Development of an AI platform for prediction of brain tumour response to therapies from multimodal human tumour spheroid data

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Introduction

Artificial intelligence (AI) has accelerated novel discoveries across multiple disciplines including medicine. Clinical medicine suffers from a lack of AI-based applications, potentially due to lack of awareness of AI methodology. Future collaboration between computer scientists, clinicians and biologists is critical to maximize the benefits of transformative medical technologies for patients.

Gliomas are the most common primary intracranial malignancy, and comprise 1.8% of human malignancies and 2.3% of cancer deaths worldwide. Gliomas account for 27% of primary and 80% of all malignant CNS tumours. In India, the incidence of central nervous system (CNS) tumours ranges from 5 to 10 per 100,000 individuals and accounts for 2% of malignancies. The World Health Organization (WHO) histopathological classification of gliomas includes four grades: grades I and II are considered low-grade gliomas (LGG) and grades III and IV (glioblastoma-GBM) are considered high-grade gliomas (HGG). Glioblastomas are the most malignant form comprising of 54% of all gliomas. In India high-grade gliomas (glioblastomas) account for 59.5% of CNS tumours. The Central Brain Tumour Registry (www.cbtrus.org) states that the five-year survival rate of adult patients with GBM is around 4.3% or less than 14 months after diagnosis. The recalcitrance of gliomas results from their infiltrative behaviour, aggressive biology, genomics, and presence of the blood-brain barrier that reduces the delivery of systemic chemotherapies. A typical treatment plan for gliomas involves 1) initial diagnosis, 2) establishing degree of infiltration, 3) localization and segmentation, 4) clinical/imaging data and in some cases 5) genomics and cell biology investigations. Post-treatment evaluation focuses on tumour progression and/or recurrence. However, as the poor survival rates indicate, these treatments have not been effective in preventing disease progression. Traditionally, these data are compiled manually by skilled pathologists and physicians. In the future, artificial intelligence (AI) will augment clinical decision making in cancer patient management, and usher in an era of personalized medicine. An example today is IBM Watson for oncology, a prototypic cloud-based AI, that helps physicians plan treatments by analysing clinical, genetic and imaging databases.

The tumour microenvironment (TME): The tumour microenvironment contributes to the complexity in GBM treatment. Hypoxia and angiogenesis are central to glioblastoma growth. As the tumor grows there is an increase in metabolic demand thereby creating an environment of low oxygen in the tumor core termed “hypoxia”. The hypoxic core of GBMs have 0.3% to 2.5% oxygen in intratumoral and peritumoral areas respectively. Hypoxia is responsible for radio and chemoresistance of the tumor. Radiotherapy and chemotherapeutic agents require oxygen free radicals for permanent DNA damage of cancer cells. Unavailability of oxygen free radicals in the hypoxic core makes these treatments ineffective. Hypoxia plays a vital role in the growth and development of the tumor.

Novel models for Glioma: A key challenge for clinical management of glioblastoma (GBM) is its highly heterogeneous nature, with heterogeneity between patients and within a single tumour representing important barriers for current therapies. Glioma cerebral organoids - preclinical GBM models are limited by the lack of a “normal” human microenvironment and the inability of many tumour cell lines to accurately reproduce GBM biology. To address these limitations, model systems have been created to retro-engineer patient-specific GBMs using patient-derived glioma stem cells (GSCs) and human embryonic stem cell (hESC)-derived cerebral organoids. The cerebral organoid glioma model shows that GSCs home toward the human cerebral organoid, invade and proliferate within the host tissue, forming tumours that closely copy patient GBMs. Furthermore, these cerebral organoid tumours form rapidly and are supported by an interconnected network of tumour microtubes that aid in the invasion of normal host tissue. These models provide a system for modeling primary human GBM ex vivo especially for high-throughput drug screening.
The principle of cancer treatment has changed from traditional surgical resection to the new era of precision medicine. Increased understanding of the genomic landscape through multi-omic approaches has revealed mutations common to specific subtypes, provided new prognostic and predictive markers, and highlighted potential therapeutic targets. Evaluating new targets using established cell lines is limited by the inexact correlation between responsiveness observed in cell lines versus that elicited in the patient. Patient-derived xenografts (PDXs) are models of cancer where the tissue or cells from a patient's tumour are implanted into an immunodeficient or humanized mouse. PDX models are used to create an environment that allows for the natural growth of cancer, its monitoring, and corresponding treatment evaluations for the original patient. These are generated from fresh tumour specimens recapitulate the diversity of cancer and reflect histopathology, tumour behavior, and the metastatic properties of the original tumour. The high degree of genomic preservation evident across primary tumours and their matching PDXs over serial passaging validate them as important preclinical tools. There is accumulating evidence that PDXs can recapitulate treatment responses of the parental tumour. The PDX models market is expected to grow at a compound annual growth rate of 16.7% from 2017-2022. The growing demand for personalized medicine, continuous support for cancer research from the public as well as private sectors, and growth in the number of R&D activities in the pharmaceutical industry are driving the growth of this sector. Unfortunately, engraftment into a mouse or matrix material exerts a selection pressure that changes the clonal composition. Also, the high cost of personalized PDX models and stringent guidelines regarding the ethical use of animals in cancer research restrain the effective use of this technology.

Patient-derived spheroids are self-assembled, cell aggregates that possess many important components of the physiological, spatial, growth and cell-cell interactions. Spheroid outer layer continues to proliferate while the core becomes necrotic due to hypoxia and nutrient deficiency. These conditions are similar to hypoxic micro-tumours in vivo. This model allows for collection of comprehensive patient to patient variable data. Conventional data analytical approaches are not sufficient to predict the GBM spheroid shape, size and cellular composition. This limitation is due to multiple visible and non-visible parameters from the system and environment that can play significant roles in the development of the spheroid. As part of this work, we aim to develop an AI-based approach that can use data from multiple sources in multiple formats and train Artificial Neural Networks (ANN) to predict the various characteristics of the GBM spheroid. These deep learning based ANN are generally not comprehensible for humans. Since the domain of healthcare is critical, therefore it is necessary to develop AI-based approaches that are understandable. The development of an AI based patient derived spheroid model that allows for effective patient therapies is timely. We believe our efforts will provide an enhanced understanding of recalcitrant glioblastoma pathology allowing for better identification of histological markers, and therapeutic targets that, in the long run, may aid in development of better strategies for diagnostics and/or development of therapeutics for improved survival and/or delayed disease progression. This will also provide a cost effective and rapid method for disease diagnosis and treatment prediction.

References


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