Genomic Methods in Cancer – Epigenetic Dysregulation

Clara, Lyon 2018

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A few words about my lab

- Genomics – data analysis
- Statistics
- Bioinformatics
- Predictive models
- Classification
- Visualization
- Understanding Biology
Genomics in Cancer

• How did we use to study cancer genes
• How genomics changed cancer research
• How genomics is used in cancer research – illustrated by our own work
• Where are we today.
Philadelphia Chromosome 1959

- Chromosome 9-22 translocation, specific to Chronic Myeloid Leukemia
- Results in the fusion of the BCR-ABL1 genes.
- Imatinib – ABL kinase inhibitor - remains one of the most successful targeted cancer drugs available.
Other Genes -> pathways

- HRAS
- BRCA
- TP53

Pathways such as: signaling, DNA-damage repair, cell-cycle.
Further progress

• Classical biology approaches to identify further components of candidate pathways and understand their function
• Those templates were also used in early versions of large-scale projects, such as TCGA
TCGA Pipeline for Comprehensive Characterization

Tissue Samples

Pathology QC

DNA & RNA Isolation, QC

Sequencing

Expression, CNA & LOH, Epigenetics

Primary Sequence Data

Data and Results QC & Storage

Data Analysis Tools

Cancer Working Groups

Comprehensive Characterization of a Cancer Genome

Biospecimen Core Resource (BCR)
Genome Characterization Center (GCC)
Genome Sequencing Center (GSC)
Genome Data Analysis Center (GDAC)
Data Coordinating Center (DCC)
Cancer Genome Hub (CG Hub)

= Process

= Data

= Results
The Epigenome
The Epigenome

• Our DNA is a faithful carrier of transgenerational inheritance.
• The Epigenome is the carrier of intragenational inheritance.
• Epigenetic patterns are faithfully transmitted along cell lineages.
• Epigenome maintenance is necessary for cells to remember who they are.
• Epigenome dysregulation ...
Pediatric High Grade Glioma
Nada Jabado’s lab
Adult Glioma – one of the first TCGA projects

Verhaak, Nature 2010
Children are not small adults

- Tumor type
- Tumor location within the brain
- Tumor history
- Tumor biology even when tumor looks the same
- Infrequent mutations in known adult GBM genes
Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma


H3.3K27M
H3.3G34R

Jeremy
The nature of the mutational partnership is determined by tumor location and age of onset.
Evolution of Glioma

Johnson et al. Science 2014
Pediatric Gliomas exhibit mutational partnerships: epigenetic + “conventional”

Epigenetic Driver Appears earliest during tumor evolution

An association of an epigenetic driver (e.g. H3K27M) and a more typical oncogenic mutation (e.g. TP53, ACVR1, FGFR1) is maintained throughout the tumor.

*Nikbakht et. al Nat Communications 2016*
Epigenetic Deregulation in Cancer

Epigenetic Modifier Mutations:

- EZH2: Melanoma
- SETD2, KDM6A: Renal Cancer
- IDH1/2: Glioma
- DNMT3A, MLL: Leukemia

Histone Mutations:

- H3F3A K27M, G34R, G34V: Pediatric GBM
- HIST1H3B, HIST1H3C: mainly DIPG
- H3F3A G34W, G34L: giant tumor of the bone
- H3F3B K36M: chondroblastoma
- HIST1H3B K36M K36I: undifferentiated sarcoma
- HIST3 K27I: found in some AML cases
- HIST3 K36M: some head and neck cancers
What do histone mutations do?
K27M are gain of function mutations inhibit EZH2/PRC2 function
K27M is a dominant negative inhibitor of polycomb repressive complex 2 (PRC2)

From Sturm et al., 2014
Genome Editing
patient-derived GBM lines

WT → CRISPR → H3K27M

H3K27M → CRISPR → WT

O/E EZH2 → WT

WT → H3K27M

H3K27M → CRISPR → WT

O/E EZH2 → WT

Inhibit EZH2

WT → H3K27M

H3K27M → CRISPR → WT

O/E EZH2 → WT

Inhibit EZH2
H3K27me3 Distribution Changes Resulting from H3K27M knock in
Effect of H3K27M mutation on the transcriptome

Normal Cell

K27M mutant

DNA methylation

DNA methylation
Glioma – single cell RNA-seq

Goals: Tumor Heterogeneity, Evolution, Cell of Origin
3D Chromatin Structure - HiC
Hi-C Contact Maps Chromosome 10

A

H3K27M

H3G34R

Histone 3 WT
Comparative Hi-C

Normal Brain

K27M

Histone WT

G34V

G34R
Do we really need this?

• Whole Genome approaches are incredible tools to explore basic biology, including that of cancer
  
  WGS - DNA
  
  WGBS – DNA methylation
  
  RNA-seq – Expression
  
  ChIP-seq – chromatin, TFBS
  
  HiC – conformation
  
  Single Cell – currently RNAseq, but other techniques are around the corner
Current Applications of Genomics in Personalized Medicine

• Mutation profiling, diagnosis – WES, WGS, Panels

• DNA Methylation profiling

• Diagnostics - need implementation in the health care system
Personalized Medicine for Pediatric Glioblastoma

• Clinical testing for H3K27M – antibody based test, liquid biopsy, CSF, etc.

• Currently, through research protocols, every pGBM case seen within our extensive network of collaborators goes through a batter of genomic assays.

• Personalized treatment?

• Palliation
Need Personalized Treatments!!!