Title

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342. UNDERSTANDING THE MOLECULAR BASES OF CHEMOTHERAPY-INDUCED COGNITIVE IMPAIRMENT: NORMAL NEURAL PRECURSORS HAVE DIFFERENTIAL SENSITIVITY TO COMMONLY USED CHEMOTHERAPY DRUGS

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INTRODUCTION: The role of neural stem/precursor cells (NPCs) in memory and attention is increasingly recognized. However, there is a need to identify the role NPCs play in the development of chemotherapy-induced cognitive decline. In this study, we first report that nonspecific DNA-damaging chemotherapy agents are toxic to NPCs, and that more targeted drugs do not affect the normal cells while killing the malignant glioma stem/precursor cells (GPCs). METHODS: We used three human NPC cultures, and multiple GPC cultures. All these cells form spheres and differentiate in appropiate conditions. RESULTS: Treatment of GPCs with erlotinib caused cell death at low concentrations, with 4 μM causing a 50% decrease in viability. In contrast, treatment of NPCs with erlotinib as high as 50 μM did not affect cell viability, which correlates with low epidermal growth factor receptor (EGFR) expression. GPCs were very sensitive to bortezomib, with doses as low as 0.5 nM causing more than 80% cell death, proportional with the base-line proteosome levels. At similar doses, NPCs were less affected, with viabilities of more than 70%. The GPCs were resistant to temozolomide, with doses as high as 750 mM producing only a 25% decrease in viability. NPCs, on the other hand, experienced a 50% decrease in viability at a dose of 100 mM. Finally, cisplatin treatment at 5 mM led to viability of less than 20% of NPCs but 70% of GPCs. The NPCs' sensitivity to temozolomide and cisplatin correlates with low expression of the drug resistence gene ABCG2. CONCLUSION: We have identified that EGFR-TK inhibition as well as proteosome inhibition are effective against GPCs, while producing minimal effects on NPCs. In contrast, temozolomide and cisplatin are more toxic for NPCs than for GPCs. As the ultimate goal of chemotherapy is the eradication of GPCs while maintaining patient cognition, that is, preserving normal NPCs, the development and use of more selective drugs is warranted.