The Cancer Genome Atlas

The Cancer Genome Atlas (TCGA) is a project, begun in 2005, to catalogue genetic mutations responsible for cancer, using genome sequencing and bioinformatics.

TCGA applies high-throughput genome analysis techniques to improve our ability to diagnose, treat, and prevent cancer through a better understanding of the genetic basis of this disease.

TCGA is supervised by the National Cancer Institute's Center for Cancer Genomics and the National Human Genome Research Institute funded by the US government. A three-year pilot project, begun in 2006, focused on characterization of three types of human cancers: glioblastoma multiforme, lung, and ovarian cancer.

In 2009, it expanded into phase II, which planned to complete the genomic characterization and sequence analysis of 20-25 different tumor types by 2014. TCGA surpassed that goal, characterizing 33 cancer types including 10 rare cancers.

Funding is split between genome characterization centers (GCCs), which perform the sequencing, and genome data analysis centers (GDACs), which perform the bioinformatic analyses.

The project scheduled 500 patient samples, more than most genomics studies, and used different techniques to analyze the patient samples. Techniques gene expression profiling, copy number variation profiling, SNP genotyping, genome wide DNA methylation profiling, microRNA profiling, and exon sequencing of at least 1,200 genes. TCGA is sequencing the entire genomes of some tumors, including at least 6,000 candidate genes and microRNA sequences. This targeted sequencing is being performed by all three sequencing centers using hybrid-capture technology. In phase II, TCGA is performing whole exon sequencing on 80% of the cases and whole genome sequencing on 80% of the cases used in the project.

Glioblastoma multiforme

The Cancer Genome Atlas effort has generated significant interest in a new paradigm shift in tumor tissue analysis, patient diagnosis and subsequent treatment decision. Findings have highlighted the limitation of sole reliance on histology, which can be confounded by inter-observer variability. Such studies demonstrate that histologically similar grade IV brain tumors can be divided into four molecular subtypes based on gene expression, with each subtype demonstrating unique genomic aberrations and clinical outcome. These advances indicate that curative therapeutic strategies must now take into account the molecular information in tumor tissue, with the goal of identifying molecularly stratified patients that will most likely to receive treatment benefit from targeted therapy. This in turn spares non-responders from chemotherapeutic side effects and financial costs. In advancing clinical stage drug candidates, the banking of brain tumor tissue necessitates the acquisition of not just tumor tissue with clinical history and robust follow-up, but also high quality molecular information such as somatic mutation, transcriptomic and DNA methylation profiles which have been shown to predict patient survival independent of current clinical indicators. Additionally, the derivation of cell lines from such tumor tissue facilitates the development of clinically relevant patient-derived xenograft mouse models that can prospectively reform the tumor for further studies, yet have retrospective clinical history to associate bench and in vivo findings with clinical data. This represents a core capability of Precision Medicine where the focus is on understanding inter- and intra-tumor heterogeneity so as to best tailor therapies that will result in improved treatment

outcomes [1].

The Cancer Genome Atlas Project (TCGA) has generated a vast amount of genomic data for about 500 glioblastoma multiforme samples [2] [3].

The Cancer Genome Atlas divides the gene expression-based classification of Glioblastoma into classical, mesenchymal, neural, and proneural subtypes, which is important for understanding Glioblastoma etiology and for designing effective personalized therapy. Signal transducer and activator of transcription 3 (STAT3), a critical transcriptional activator in tumorigenesis, is persistently phosphorylated and associated with an unfavorable prognosis in Glioblastoma. Although a set of specific targets has been identified, there have been no systematic analyses of STAT3 signaling based on Glioblastoma subtype. METHODS This study compared STAT3-associated messenger RNA, protein, and microRNA expression profiles across different subtypes of Glioblastoma. RESULTS The analyses revealed a prominent role for STAT3 in the mesenchymal but not in other Glioblastoma subtypes, which can be reliably used to classify patients with mesenchymal Glioblastoma into 2 groups according to phosphorylated STAT3 expression level. Differentially expressed genes suggest an association between Notch and STAT3 signaling in the mesenchymal subtype. Their association was validated in the U87 cell, a malignant glioma cell line annotated as mesenchymal subtype. Specific associated proteins and microRNAs further profile the STAT3 signaling among Glioblastoma subtypes. CONCLUSIONS These findings suggest a prominent role for STAT3 signaling in mesenchymal Glioblastoma and highlight the importance of identifying signaling pathways that contribute to specific cancer subtypes.

1)
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2)
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