Telomere/telomerase and radiosensitivity

Wenbo Wang1,2, Lei Yang1,2, Yunfeng Zhou1,2

1Hubei Cancer Clinical Study Center, Hubei Key Laboratory of Tumor Biological Behaviors, Zhongnan Hospital, Wuhan University, Wuhan, China
2Department of Radiation and Medical Oncology, Zhongnan Hospital, Wuhan University, Wuhan, Hubei, China

Correspondence: Yunfeng Zhou
E-mail: yfzhouwhu@163.com
Received: February 13, 2015
Published online: March 16, 2015


What we have known for the relationship between telomeres, telomerase and radiosensitivity?

Telomeres are the special structures at the ends of chromosome, which are essential for protection against DNA damage signals and ensure genome stability [1]. With the discovery of telomeres and the research in duplication of chromosomes, telomerase is a specialized ribonucleoprotein complex with reverse transcription activity that is minimally composed by the telomerase reverse transcriptase and a RNA template, which is called telomerase RNA component (TERC), for telomere extension during de novo addition of TTAGGG repeats onto chromosome ends. Maintenance of telomere involves networks of kinds of telomere-associated proteins. They are comprised of telomeric DNA and a sequence of telomeric interacting proteins (including TRF1, TRF2, POT1, TPP1, RAP1 and TIN1), both of which are responsible for telomere functions [2-3]. We have explored various approaches to the treatment of cancer, targeting at telomerase and telomere, including immunotherapy, telomerase-directed gene therapy and telomerase inhibitors [4-7].

Radiotherapy is the major treatment for malignancy, however the high radioresistance of tumor cells is still the common reason for the failure of radiotherapy. Currently, there are no clinical targeted therapeutic drugs to increase tumor radiosensitivity specifically. Meanwhile, classical radiation biology insists that the main factor affecting the tumor radiosensitivity is DNA repair capacity.

The mechanism of the relative expression levels of hTR, hTERT and dyskerin remains unknown. Therefore, we select important markers of tumor cells that differ them from normal cells, and telomerase that protect chromosomes from the fusion and that reduce DNA damage by telomere maintenance as the study objects. DNA repair processes interact with telomeres and play a role in the maintenance of telomere length. We explore the influence of telomerase on radiosensitivity and its potential mechanism, aiming to find targeted therapeutic drugs to increase tumor radiosensitivity.

Could we modify the radiosensitivity by exploding the function of telomere and telomerase?

Telomere damage has been existed in so many cancer development in humans [8-11]. Further work on the mechanisms of telomeric DNA, telomerase, and telomere-binding proteins function together will greatly facilitate our search for diagnostic of telomere-relevant diseases. Furthermore, it can be regarded as a potential target for therapeutic tools.

To study the impact on the radiosensitivity of telomerase, our group established human laryngeal carcinoma cell line Hep-2R with radiation tolerance by radiation-induction,
resulting in telomerase activity increasing. According to this, it may be possible to speculate radiosensitivity of tumor cells based on telomerase activity. In order to confirm it, we detected telomerase activity, telomere length and cellular radiosensitivity in different human breast cancer cells, laryngeal squamous cell carcinoma cells and their radioresistant cells, human cervical cancer cell lines and glioma cell lines. The study indicated that we could predict the radiosensitivity of tumor cells based on telomere length, instead of telomerase activity [12-13].

Our group radiated Hela cells with γ-ray of different doses in the early period to study the influence of γ-ray on telomerase. By detecting telomerase activity of each group after 24 、72 、120 hours’ radiation, we found that the activity of telomerase significantly increased and the rate different with doses. Thus, we speculated that there was a close relationship between telomerase and radiosensitivity[14]. To identify this suppose, we chose ASODN and AZT to interfere telomerase subtraction hTR and hTERT. The results showed that telomerase activity of Human glioma U251 cells and Hela cells decreased, DNA damage reduced and radiosensitivity increased. However, there was no change in telomerase length under the circumstance of hTR suppressed by ASODN, which was significantly different from that telomerase became shorter after hTERT interfered by AZT. Furthermore, we identified the conclusion that telomere length and radiosensitivity would increase, DNA damage would reduce when telomerase activity was suppressed by means of combining AZT with γ-ray in laryngeal squamous cell carcinoma xenografts in nude mice [14-15].

Although telomerase activity cannot predict the radiosensitivity of cancer cells, however, since telomerase is highly expressed in most cancer cells and its increasing activity after radiation. Our research team combines CArG element with hTERT promoter to form a new kind of chimeric promoter, and that combines gene with ray skillfully and treats tumor with local therapy as well as inducing the expressing of therapeutic gene [16]. We combine ray with gene to create joint destruction in tumor cells. On the one hand, we can lower the radiation dose and reduce the damage of normal tissues, on the other hand, the veracity and controllability of ray can result in the positioning express of tumor destruction gene [17]. Our research team has successfully construct a new kind of chimeric promoter system based on hTERT, and verified its radiosensitization effect in cervical cancer 、lung cancer and liver cell model [7]. Meanwhile, Lewis lung cancer’s transplantable tumor in mice has also verified its radiosensitization effect [18]. This research has both solved the difficulty in exogenous gene’s targeting expression and lowered the radiation dose, which benefits the destruction of normal tissue. Radiation induced regulatory mechanism and telomerase reverse transcription promoter can be applied in many tumors and has the advantage of wide resistant variety.

Recently, we do further studies through the Y2H system to find novel hTERT-binding proteins to tease out the role of hTERT in radiosensitivity. UBE2D3, a member of the E2 family, proved to be interacted with hTERT, and played a crucial role in the process of hTERT-mediated radiosensitivity. We identified that E2 appears to act as a regulator for signaling in the hTERT pathway. UBE2D3 was suggested to modulate MCF-7 cell radiosensitivity by acting as a regulator for hTERT and cyclin D1 protein expression [19].

Telomere maintenance relies on multiple elements. One of the critical players is a six-protein complex, known as the telosome, which is composed of TRF1, TRF2, RAP1, TIN2, TPPI and POT1. Each of these proteins has evolved specific functions for telomere maintenance, including the regulation of telomerase access and activity as well as the interaction with many DNA repair/recombination factors. Using cDNA microarray technology, we found that the gene expression of telomere binding protein POT1 was elevated in radioresistant cells [20]. POT1, one of the telomere-associated proteins, is a significant part of the telosome in mammalian telomeres. Moreover, our study revealed that telomere binding protein TPPI, TRF2 and CTC1 could also regulate cellular radiosensitivity [21-24]. We demonstrated that knockdown of anyone of these proteins could lead to increased radiosensitivity in human cancer cells. But the effects on telomere length or telomerase activity were different.

For example, in our previous study, we found that there was a significant correlation between TPPI expression, telomere length and cell intrinsic radiosensitivity in colorectal cancer cells. Radiosensitive cells have less production of TPPI and shorter telomeres than that in radioresistant cells [21]. Moreover, TPPI overexpression decreases sensitivity of HCT116 cells to radiation by inhibiting apoptosis and prolonging G2/M arrest mediated by ATM/ATR-Chk1 signal pathway after ionizing radiation. Lastly, we found that TPPI overexpression could accelerate the repair kinetics of total DNA damage and telomere dysfunction after ionizing radiation. In summary, our research demonstrated that TPPI overexpression in human colorectal cancer cells could protect telomere from DNA damage and confer radioresistance [21]. These results suggested that TPPI may be a potential target in the radiotherapy of colorectal cancer.

What will the direction go on for the next explosive of telomere related radiosensitivity?
Although further research is required, we are now gaining a more comprehensive understanding new signaling pathways involved in ensuring telomere integrity. In future, to investigate more about how hTERT affect radiosensitivity of tumor cells, our research group will continue to study the function of proteins interacted with hTERT. Meanwhile, in order to improve the specific chimeric promoter induced gene therapeutic effect and the therapeutic effect in gastric cancer’s peritoneal metastasis, our research team plans to study the telomerase hTERT’s specific chimeric promoter that induced gene therapy in gastric cancer’s peritoneal metastasis in nude mice. Although the telomere binding proteins act as a significant part in telomere function, the effects of radiation on the expression of telomere binding proteins are unclear. Our group plans to investigate the role of different doses of radiation on the expressions of telomere binding protein in tumor cells at different time points. In addition, to further study the mechanisms of telomere homeostasis mediated by POT1/TPP1 complex on the regulation of cellular radiosensitivity, we plans to draw network of proteins regulating radiosensitivity mediated by POT1/TPP1 complex using TAP-SWATH technology in the radiation sensitive/resistance cell line model through biological bioinformatics analysis. Our study will better analyze the mechanisms on cellular radiosensitivity regulation which does not depend on the telomerase.

References