Genomics: Personalized Medicine in Brain Cancer?

Stephen Shiao MD, PhD
Assistant Professor
Cedars-Sinai Medical Center
Department of Radiation Oncology
What is genomics?

The study of the structure and function of genomes which are the complete set of “instructions” encoded by the DNA and RNA of a cell.
The relationship between DNA, RNA and Protein

www.whoi.edu
Why genomics and cancer?

- Cancer is a disease of **genomic alterations**
- Identification of all the genomic changes would help define new and more detailed cancer subsets which has the potential to transform drug targeting, diagnosis and prevention of cancer.
Cancer and the Genomics Revolution

- Cancer biology and genome sequencing technology have advanced together at extraordinary rates
- Cancer genomics have identified over 500 genes associated with various cancers
Next Generation Sequencing

Massively parallel sequencing has dramatically enhanced sequencing time:

1980s – slab gel sequencing, time to sequence a single human genome = 146 years
1990s – capillary sequencing, human genome = 7.5 years
2005 Massive parallel pyrosequencing, human genome = 33 days
2007 Sequencing by synthesis, human genome = 15 days
2010 Single molecule sequencing, human genome = 4 hours
2013 Multiple new parallel sequencing techniques, human genome = 15 minutes
Next Gen Sequencing: Gene Regulation

- Epigenetics (DNA, Histone Methylation)

- NoncodingRNA, MicroRNA (lncRNA, miRNA)

- Copy number alterations (Single-nucleotide polymorphism (SNP) analysis)
Mapping genomic data onto both known and inferred regulatory networks is the next level of analysis being applied to cancer biology.
Traditional pathologic classification has been problematic in that they have no biological basis and were unable to predict rational therapeutic strategies for any given tumor.
Glioblastomas are heterogeneous

Subtypes can predict survival

Why do subtypes predict survival and can we change our practice to find better targets?

The Dream

- As a new generation of drugs are developed that target specific protein targets, personalized treatment for brain cancer will mean more than classifying patients but rather identifying small subset of patients who are likely to respond to a particular agent.

- Drug signatures may have the potential to guide clinical trial by enabling the selection of patients who have the best chance of responding to the drug under investigation.
Chemosensitivity can be tested in vitro

- Pathway specific gene expression
- Drug specific gene expression signatures

Gene Chips
- Foundation Medicine
- Cedars-Sinai
Wuchty and colleagues integrated miRNA and gene expression data from glioma tumor samples and found a network of miRNAs strongly associated with the kinase WEE1.

Mir and colleagues profiled protein expression level of all human kinases between different cancers and demonstrated that the Wee1-like protein kinase is overexpressed in GBM.
What is WEE1?

WEE1 is a kinase that mediates DNA-damage induced cell cycle arrest which allows mutated tumor cells to keep dividing despite DNA damage.
Mir et al found that genetic or pharmacologic inhibition of WEE1 sensitizes glioma cells to radiation and DNA damaging agents in cells and mice

This observation led Merck to develop a WEE1 inhibitor (MK-1775)

NCT01849146: WEE1 Inhibitor MK–1775, Radiation Therapy, and Temozolomide in Treating Patients With Newly Diagnosed or Recurrent Glioblastoma Multiforme
Challenges in the Age of Genomics: Too much of a good thing?

- Management and curation of large amounts of genome-wide data
- Integration of genomic data to understand how diverse alterations in cellular networks gives rise to brain tumors
- Translation into therapy
Genomics at Cedars: Ongoing Projects

- Modeling GBM in mice (Breunig Laboratory)

- Genomic pathway analysis for tailored therapy (Cedars-Sinai Pathology and Foundation Medicine)

- Genomic analysis – Genome Wide Association Studies (GWAS) (Cedars-Sinai Medical Genetics Research Institute)
Conclusions

- Database infrastructure is currently being developed and deployed to efficiently warehouse information to allow both computation and molecular biologists to perform integrated genome-scale analysis of clinical tumor samples on scale previously unimaginable.

- Bioinformaticians have developed approaches for analyzing this information have led to improve classification of tumor subtypes with corresponding insights into glioma biology.

- We are just beginning to probe the dense web of connected intracellular pathways that drive the formation, progression and response to treatment of brain tumors.

- The challenge for researchers, physicians and patients is now to use this information to develop treatment plans that incorporate this information to maximize the outcome for each patient.
Useful Links

1. The Cancer Genome Atlas -
   http://cancergenome.nih.gov

1. A Brief Guide to DNA Sequencing -
References


