p53 Status and Tumor Cell Response to Radioimmunotherapy using 125I-mAbs

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Introduction: While radioimmunotherapy (RIT) of non-Hodgkin's B-cell lymphoma with Zevalin® and Bexxar ® (anti-CD20 labelled to 90Y or 131I) has demonstrated its efficiency. However, new strategies must be developed in order to treat solid tumours by RIT. In a previous study, we proposed to use the highly cytotoxic Auger electrons emitted by 125I to overcome the radioresistance of solid tumours. We showed that tumour killing achieved with non-internalizing labeled monoclonal antibodies (mAbs) is more significant than that of internalizing 125I-mAbs. This suggests that while the nucleus remains the main target of irradiation, the membrane is also a sensitive target. In the present study, we investigated the role of the nuclear p53 protein and that of ceramide, a major mediator of apoptosis, in the cellular response to 125I mAbs exposure. Material and Methods: Two carcinoma colic cell lines, H3E5 (p53 wt) and HCT116-KO (p53 deficient) expressing cell surface HER1 and CEA receptors were exposed for 2 days to increasing activities (0-4 MBq/mL) of either internalizing (anti-HER1) or non-internalizing (anti-CEA) 125I-mAbs. Survival was assessed by standard clonogenic assay and dosimetry was investigated using the MIRD scheme. For this purpose, uptake of radioactivity per cell was measured, and S-factors for 125I were specifically calculated for cell surface and cell cytoplasm localisation. Then, first experiments were carried out with alkaline comet assay to observe DNA damage from RIT. Results: For both cell lines, we confirmed that the toxicity due to 125I decays was greater with non-internalizing rather than with internalizing 125I-mAbs. Moreover, we showed that H3E5 cell line was more sensitive to X-ray external beam irradiation rather than HCT116-KO. By contrast, for both 125I localisations, preliminary experiment showed no significant difference on the survival between the two cell lines. These results would indicate that p53 status does not mediate the response to RIT with Auger electrons. A tentative explanation may involve the low dose rate induced by RIT. Under these conditions, no detectable DNA damage was measured by the alkaline comet assay. Conclusion: Our preliminary results seem to indicate that p53 status does not interfere with tumour cell response to RIT. Ongoing experiments are assessing the role of ceramide as a mediator of apoptosis, to explain membrane irradiation efficiency.

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