Roles and perspectives of photon beam radiotherapy (RT) in the next era of particle RT: the personal opinions of a radiation oncologist in Okinawa

Takafumi Toita, MD
Department of Radiology, University of the Ryukyus, Graduate School of Medical Science.

The number of cancer patients has increased rapidly in recent years. Research designed to overcome cancer is one of the most exciting challenges in the scientific field currently. Radiotherapy (RT) is an important cancer treatment that can eradicate cancer cells without causing significant damage to normal tissues. The most popular mode of RT uses a photon (X-ray) beam from a linear accelerator (LINAC). Photon RT has excellent clinical versatility and the ability to cure cancer patients. In Okinawa, there are seven facilities with eight LINACs and approximately 1,900 cancer patients are treated per year. Photon RT has some weakness in terms of both physics (low energy and poor dose conformity) and biology (low linear energy transfer: LET, low relative biological effectiveness: RBE, and high oxygen enhanced ratio: OER). To overcome the physics-related weaknesses, several modalities, such as stereotactic radiosurgery: SRS, stereotactic radiotherapy: SRT and intensity modulated radiotherapy: IMRT have been developed with advances in imaging and RT-planning technologies. Biological weaknesses of photon RT have also been challenged using strategies such as altered fractionation, concurrent delivery of chemotherapy: CCRT, and bio-radiotherapy: BRT. Carbon ion RT is a novel treatment with excellent dose conformity and strong cytotoxicity particularly advantageous for highly radio-resistant tumors. Excellent oncologic outcomes have been reported for this treatment. However, I do not think that carbon ion RT is the universal treatment for all cancer patients of various clinical situations. I think that a narrow therapeutic window for carbon ion RT, in terms of biology, is one of the critical issues regarding its delivery in certain situations, e.g., a large target volume comprising a mixture of cancer cells and normal cells and target locating closely to the critical normal structures. There is a plan to

install carbon ion RT facility in Okinawa. In Okinawa, patients with loco-regionally advanced disease with/without systemic metastases are more prevalent compared with those with locally confined early-stage cancer. As radiation oncologists in Okinawa, we must perform appropriate decision -making regarding the use of photon RT with novel treatment techniques (e.g., SRT, IMRT, CCRT, BRT) and customizing carbon ion RT for individual patients before carbon ion RT application.

PH domain-only protein PHLDA3 is a novel p53-regulated repressor of Akt and a novel tumor suppressor of neuroendocrine tumors -towards development of tailor-made therapies for neuroendocrine tumors-

Division of Rare Cancer Research, National Cancer Center Research Institute

Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan

Rieko Ohki

Both p53 and Akt are critical players regulating tumorigenesis with opposite effects. In addition, p53 and Akt negatively regulate each other to balance oncogenic and tumor suppressive signals within a cell. We previously reported a novel p53 target gene, *PHLDA3*, encoding a PH domain-only protein that represses Akt. We showed that PHLDA3 suppresses Akt translocation to the cellular membrane and subsequent phosphorylation/activation (Cell, 136, 535-550, 2009).

We report here that the genomic region of the *PHLDA3* gene undergoes loss of heterozygosity (LOH) at a remarkably high frequency in human neuroendocrine tumors (NETs). The *PHLDA3* locus undergoes methylation in addition to LOH, suggesting that a 2-hit inactivation of the *PHLDA3* gene is required for NET development. We also demonstrate that PHLDA3 represses Akt activity and Akt-regulated biological processes in endocrine cells, and that *PHLDA3*-deficient mice develop abnormal in endocrine tissues. In addition, the tumor-suppressing pathway mediated by MEN1, a well-known suppressor of PanNETs, is dependent on the pathway mediated by PHLDA3, and inactivation of PHLDA3 and MEN1 cooperatively contribute to PanNET development. Novel PHLDA3-mediated pathway of tumor suppression that is important in the development of PanNETs is demonstrated, and the findings may contribute to personalized medicine of PanNET patients. (PNAS, 111, E2404-E2413, 2014).

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Rieko Ohki, Ph.D.

1997	Ph.D., Dept. of Biochemistry and Biophysics, Faculty of Sciences, University of Tokyo (Japan)
1997- 1999	Postdoctoral Research Fellow Department of Immunology (Professor Tadatsugu Taniguchi), Graduate School of Medicine and Faculty of Medicine, University of Tokyo
1999 - 2002	Postdoctoral Research Fellow Department of Life Science (Professor Fuyuki Ishikawa), Graduate School of Bioscience and Biotechnology, Tokyo Institute of Technology
2002 - 2011	Research Associate Radiobiology Division (2002-2008), Growth Factor Division (2008-2010), Division of Cancer Biology (2010~2011), National Cancer Center Research Institute
2011 - present	Group leader Division of Refractory Cancer Research (2011-2014), Division of Rare Cancer Research(2014-), National Cancer Center Research Institute

Speciality and Present Interest:

Identification and analysis of genes involved tumorigenesis

Phone: 81-3-3542-2511 ext.4460

E-mail: rohki@ncc.go.jp