Utilizing genomic tools to characterize the tumour landscape of glioblastoma

By Puja Bagri

Revolutionary innovations in next-generation DNA sequencing technologies have given way to significant advances in our understanding of cancer genomics and tumour biology. New developments in these methods are increasing the speed and efficiency of genome sequencing, while reducing the associated costs. This has allowed for tremendous growth in cancer research, providing novel approaches to characterize the genomic tumour landscape, and leading to better therapeutic options.

Cancers result from accumulative genomic alterations; thus, understanding the genome of cancer patients can provide a thorough blueprint of an individual's cancer cells and offer improved insight for diagnosis and therapy. A collaboration between Dr. Sheila Singh at McMaster University and Drs. Jason Moffat and Sachdev Singh from University of Toronto entails research using cutting-edge new technologies and a patient-centered approach to better understand a fatal form of brain cancer, glioblastoma (GBM). GBM is the most common primary brain tumour in adults, accounting for 80% of all malignant brain tumours (1). Incidents of GBM are most common in adults over the age of 40, and it is estimated there are 13, 000 new cases diagnosed every year in North America (2). The multi-model strategy currently being used to treat GBM includes surgery, chemotherapy, and radiation, but fails to provide effective protection due to the resistance of the tumour cells (3). The ability of the tumour cells to invade and infiltrate healthy surrounding tissue makes complete eradication nearly impossible and tumour recurrence inevitable. Due to recurrent, therapy-resistant tumours, patients have an average survival time of only 12-15 months, and with less than 10% of patients surviving beyond 5 years (4).

Research being conducted in Dr. Sheila Singh's lab focuses on what causes GBM tumour recurrence. They are utilizing cutting-edge genomic tools such as next-generation RNA sequencing (RNA-seq), proteomics and CRISPR (clustered regularly interspaced short palindromic repeats) to characterize the tumour landscape of recurrent GBM, and will be developing immunotherapeutic modalities targeting novel markers of GBM. As described by Dr. Sheila Singh's graduate student, Chirayu Chokshi, the ultimate goal of this project is to generate a "translational pipeline from initial target discovery (through target validation and exploration of mechanism), [and] develop new biotherapeutics against novel cancer targets, conduct preclinical testing in our advanced patient-derived animal model of treatment-resistant GBM, and finally, translate these findings into early clinical trails to provide hope for future GBM patients".

Although great progress has been made in understanding the genomic abnormalities involved in GBM tumourigenesis due to large-scale molecular profiling efforts, there are still many challenges preventing the development of a successful treatment. According to Chokshi, the futility of current GBM treatments is due to the heterogenous nature of this disease. Even though molecular profiling of GBM has allowed scientists to identify potential therapeutic targets, no single driver mutation can explain GBM tumourigenesis or be targeted to treat all patients. Hence, the molecular diversity of GBM is what makes it so difficult to treat. Not only is there great intra-tumour (within each patient) heterogeneity, there is also significant patient-to-patient (inter-tumour) heterogeneity as well.

For these reasons, the Singh lab is interested in applying a patient-specific approach for treating GBM. Their strategy is to target the cells causing tumour recurrence by utilizing a patient-derived xenograft model, which will allow for the discovery of driver mutations. Using RNA-seq, they plan to track GBM cell populations that undergo clonal evolution as a result of selective pressures exerted by standard treatments, and identify the cellular composition of the population causing tumour recurrence in their in vivo model. This will allow them to determine the intracellular pathways that drive GBM relapse in individual patients, which can then be targeted during therapy. This approach is very promising and has the potential to help prevent tumour recurrence.

While there are still several challenges due to the molecular complexity of GBM, genomic tools

are giving scientists hope that viable treatments will soon be available. The Singh lab believes that the power of genomic tools extends past the ability to characterize GBM tumours, and will eventually lead to better disease outcomes for patients. ■

References

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