The role of epigenetic modifications in the long term memory of cancer treatment

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Background: Due to the amelioration of Cancer treatments and to demographics, the number of cancer survivors is continuously increasing. This positive outcome is however shaded by the fact that cancer survivors are at increased risk of developing serious health conditions later in life, notably Type 2 Diabetes. The therapeutic agent associated with the higher prevalence of metabolic complications has been clearly identified to be radiation therapy but the mechanisms involved are unknown. Here, we hypothesize that irradiation alters the epigenome of precursor cells which in turn alters metabolic function in differentiated cells.

Aim: To determine if irradiation alters the DNA methylome of muscle cells, leading to altered differentiation potential and metabolic phenotype later in the cell life.

Methods: Human and Rat myoblasts were irradiated and left to recover for 2 and 4 weeks, respectively. Insulin sensitivity and response of fully differentiated myotubes were investigated by analysis of downstream targets in the insulin signalling pathway. Differentiation potential of irradiated cells after full (4 weeks) growth recovery was assessed by monitoring expression levels of myogenic markers such as myogenin and myosin heavy chain. DNA methylation was investigated using a whole-genome assay by capture of methylated DNA and subsequent deep sequencing.

Results: In rat myoblasts, irradiation induced a delayed differentiation as measured by myogenin expression. Insulin-induced ERK phosphorylation was increased in irradiated rat cells, while no change was found for Akt phosphorylation. Interestingly, genes regulating muscle differentiation and metabolism were found to be hypermethylated in irradiated cells. Different cultures of human myoblasts responded differentially to irradiation resulting in different response through insulin and AMPK pathways, which might reflect sex- or individual-specific response to irradiation.

Conclusion: Our preliminary studies suggest that irradiation could alter metabolic response of irradiated myoblasts, by altering muscle differentiation dynamics and insulin signal. The memory of irradiation could be held by epigenetic modifications.