Optimizing the fractionation of radiation therapy –
to avoid radio-resistance and evoke immune response.

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Background

During the last decades the central dogma in radiation biology has been questioned. Non-irradiated cells communicating with irradiated cells may exhibit radiation damage; a bystander effect. At the same time, new data indicate that cellular communication can cause an opposite rescue effect, where cancer cell become radio-resistant. Together, the bystander and rescue effect emphasize that the radiation response is dependent on cellular signaling and that the irradiated cell must be envisioned in its biological context.

Immunotherapy is the latest and most promising addition to the arsenal of treatment options against metastatic cancer. To improve response rates to immunotherapy, promising data indicate that radiation can turn the tumor into an in-situ-vaccine. The optimal doses and fractionation of the radiation combined with immunotherapy remains to be investigated.

Aims and Methods

The first part of the project aims at studying the role of cellular communication on the radiation response. This is done in vitro by allowing and inhibiting communication between cells, and by targeting specific signaling pathways.

The second part concerns the combination of radiation and immunotherapy. We are setting up a translational research platform, including a mice model and a clinical study with the objective to better understand and clarify the role of radiation in awakening an immune-response.

Preliminary Results

Our data shows that the cancer cells protect themselves against radiation damage through cellular communication. The denser the cancer cells grow, the more radio-resistant they become (Adrian et al. 2018). The experiments show that this rescue effect is mediated through signals in the medium, and can be transferred to sparsely seeded cells using cell-conditioned medium (i.e. medium that has been “fed” with signals excreted from cells). Further, using modulated beam irradiation where 50% of the cells
are spared from irradiation, the in-field cells that are irradiated and communicating with the non-irradiated cells become radio-resistant.

We have now continued to characterize this effect and its underlying signaling pathways. Through inhibition of specific cell surface receptors, we have been able to reverse the radioresistance caused by conditioned medium. Also, the split-dose recovery, hence the radiation repair occurring the first hours after irradiation, has been found to be involved in the aforementioned rescue-effect and can be targeted through receptor inhibition. A manuscript presenting these findings will be prepared in the coming months. Moreover, we have found evidence for a possible in vivo effect where fractionation sensitivity differs depending on tumor size.

The immunotherapy experiments are just about to be started and we are waiting the first results during 2018.

Significance

The overall goal of the PhD-project is to improve the understanding of radiation biology by involving the new role of both signaling mediated radiation responses and its immune-sensitizing effect. By doing this, we aim at optimizing dose and fractionation schedules, to increase the therapeutic window by reducing the role of signaling mediated radio-resistance and take advantage of the immune-stimulating effects. Hereby, we want to develop new and better treatment options for cancer patients.

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