Identification of a mitochondrial control of radioresistance in human breast cancer models

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Abstract

Radioresistance is one of the leading causes of treatment failure in breast cancer (BC). Besides the well-known Oxygen Effect accounting for the stabilization of DNA damage and hypoxia accounting for the opposite, we hypothesized that other metabolic adaptations could account for BC radioresistance. Accordingly, considering that mitochondrial DNA is more sensitive to ionizing radiations than nuclear DNA and based on indications from one of our previous studies (1), we here aimed to test whether an acceleration of mitochondrial turnover could improve BC cell recovery after a single X-ray insult. Our overall aim is to provide a precise understanding of how mitochondria control radioresistance.

To test our hypothesis, we generated radioresistant (RR) human BC cell lines by exposing MCF-7 and MDA-MB-231 cells to increasing doses of X-ray irradiation over time. Acquired radioresistance was verified through proliferation and colony formation assays. Cellular metabolic profiling was determined using Seahorse bioanalysis, metabolite assays (ISCUSflex analyzer) and JC-10 staining (mitochondrial potential). MitoTimer, a mitochondria-targeted fluorescent reporter that changes its fluorescence wavelength over time from red to green, was used to probe mitophagy.

Metabolic comparison revealed that MDA-MB-231 RR had a more oxidative phenotype compared to their parental counterpart. Conversely, MCF-7 RR had a more glycolytic phenotype. Moreover, MDA-MB-231 RR cell line showed faster mitochondrial turnover reported by MitoTimer analysis, thus suggesting an association between mitophagy and acquired radioresistance. Using these models, further studies are ongoing firmly establish a causal link between radioresistance and accelerated mitochondrial dynamics (fission, mitophagy, mitochondrial biogenesis, fusion).

References

1. Grasso D. et al., Front. Pharmacol., 2020; 11:263.