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The TUSCC project: What can elephants teach us about cancer prevention and treatment in humans

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Although logic would suggest the contrary, it seems that cancer incidence is not related to body size (number of cells) and species life span (number of cell divisions). Large, long-living mammals, such as elephants, have no increased risk of developing cancer compared to smaller mammals with fewer cells and shorter lifespans. This lack of correlation between body size, life span and cancer risks is known in evolutionary biology as Peto's Paradox. Recent reports have shown that elephants have an expanded number of TP53 gene copies, a crucial tumour-suppressor gene encoding the tumour protein p53. However, the redundancy in tumour suppressor genes cannot resolve Peto's paradox completely in elephants, since they should have developed a trade-off between the aggressive elimination of damaged cells and senescence due to depletion of their stem cell pool.

While limited research and experimental efforts have focused on resolving the paradox up to now, there are a growing number of alternative hypotheses that have been proposed. In the project "Tumour Suppression and Subdual of Cancer (TUSSC) in elephants", we aim to investigate three alternative mechanisms (metabolism, inflammasome and telomere length) which could play an important role in cancer suppression by comparing captive and free-roaming elephants.

Here, we will present the first results of our project and highlight what implications Peto's paradox could have for radiation protection and radiation therapy strategies. Blood samples were collected from elephants by experienced wildlife veterinarians in the Zoo of Naples (Italy) and at Botlierskop, a private game reserve with free-roaming elephants (South Africa). After collection and transport to the laboratories, the elephant blood samples were irradiated and cell death and DNA repair response was compared to human samples. In addition, comparative next generation sequencing will be performed on human and elephant blood samples, to investigate which specific pathways are up- or downregulated after radiation exposure. The results of the Annexin V/PI apoptosis assay illustrate that elephant cells go into apoptosis at much higher rates than human cells, even after exposure to doses as low as 0.125 Gy. DNA double-strand break (DSB) induction and repair was evaluated using the γ-H2AX foci assay. While no statistically significant difference could be observed in the number of DNA DSBs at 1 hour post-irradiation, the 24 hours result confirm that elephant cells repair the induced damage faster.

The first results of the project confirm the working mechanisms of the tumour suppressor gene and striking differences in DNA repair capacity between human and elephant cells. It is envisaged that this project could rapidly advance the development of new strategies for the prevention of radiation-induced cancers or the sensitization of cancer cells to radiotherapy. In addition, future experiments are planned with elephant fibroblast cells and carbon-ions, which will also increase our understanding of the role of TP53 in the DNA damage response after high-LET radiation.

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