RESVERATROL EFFECTS ON MIGRATION AND WNT SIGNALING PATHWAY IN CANCER STEM CELL LINES FROM GLIOBLASTOMA MULTIFORME

Chiara Cilibrasi[1,2], Gabriele Riva[1,2], Valentina Butta[1,2], Leda Dalprà[2,3], Angela Bentivegna[2]

PhD in Neuroscience, University of Milan-Bicocca, Department of Surgery and Translational Medicine, Monza-Italy[1]
University of Milan-Bicocca, Department of Surgery and Translational Medicine, Monza-Italy[2]
Department of Clinical Pathology, Medical Genetics Laboratory, San Gerardo Hospital, Monza-Italy[3]

Introduction Glioblastoma multiforme (GBM) is a grade IV astrocytoma and the least successfully treated solid tumors: current therapies provide a median survival of 12-15 months after diagnosis, due to the high recurrence rate. GBM is characterized by an highly infitrative nature and a remarkable intratumoral heterogeneity, mirrored by the presence of distinct sub-populations of cells with different tumorigenic capabilities: Glioma stem cells (GSCs) are believed to be the real driving force of tumor initiation, progression and relapse. Better therapeutic strategies GSC-targeted are needed.
Resveratrol (RSV) is a polyphenolic phytoalexin with pleiotropic health benefits. Many studies highlighted its antiproliferative and proapoptotic effects and its ability to reduce tumor invasion and cell migration in several types of cancers, including GBM.
RSV might represent an attractive agent for the treatment of GBM because of its minimal toxicity and blood brain barrier permeability.
Material and Methods In this study, we analyzed the effects of RSV exposure (48-72-96h) on cell motility, through Wound Healing assay, in six GSC lines isolated from GBM (GBM2, GBM7, G179, GliNS2, G144, GBM04). Moreover we evaluated the effect of RSV administration on WNT signaling pathway using RT-PCR technology on Applied Biosystems platform. The WNT signaling expression profile was performed using PCR custom arrays (Qiagen) on untreated and treated (100μM 96h RSV) cells in order to explore expression variations of 7 WNT-related genes (WNT1, FZD4, CTNNB1, EP300, CREBBP, TCF7, MYC) after RSV exposure.
Results RSV strongly reduces cellular motility in all GSC cell lines and differently modulates WNT signaling pathway in the GSC cell lines taken into account. WNT1 is upregulated in GBM04 and G144 cell lines, while FZD4 is upregulated in GBM2, GBM04 and G144 cell lines after treatment. CTNNB1 and EP300 show an unchanged transcriptional activity in most of the cell lines. CREBBP and TCF7 are upregulated in some cell lines and downregulated in others. MYC is upregulated in most of the cell lines.
The validation of these data in order to verify, at protein level, the RSV modulation of MMPs and WNT signaling pathway is in progress.
Conclusions RSV treatment could represent, in combination with other therapeutic strategies, a new approach in order to inhibit the infiltrative nature of GSCs. Moreover the study of the WNT signaling pathway could suggest new insights on GBM oncogenesis.