FGF2 signalling is critical for DNA repair in human epidermal stem cells

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The sensitivity of stem cells to DNA damaging agents is a matter of debate. For mouse somatic stem cells, both radiosensitive and radioresistant stem cells have been described. By contrast, the response of human stem cells to ionizing radiation has been poorly studied. We evaluated in the present work the radiosensitivity of the epithelial stem cells from human interfollicular epidermis. We used flow cytometry and antibodies against cell surface markers (a6 integrin and CD71) to isolate keratinocyte stem cells and progenitors from human foreskin. Using a short-term cell survival assay (XTT at 72 h) and a long-term cell survival assay (CFE at 2 weeks), we demonstrated that keratinocyte progenitors were radiosensitive whereas the stem cells were more radioresistant (1). Using microarrays, we found that radiation exposure induced specifically several cytokines and growth factors genes in the stem cells, and notably the FGF2 pathway. Furthermore, DNA repair genes were found overexpressed in the stem cells. We thus postulated that the stem cells might have a more efficient DNA repair than the progenitors and might acquire an activated stress signalling response compared to the progenitors. We first studied the DNA repair of double strand breaks with the ?H2AX foci assay to evaluate the repair of DNA double strand breaks. After irradiation, the number of foci per cell decreased much more rapidly in the stem cells, suggesting a faster repair of DNA breaks. Moreover, using new bioarrays that measure DNA repair enzyme activities, we found that several repair enzymes were more active in the stem cells. Thereafter, to address the relationship between FGF2 and DNA repair, we inhibited this pathway at the level of the FGF2 receptor. Blocking FGF2 signalling inhibited the rapid decrease of ?H2AX foci in stem cells, suggesting a direct role of FGF2 in DNA repair. These results show that keratinocyte stem cells are a radioresistant cell population with a high DNA repair capacity. Moreover, we demonstrate that the FGF2 pathway plays a direct and specific role in DNA repair in epidermis stem cells. As stem cells are a long-term reservoir, these processes may be important for epidermis renewal and for carcinoma formation.

(1) Rachidi W, Radiother Oncol, 2007, 83, 267

Article published by EDP Sciences and available at http://www.radioprotection.org or http://dx.doi.org/10.1051/radiopro:2008521