Radiobiological characterization of primary neuroblastoma cell lines

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Neuroblastomas (NBs) are the most common extra-cranial solid tumor of infancy, representing 7-10 % of pediatric cancers and 15 % of all pediatric cancer deaths. They are embryonic tumors that originate from sympathoadrenal cells of the neural crest. One of the main features of these tumors is their enormous phenotypic heterogeneity: from low risk patients with spontaneous regression (stage 4S/MS) to high-risk tumors (stage 4/M), frequently metastatic and resistant to treatments. Amplification of MYCN is considered a prognostic factor for high risk NB. There is emerging evidence that cancer stem cells (CSCs) determine tumor evolution and also resistance to treatments and relapses. In fact, CSCs are resistant to chemotherapy and radiotherapy and their mechanisms of DNA damage repair are involved in this skill. In addition to that, tumor stromal cells have emerged as a key point for the biology of CSCs and their environment. There are many underlying biological mechanisms of NBs that remain unclear. Less than 40 % of patients older than 12 months with metastatic disease at diagnosis survive, despite of multimodality treatment. So we have focused on radiotherapy treatments against high risk NB, that have been changing from hypofractionated total body irradiation to local primary tumor radiation.

The main objective of our study was the radiobiological characterization of NB using different cell lines as model. We also consider extremely interesting to know the relevance of non-tumorigenic cells in NB tumors insulted by ionizing radiation (IR). Viability and survival, tumorspheres growth, repair of DNA damage and cell cycle checkpoints efficiency of irradiated NB cells have been analyzed. Our results demonstrated: (1) primary non-tumorigenic NB cell line (NB14t) shows higher viability against IR as compared to 3 tumorigenic cell lines with different genetic background and phenotypic features. (2) NB14t has an efficient clearance of double-strand breaks (DSBs), assessed by the *foci* assay, caused by IR and a correct efficiency of G1 cell cycle checkpoint. (3) IR induces G1 arrest in NB14t cell cycle before a differentiation process. (4) Tumorigenic and amplified MYCN cell line (IMR-32) shows lower viability against IR than the other cell lines tested. (5) In IMR-32, efficiency of repair of DSBs caused by IR is clearly lower. These cells have a dramatic lower capacity of tumorspheres formation after IR exposition too. (6) Co-culture of a non- tumorigenic NB cell line could have radioprotective effect on tumorigenic and amplified MYCN cell line (IMR-32).

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