Systems pharmacology and machine learning for optimizing treatments of brain tumors

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Glioblastoma (GBM), the most frequent and aggressive brain tumor in adults, is associated with a dismal prognostic despite intensive treatment involving surgery, radiotherapy and temozolomide (TMZ)-based chemotherapy. The initial or acquired resistance of GBM to TMZ appeals for precision medicine approaches for the design of novel efficient combination pharmacotherapies. To that end, a comprehensive approach combining quantitative systems pharmacology (QSP) and machine learning was undertaken to design TMZ-based drug combinations circumventing the initial resistance to the alkylating agent. A QSP model representing TMZ cellular pharmacokinetics-pharmacodynamics and dysregulated pathways in GBM based on ordinary differential equations was developed and validated using multi-type time- and dose-resolved datasets. In silico drug screening based on numerical optimization and subsequent experimental validation identified a strategy to re-sensitize TMZ-resistant cells consisting in combining TMZ with inhibitors of the base excision repair and of homologous recombination. Using machine learning, model parameters driving response to such optimal multi-agent therapy were derived to assist decision making in patients. Thus, we successfully demonstrated the relevance of combined QSP and machine learning to design efficient drug combinations re-sensitizing glioblastoma cells initially resistant to TMZ. The developed framework may further serve to identify personalized therapies and administration schedules by extending it to account for additional patient-specific altered pathways and whole-body features.
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