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RNA-seq reveals tumor radiation response and novel molecular targets on α-emitting meta-211At-astato-benzylguanidine therapy for malignant pheochromocytoma

Purpose: Targeted α-particle therapy is a promising option for patients with malignant pheochromocytoma. Recent observations of *meta*-211At-astato-benzylguanidine (211At-MABG) in a pheochromocytoma mouse model showed a strong anti-tumor effect, but its molecular mechanism remains elusive (Y. Ohshima et al., 2018). Here, we showed the first comprehensive RNA-sequencing (RNA-seq) data of pheochromocytoma cells from *in vitro* 211At-MABG administration experiments, and screened key genes and pathways in the tumor α-particle radiation response, in order to obtain novel molecular imaging and therapeutic targets.

Methods: We evaluated genome-wide transcriptional alterations of rat pheochromocytoma cell line (PC12) at 3, 6, 12 h after 211At-MABG treatment. In order to highlight 211At-MABG specific gene expression, we carried out the control experiment of 60Co γ
-rays irradiation. Ten-percent and eighty-percent iso-survival dose (0.8 and 0.1 kBq/ml for 211At-MABG, 10 and 1 Gy for 60Co γ-rays) were used for the comparison of both treatments.

Results: Enrichment analysis of the differentially expressed genes (DEGs) and analysis of the gene expression profiles of the cell cycle checkpoints showed similar modes of cell death via p53-p21 signaling pathway following 211At-MABG treatment and γ-ray irradiation. Ten percent iso-survival dose of γ-ray irradiation and 211At-MABG showed cell cycle arrest at G2/M phase. Representative DEGs of 211At-MABG-treated cells between 80\% and 10\% survival showed the expression of key genes not only on the decrease in the survival, but also on the anti-therapeutic effects such as DNA repair, invasion, and metastasis. Furthermore, representative DEGs between γ-ray irradiation and 211At-MABG demonstrated that the expression of four potential genes including Otub1 related to ubiquitin mediated proteolysis was remarkably elevated only after treatment with 211At-MABG. Western blot analysis indicated the increase of translocator protein 18 kDa (TSPO) expression in 211At-MABG treated cells, suggesting the potential PET imaging probe.

Conclusion: Comprehensive RNA-seq revealed contrasting cellular responses to γγ-ray irradiation and targeted α-particle therapy leading to the identification of four novel potential genes (Mien1, Otub1, Vdac1 and Vegfa) for molecular imaging and therapeutic targets of 211At-MABG therapy. Moreover, our results suggest possible mechanism of the anti-tumor effect of 211At-MABG in pheochromocytoma.

Reference: Y. Ohshima, H. Sudo, S. Watanabe, K. Nagatsu, A.B. Tsuji, T. Sakashita, Y.M. Ito, K. Yoshinaga, T. Higashi, N.S. Ishioka, Antitumor effects of radionuclide treatment using α-emitting *meta*-211At-astato-benzylguanidine in a PC12 pheochromocytoma model, *Eur. J. Nucl. Med. Mol. Imaging*, **45**, 999-1010. (2018)

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