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The role of miRNAs in the response of human keratinocytes to ionizing radiation

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Understanding the mechanisms of cutaneous radiosensitivity is an important issue since skin is the most exposed organ to ionizing radiations and among the most sensitive. Recent publications describe microRNAs (miRNAs), a group of short non-coding RNAs that negatively regulate gene expression, as potential modulators of cellular response to ionizing radiation (IR), both in vitro and in vivo in various cell types and tissues. However, in epidermal cells, the involvement of the miRNAs machinery in the cellular response to IR remains to be clarified. To address this question, we settled up an expression study of miRNAs in primary human keratinocytes. We analyzed the results of global miRNA profiling, performed by microfluidic system of qPCR assay, which permit to assess the expression of almost 800 annotated miRNAs. The keratinocytes derived from 3 or 4 independent donors were cultured to a proliferative or a differentiated state mimicking basal and suprabasal layers of human epidermis. These cells were irradiated at 10 mGy or 6 Gy and RNA was extracted 3 hours after irradiation. We found that proliferative cells irradiated at 6 Gy display a global fall of miRNA expression whereas differentiated cells exposed to the same dose display a global increase of miRNAs expression. To test if those global effects could be due to a specific regulation of the miRNA biosynthesis by IR, we investigated expression of DICER1 or EIF2C2, two crucial components of the miRNA pathway. We didn' t observe any significant modulation of these proteins expression after irradiation. Using a bilateral paired t-test, we identified miRNAs weakly but significantly modulated after 6 Gy irradiation, whereas only 2 miRNAs were modulated after low-dose irradiation in proliferating cells. To go further into the biological meaning of this miRNA response, we over-expressed some of the responding miRNA in proliferating cells by pre-miR transfection: we observed a significant decrease of cell viability 72h after irradiation. Altogether, our results indicate that the miRNAs play a weak but significant role in response to ionizing irradiation to ensure the short-term survival of irradiated human skin primary keratinocytes.

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