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125I-monoclonal antibodies triggercell membrane-mediated bystander effects.

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Objectives
The observation of radiation-induced bystander response has important implication for understanding the efficiency of radiotherapy particularly after low-dose exposure. We investigated the role of bystander phenomena in cells exposed to low-dose radioimmunotherapy (RIT) using 125I-monoclonal antibodies (mAb).
Methods: Contribution of bystander effects was assessed using standard medium transfer experiments between donor and receiver cells. To identify the role of the internalization of mAbs in the bystander response, cells were incubated in the presence of sodium azide, a drug blocking the internalization of antigens. The role of cell membrane rafts in 125I-mAbs-induced bystander effects was investigated by incubating donor cells undergoing RIT with either Methyl-β-cyclodextrine or Filipin, two lipid raft disruptors. Finally, the potential role of oxidative processes in bystander effects was tested using N-Acetyl-L-Cystein (NAC) or DMSO, two radical scavengers.
Results: Following treatment with anti-CEA or anti-HER1 125I-mAbs, we observed a decrease in survival of both donor(to 60% of control) and receiver cells (to 25% of control), confirming the presence of bystander effects. No cell killing in receiver cells was observed after donor cells were treated with the non-targeting mAb125I-PX, indicating the specificity of the latter response. Importantly, when anti-CEA or anti-HER1 125I-mAbs were trapped at the surface of donor cells, no significant difference in survival was observed, compared with the above results, obtained in response to internalized 125I-mAbs, both for donor or receiver cells. These results suggest that internalization of 125I within the cell is not required for the generation of a cytotoxic bystander response. In addition, the disruption of lipid rafts significantly increased clonogenic survival in donor ($P<0.001$) and receiver cells ($P<0.05$), indicating the important role of the cell membrane and more specifically of lipids raftsin the production of bystander effects. Furthermore, the observation that NAC increased the survival of donor and receiver cells indicated the involvement of oxidative stress in bystander effects associated withtreatment using125I-mAbs.
Conclusions: These results provide evidence that the cell membrane plays an essential role in the mediation of bystander responses induced by125I-mAbs.

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