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Pleiotropic impacts of chloroquine encompass concurrent activation of pro-survival and pro-death signaling in glioblastoma stem cells: Implications for chloroquine-mediated radiosensitization

Abstract: Glioblastoma is the most malignant form of brain tumor in adults. High degree of intrinsic and acquired radioresistance is the major challenge to glioblastoma therapy with effective radiosensitizing treatments remaining an unmet medical need. The biological paradigm of glioblastoma is based on a premise that so-called glioblastoma stem-like cells are as the major cellular determinants of glioblastoma radioresistance and tumor re-growth after (or under) cytotoxic non-targeted therapies. Pleiotropic agent chloroquine has attracted considerable attention in the past decade for its potential radiosensitizing effects in difficult-to-treat cancers including glioblastoma. However the molecular and cellular mechanisms underlying anti-tumour actions of chloroquine remain poorly understood. Our investigations reveal a previously unknown mechanistic duality and antagonistic impacts of chloroquine manifest in the concurrent activation of both survival-promoting and death-inducing molecular signaling in glioblastoma stem cells via transcription-dependent and transcription-independent mechanisms. Our findings indicate that the ultimate outcome of chloroquine treatment is determined by the balance between pro-death and pro-survival signals elicited at the level of transcriptional control as well as via direct impacts on the abundance of key regulators of the DNA damage response and cell fate including ATM, p53, p21, HIPK2 and AKT. We propose a conceptual framework for predicting the efficacy of chloroquine for glioblastoma radiosensitization based on the status of tumor suppressor p53, which has a decisive impact on the balance between pro-survival and pro-death responses activated by chloroquine. Our model based on findings with glioblastoma stem cells has a broader impact and is applicable to other radioresistant cancers. A more detailed discussion will focus on the current and perspective approaches to individualized molecular diagnostics for glioblastoma.

Keywords: glioblastoma / glioblastoma stem cells / chloroquine / radiosensitization

Biography: Dr. Ella Kim has received her Ph.D. at the Institute of Molecular Biology (Kiew, Ukraine) in 1990. In 1992, Dr. Kim took a postdoct position at the Barrow Neurological Institute (Phoenix, AZ USA). In 2003, she received an EMBO Fellowship for a research project on transcriptional control by tumour suppressor p53 at the Heinrich-Pette-Institüt (Hamburg, Germany). Since 2003, Dr. Kim directs own research on molecular and cellular mechanisms of glioblastoma progression. Since 2011, Dr. Kim directs the Laboratory of Experimental Neurooncology at the Clinic for Neurosurgery of the University Medical Centre of Mainz (Germany).

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