Abstract 2216: Study of PDL-1 regulation and expression in glioblastoma and its role in cancer resistance

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Abstract

Among the high-grade malignant gliomas (III-IV), grade IV glioma, or glioblastoma (GBM), is the most common and destructive form of brain cancer. Despite rigorous molecular, preclinical, and clinical research these tumors remain a challenge to treat and 70% of patients diagnosed with GBM will succumb to the disease within 2 years. New immune-based cancer treatments are currently in development, among which, anti-PD-1 is in a phase II clinical trial for recurrent glioblastoma. Tumor cells exploit PDL-1/PD1 pathway to induce T cell exhaustion and evade host antitumour immunity. PDL-1 expression on glioblastoma has been shown to correlate with a bad prognosis. There is strong demand for knowledge about the mechanisms regulating PDL-1 expression in glioblastoma. Our research group, has previously identified a relevant role for FKBP51, and its spliced isoform FKBP51s, in PDL-1 expression and melanoma resistance to the therapy. FKBP51 is an immunophilin capable of immunosuppression, originally cloned in lymphocytes. Because FKBP51 was identified as highly expressed in glioblastoma, correlating with tumor aggressiveness, we investigated whether this protein and/or its spliced isoform FKBP51s could be involved in regulation of PDL-1 expression in glioblastoma. In addition, we looked at the role of these protein-isoforms in glioblastoma resistance to chemotherapy. To this aim, we used two different glioblastoma cell lines termed D54 and U251. Our results suggest that, differently from melanoma, in which PDL-1 is inducible and associated with FKBP51 splicing, glioblastoma cell lines express high basal levels of PDL-1. Interestingly, both the canonical and the spliced FKBP51 isoforms were highly expressed in the glioblastoma cell lines. Expression of PDL-1 was regulated by FKBP51s knockin and knockout and the levels changed in accordance with FKBP51s levels. Moreover, in glioblastoma cells silenced for FKBP51s, the decrease in PDL-1 levels was associated with a significant increase in apoptosis, either spontaneous apoptosis and the one stimulated by etoposide or temozolomide. Two recently developed compounds, selective inhibitor of FKBP51, termed SAFit1 and SAFit2 were able to reduce expression of PDL-1 on glioblastoma cell lines. Particularly, SAFit 2 was found to be more effective, in accordance with the notion that it is more brain-permeable than SAFit1. SaFit 2 was also shown to increase sensitivity to etoposide of glioblastoma cell, although to a lesser extent when compared to FKBP51siRNAs. In conclusion, our preliminary results suggest that FKBP51s plays a relevant role in glioblastoma resistance and PDL-1 expression. Future studies are needed to shed light on the mechanisms underlying FKBP51s-induced PDL-1 expression and signaling pathway downstream to FKBP51s/PDL-1 that sustain glioblastoma resistance.

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