Exome Sequencing of 243 Liver Tumors Identifies New Mutational Signatures and Potential Therapeutic Targets

Jessica Zucman-Rossi
INSERM U1162/University Paris Descartes
Paris
Disclosures

• Jessica Zucman-Rossi is consultant for IntegraGen
Geographical Heterogeneity in Hepatocellular Carcinoma Distribution

- >50% of HCC related to Alcohol, HCV, HBV, Metabolic Sd, HM
- 80% of HCC related to HCV
- 90% of HCC related to HBV

HCC incidence/100,000
- < 2.5
- < 4.0
- < 6.0
- < 9.3
- < 94.4

Hepatocellular carcinoma is the second leading cause of death among cancer patients worldwide

Globocan, 2012
Aims of Our Research in Genomics

We need to understand **HCC genomic diversity**

=> to translate the molecular diversity in biomarkers to improve clinical care of patients with hepatocellular carcinoma

- Prediction of HCC occurrence
- Diagnosis
- Prognosis
- Prediction of response to treatment
Clinical diversity of liver tumors (243 patients)

Hepatocarcinogenes is a multistep process

Risk factors#

- Alcohol
- HCV
- Metabolic syndrome
- HBV with/without Aflatoxin B1
- Unknown etiology
- Hemochromatosis
- Other etiologies

Precancerous lesions

- Dysplastic macronodule
- Early HCC
- Small and progressed HCC
- Classic HCC

Malignant transformation

- Poor prognosis HCC

Cirrhosis

Non-cirrhotic liver

HCC METAVIR F0-1

HCC METAVIR F2-3

#43 patients with ≥2 etiologies

Schulze*, Imbeaud*, Letouzé* et al, Nature Genetics, March 30th, 2015
Sequencing the whole coding region of the genome (20,000 genes)

28,478 somatic gene mutations
Range: 1 to 6,184/tumor

Each tumor is the result of an unique combination of mutations.

Schulze*, Imbeaud*, Letouzé* et al, Nature Genetics, March 30th, 2015
Genome sequencing => Identification of 161 cancer driver genes

Schulze*, Imbeaud*, Letouzé* et al, Nature Genetics, March 30th, 2015
Different Risk Factors = Different Mutated Genes

**HBV**
(33 sample, 14%)

- TP53/Cell cycle
- Epigenetic regulators
  - IRF2
  - CDKN2B
  - CDKN2A
  - MDM2
  - RB1
  - HUWE1
  - CCND1
  - CCNE1
  - CDK4/6
  - CDK2
  - TP53
  - ATM
  - EP300
  - CREBBP
  - PRKDC
  - ATR

**Alcohol**
(96 sample, 39%)

- Telomere maintenance
  - TERT
  - WNT/β-catenin
  - ARID1A
  - ARID2
  - SMARCA2
  - SETD2
  - SMCHD1
  - SLX4
  - BAF
  - pBAF
  - AXIN1
  - APC
  - AXIN2
  - ZNRF3
  - FZR1
  - WNT10B
  - WNT10A
  - WNT7B

**Epigenetic regulators**

- MLL complex
- SMCHD1
- PHF20L1
- NCOR2
- SETD2
- SLX4

**Chromatin remodeling**

- SCHULZE*, Imbeaud*, Letouzé* et al, Nature Genetics, March 30th, 2015
Nucleotide signatures are associated with risk factors

- Overall 8 signatures were found operative in at least one HCC in our series:

=> new risk factors remain to be identified

Schulze*, Imbeaud*, Letouzé* et al, Nature Genetics, March 30th, 2015
Associations Between HCC Driver Genes and Tumor Progression

- Cirrhosis → Low grade dysplastic nodule → High grade dysplastic nodule → Early HCC → Small and progressed HCC → Classic HCC → Poor prognosis HCC

- TERT promoter mutations
  - 0, 6, 19, 61, 59, 65, 73

- Frequent cancer drivers
  - CTNNB1
  - TP53
  - ARID1A
  - FGF3/4/19/CCND1

- => new prognostic biomarkers

#Nault*, Calderaro* et al, Hepatology 2014

Schulze*, Imbeaud*, Letouzé* et al, Nature Genetics, March 30th, 2015
Genes targetable by drugs => FDA-approved drugs could target 28% of HCC patients

Schulze*, Imbeaud*, Letouzé* et al, Nature Genetics, March 30th, 2015
Conclusions

- Sequencing effort defined 161 putative drivers
- Mutational signatures are related to risk factors in HCC
- 28% of HCC harbor at least one potentially targetable alteration.

First step to develop a more personalized care of the patients with hepatocellular carcinoma
Network of European researchers and clinicians

**Inserm UMR1162, Paris**
Jessica Zucman-Rossi
Sandrine Imbeaud
Eric Letouzé
Kornelius Schulze
Jean-Charles Nault
Shalini Datta
Jayendra Shinde
Sandra Rebouissou
Stefano Caruso
Clement Meiller
Frédéric Soysouvanh
Anna-Line Calatayud
Gabrielle Couchy
Guillaume Morcrette
Emilie Gelabale
Julien Calderaro
Laura Pelletier
Josselin Bouchaud

**Heptromic, Barcelona/Milano/NY**
Josep Llovet, Roser Pinyol
Augusto Villanueva,
Vincenzo Mazzaferro

**Cambridge**
Ludmil Alexandrov
Mike Stratton

**Integragen, France**
Mélanie Letexier

**Bordeaux Hospital**
Paulette Bioulac-Sage
Charles Balabaud
Jean Saric
Jean-Frédéric Blanc

**Créteil Hospital**
Serge Zafrani
Daniel Azoulay
Alexis Laurent

**Milano**
Massimo Roncalli

**CRB**
Bruno Clement
Françoise Degos
All clinicians and pathologists

**Patients**