Chloroquine inhibits the malignant phenotype of glioblastoma

Glioblastoma (GBM), the most common and aggressive primary brain tumor, is characterized by excessive growth and infiltration of the normal brain which prevents the complete surgical resection. These tumors also are refractory to standard treatment strategies, which consist of both radio- and chemotherapy. Consequently, clinical responses are invariably transitory and the prognosis barely exceeds 14 months as local or distant (or both) recurrence is inevitable. Therefore, several innovative therapeutic strategies have been studied and developed. One such option involves the use of chloroquine (CQ), a known antimalarial drug, that has shown promising results in several pre-clinical studies against malignant brain tumors. The molecular properties of CQ allow it to accumulate in the area of the cells where proteins are built and block this very process.

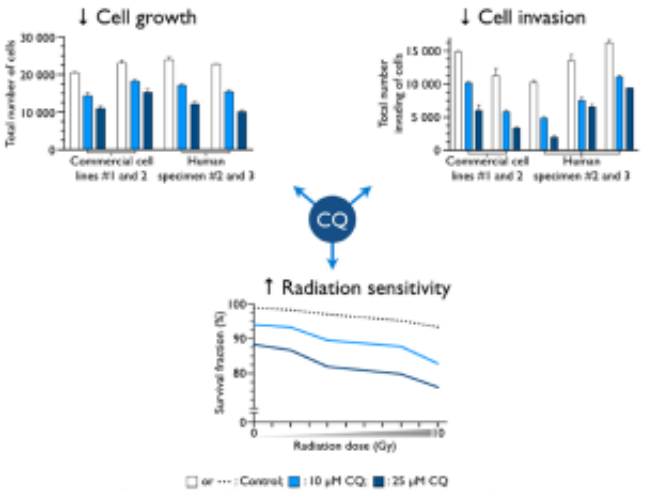

Fig. 1. Anti-glioblastoma effects of chloroquine.

The aggressiveness of malignant brain tumor cells is instigated by the aberrant effects of certain proteins such as growth factors and their cell-surface receptors. We thus hypothesized that CQ could be an effective drug to hinder the production of proteins responsible for the malignant behavior of GBM. Accordingly, we investigated the efficiency of CQ to impede different characteristics of the tumor cells, such as rapid growth, invasion and resistance to radiotherapy.

Using fluorescence-based cell counting to monitor cellular division, we showed that CQ treatment reduced by half the cell growth of primary cultures from human GBM specimens and commercial GBM cell lines. Moreover, utilizing fluorescent antibodies and cellular imaging, we noticed that adding CQ to the cultures medium caused changes typically associated to programmed cell-death

(or cellular suicide).

We then investigated the effect of CQ treatments on the capacity of GBM cells to migrate and degrade proteins of the surrounding environment (extracellular matrix). We observed that CQ abrogated by 50% the activity of the Matrix metalloproteinase-2, an enzyme secreted by GBM cells that breakdown components of the environment surrounding the cells. Furthermore, we used Boyden chambers to simulate cellular invasion and measured that treatments with CQ significantly hindered the migration ability of GBM cells.

Finally, we tested whether CQ treatments could improve the sensitivity of GBM cells to radiotherapy. We used fluorescence- and colorimetric-based cell counting to monitor cell-arrest in proliferation and induction of cell-death, two processes occurring following treatments with radiation. We noticed that concomitant treatments with CQ and radiotherapy markedly sensitized GBM cells to radiation resulting in improved efficacy of radiotherapy. Indeed, cells treated with both CQ + radiation showed a decreased cell growth and higher cell death compared to cells exposed to radiation alone. Interestingly, we noticed that radiation promoted invasion of tumor cells and that CQ treatment prior to radiotherapy was enough to substantially restraint this effect.

To explain these results, we investigated whether CQ reduced the production of Transforming Growth Factor-beta (TGF-?) by GBM cells, a protein known to promote multiple features in the malignant behavior of GBM. We thus assessed the ability of GBM cells to secrete TGF-? as well as it’s cellular activity and concluded that CQ was a potent inhibitor of TGF-? production and that this protein was partly responsible for the malignant progression of GBM.

This study suggests that CQ, alone or as a complement to current treatment strategies, could be used to restrain different attributes of malignancy in GBM. This could improve the clinical management and greatly benefit GBM afflicted patients by increasing tumor control.

Publication

Chloroquine inhibits the malignant phenotype of glioblastoma partially by suppressing TGF-beta.
Roy LO, Poirier MB, Fortin D
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