ABSTRACT

IN VITRO RADIOBIOLOGICAL EFFECTS OF ¹³¹I ON THYROID CELLS: TOWARDS A MECHANISTIC UNDERSTANDING OF THYROID STUNNING

NIRMAL BHOGAL

Department of Anatomy and Cell Biology, Sahlgrenska Academy at Göteborg University, Sweden

An ongoing controversy in nuclear medicine is a phenomenon known as thyroid stunning observed during ¹³¹I therapy of thyroid cancer. Specifically, this involves an unexpected reduction of the ¹³¹I uptake in the tumor or thyroid remnant after administration of the therapeutic ¹³¹I dose. The preceding ¹³¹I test dose given for diagnostic scanning is inferred a causal role. However, previously no explanation to the stunning mechanism has been offered. In papers I-II of this thesis, ¹³¹I-induced thyroid stunning was investigated for the first time in vitro in cultured thyroid cells. Growth-arrested (GO) cells forming a tight and polarized epithelium on filter in bicameral chambers were continuously exposed to ¹³¹I for 48 hours after which iodide transport from the basal to the apical chamber compartment was evaluated using ¹²⁵I as a tracer. ¹³¹I dose-dependently inhibited ¹²⁵I-transport (by 50-90% at 3-80 Gy) 24 hours and onwards (for at least three days) after irradiation was stopped. Kinetic studies further showed that the stunning phase was preceded by accelerated ¹²⁵I-transport. TSH receptor signalling and secretion of thyroglobulin participating in thyroid hormone production did not change after irradiation. Stable iodide did not reproduce the radiation effect. Also, the cell number was not affected. Together, these findings indicate that ¹³¹I induces biphasic changes of thyroidal iodide transport without simultaneously affecting pro-hormone biosynthesis and thyroid regulation by TSH. Ionizing radiation from ¹³¹I may thus negatively affect iodide transporter(s) specifically. In papers III-IV, a possible correlation between ¹³¹I-induced thyroid stunning and radiation induced DNA damage signalling to the ataxia telangiectasia mutated (ATM) kinase was investigated. Using genotoxic agents to induce preferentially DNA double strand breaks (DSB) (by calicheamicin 1y), DNA strand cross-linking (by cisplatin), and radiomimetic DNA lesions i.e. DSB in minority (by bleomycin), ¹³¹I-transport was found to be significantly inhibited, although most effectively by calicheamicin 1y, at sublethal drug concentrations. This was preceded by ATM-dependent phosphorylation of the H2AX histone variant, indicating nuclear foci of DNA-DSBs, after all treatments including cisplatin. Formation of H2AX foci was much less abundant in cells receiving ¹³¹I at 1-10 Gy for 4-48 hours. However, the same absorbed doses of ¹³¹I induced ATM-mediated global activation of Chk2, a key DNA damage checkpoint kinase, and transient cell cycle arrest of subconfluent cells. After recovery of cell cycle progression many of the irradiated cells formed micronuclei indicating chromosomal missegregation during mitosis. In contrast, ¹³¹I did not induce micronucleation in quiescent cells, although a delayed GO/M transition timing with the stunning phase was observed with cell cycle entry was evoked by epidermal growth factor stimulation. Collectively, this correlates ¹³¹I-induced inhibition of iodide transport to DNA damage, presumably DSBs. Nevertheless, proliferating thyroid cells are more radiosensitive than quiescent cells in terms of risk of developing genomic instability. In conclusion, thyroid stunning is a real phenomenon that may compromise the outcome of ¹³¹I therapy.

Keywords: thyroid, radiiodide, stunning, ¹³¹I, stress response, DNA damage. Chk2, H2AX, micronuclei, cell cycle