt. "This observation is diametrically opposed to the role of Plk1 in cancer cells of varying origins which, following the inhibition of Plk1, quickly cease dividing and go into apoptosis." In order to further verify the surprising findings in the Plk1 iKD animals, the researchers examined various primary cells in culture under controlled conditions. Just as previously in the animal experiment, Plk1 expression was inhibited through RNA interference and analyzed. In this system, too, the results of the animal experiments were confirmed: In contrast to tumor cells, healthy cells are only dependent on Plk1 expression to a minimal degree. As such, healthy cells are virtually undamaged if the Plk1 gene is silenced while the cancer cells are combated.

"Inducible RNAi-based mouse models represent an attractive way of reversibly con-trolling gene expression in order to study the targeted inactivation of genes. Our work is a feasibility study which considers

whether inducible RNAi-based mouse models are suitable for predicting the toxicity of targeted cancer drugs," explained Klaus Strebhardt. "The similar results of the Plk1 knockdown in transgenic animals and cultivated primary cells have served to validate the preclinical relevance and the predictive value of the inducible iKD mouse model. This new animal model provides information on mechanism-based toxicities which could occur as a result of the pharmacological inhibition of Plk1. Our approach can be applied to many other can-cer-relevant target genes."

More information: Raab, M. et al.: Toxicity modeling of Plk1-targeted therapies in genetically engineered mice and cultured primary mammalian cells, *Nature Communications*, July 19th 2011. Doi: 10.1038/ncomms1395

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