Pharmacological augmentation of heavy ion cancer therapy *

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Heavy Ion Therapy led to unique treatment options in certain types of cancer, extending to more challenging disease entities. However, effects which abrogate treatment success can be active in the patient. For example, tumors generally induce inflammation and a hypoxic environment. This leads to cells which are resistant against direct effects of X-rays and results in a very limited access by the immune system. Which is disadvantageous, as the immune system was shown to contribute significantly to radiotherapy success. Therefore, we devised a pharmacological system which is addressing the resistance against direct effects of radiation and to relieve tumor induced immune suppression. The method was shown to improve the tumor phenotype and to enhance the sensitivity to X-ray- and particle irradiation, yielding more killed cells, expressing more immune activating ligands.

Description of the field

Radiotherapy, Pharmacology and Immune Therapy evolved in different fields of science, following more physical, chemical and biological lines of thinking, respectively. However, it has turned out that the immune system is heavily influencing direct and indirect effects of radiation. Therefore, we recently argued to transform the way radiation is interacting with the immune system of the patient and the tumor pharmacologically.[1]

Description of the project

Exploiting the recent knowledge about exposure pathways and molecular hallmarks of the immunogenicity of radiation and drugs, we first combined two pharmacological entities with radiation. Chloroquine is an established anti malarial drug even in preventive use, CDDO-Me is an anti inflammatory synthetic triterpenoid which is in clinical studies. To further improve the immunological and direct radiation effects, a combined c-Met / VEGFR2 Inhibitor (TKI) was added to the combination, which is already approved for medullary thyroid cancer.

Results

The combination of Chloroquine and CDDO-Me led to increased surface translocation of the immune relevant molecules CD95, MHC-I, Rae-1, Calreticulin and TRAIL. Adding the TKI further enhanced the pro-apoptotic properties of the combined treatment in CT26.WT tumor cells. As apoptotic cells were shown to express more immune relevant molecules on the surface, increased apoptotic cell death is thought to be beneficial for the induction of tumor immune responses. This effect of enhanced tumor cell killing was even more pronounced using carbon ions.

Outlook

Despite this treatment has so far only been tested in vitro by us, a solid and significantly increasing amount of clinical and preclinical evidence points to the beneficial effects of the pharmacological components used for supporting immune therapies. Therefore, it could be envisaged that in a combined treatment, there is significant translational potential for use in carbon ion therapy and other radiation based therapy forms as well.

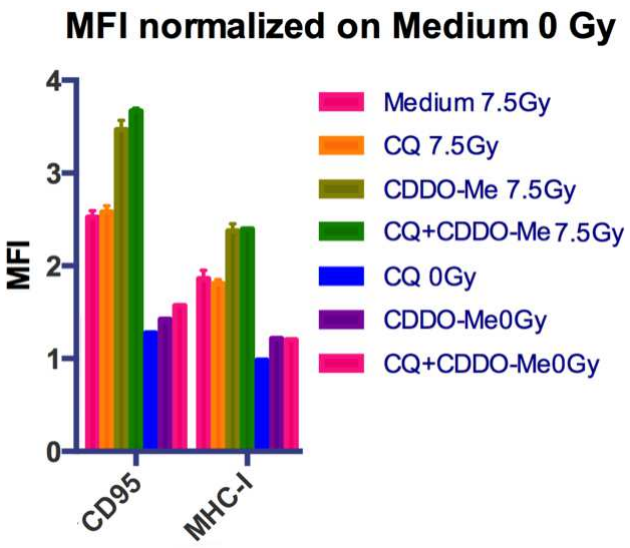

Figure 1: Increased surface translocation of CD95 and MHC-I after irradiation under the influence of Chloroquine, CDDO-Me and the combination thereof. Note: The drug effects became pronounced only in irradiated cells while there was only little change in non-irradiated cells.

References

[1] M. Durante, N. Reppingen and K. Held, “Immunologically augmented cancer treatment using modern radiotherapy ”, Trends in Molecular Medicine, September 2013, Vol. 19, No. 9, 565-582, http://dx.doi.org/10.1016/j.molmed.2013.05.007

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