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ESTRO 2023 Biology Track Report

Lipids and metabolomics in radiation response: an emerging paradigm in radioresistant cancers?

Chair: *Brita Singers Sørensen, Denmark*
Co-chair: *Marcel van Vugt, The Netherlands*

Speakers:

Natividad Gomez-Roman, UK
François Paris, France
Terence Burns, USA

The link between metabolic alterations and radiation response was the subject of the first symposium of the radiobiology track at ESTRO 2023. It took place on Saturday 13 May.

Natividad Gomez-Roman highlighted how cancer cells are addicted to cholesterol for proliferation, metastasis and response to treatment. In normal cells, the homeostasis of cholesterol is thinly regulated by extracellular uptake, synthesis via the mevalonate pathway, esterification and efflux. In cancer cells, cholesterol levels are not regulated in the same way; for example, the synthetic pathway does not switch off at high concentrations and there are differences in gene transcription methods and in trafficking.

The talk was focused on glioblastoma, in which the role of cholesterol is controversial because in-vitro studies show that the targeting of cholesterol reduces rates of cell survival, whereas in vivo this effect is not seen. A three-dimensional human glioblastoma model was used to perform a systematic analysis of the radiosensitising activity of drugs that target cholesterol pathways. Statins act on the cholesterol synthetic pathway and are effective in reducing rates of glioblastoma cell survival, but quite cytotoxic also to astrocytes. When statins were combined with irradiation, increased numbers of DNA double-strand breaks and mitotic catastrophes were observed. The cytotoxic effect was maintained also with the presence of a compound called AY9944, which targets the synthetic pathway downstream, and has no toxic effect on normal cells. The most cytotoxic activity was observed with a third compound, U18666A, which not only inhibits the cholesterol synthetic pathway, but also intracellular cholesterol transport and trafficking. Based on this observation, the role of the cholesterol transport and trafficking pathway in glioblastoma patient survival was investigated. Transcriptomic analysis through the use of the cancer genome atlas and genotype tissue expression (GTex) datasets demonstrated a greater expression of cholesterol-trafficking genes in glioblastoma stem cells than in normal cells. The presented data opens new, interesting therapeutic possibilities in glioblastoma care.

François Paris's talk was focused on the inhibition of the proliferation of tumour cells by ceramide. Ceramide is produced after oxidative stress, including that caused by irradiation, due to acid sphingomyelinase activation, and it is involved in several processes that induce cell death. Ceramide production causes gastrointestinal toxicity in mice when they are irradiated on the bowel, and it was demonstrated that the use of acid sphingomyelinase knockout mice avoided this toxicity. Thus, the knockdown of ceramide limits cell radiosensitivity. This radiosensitising effect is observed also in tumour cells, but at the tumour level, a role has been demonstrated also for endothelial cells in the production of ceramide and inhibition of tumour cell proliferation. Ceramide is not just produced intracellularly but also in the bloodstream. The importance of bloodstream secretion was demonstrated by the addition of the medium of irradiated endothelial cells (acute secretory associated phenotype, ASAP) to the Michigan Cancer Foundation-7 (MCF7) cell line. In the presence of ASAP, a reduced number of cells and a lower index of ki67-positive cells were observed; the effect was blocked with antibody anti-ceramide. Efforts were made to understand in what way the secreted ceramide might be involved in inhibition of proliferation and it was found that the presence of ASAP decreased laminin B1 expression. Laminin B1 is implicated in the maintenance of chromatin plasticity; the absence of laminin B1 induces chromatin decondensation,

changes of the heterochromatin in euchromatin, and enables an increased rate of transcription of genes, which induces cell cycle arrest. This interesting data has been observed in vitro and should be confirmed in vivo in mouse models.

Terence Burns discussed the effect of irradiation in glioblastoma and focused on radiation-induced metabolic alterations that are associated with tumour aggressiveness and poor prognosis. When the brain is irradiated before a tumour xenograft, greater tumour aggressiveness is observed. The effect is due to cell senescence and the autocrine/paracrine secretion of senescence-associated secretory phenotype, which acts as a double-edged sword with both antitumour- and pro-tumourigenic effects. After irradiation, there is a downregulation of laminin B1 and an upregulation of p21. Senescence-driven aggressiveness is dependent on the presence of p21, and the use of a p21 knockout animal removes the effect.

Probably several other mechanisms are involved in the radiation-induced aggressiveness. The analysis of metabolome of different tumour lines shows huge differences between irradiated and non-irradiated brains in preclinical models. Preclinical models have evident limits compared with clinical settings. Dr Burns presented his outstanding studies, which involve intraoperative dialysis and reservoir placement in patients. The analysis of cerebrospinal fluid biomarkers and the pharmacodynamic analysis of metabolic agents after brain irradiation and systemic treatments could provide insight into physiopathology and help in the search for more effective targets that enable treatment.

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