Press release
Thursday 2 April 2015

French team identifies new genes implicated in liver cancer

Another step towards personalised medicine for cancer patients

The International Cancer Genome Consortium (ICGC) was formed in 2008 to bring together researchers from around the world to carry out in-depth analysis of 50 cancer tumour types or sub-types. It also aims to make all its results available as quickly as possible to the whole scientific community, to help speed the pace of research into the causes of cancer and the fight against the disease.

France's National Cancer Institute (INCa) and the Cancer arm of the National Alliance for Life Sciences and Health (Aviesan) coordinate French participation in and support for the programme, which includes research into breast cancer, aggressive prostate cancer and liver cancer. Jessica Zucman-Rossi, a research director at the French National Institute for Medical Research (UMR 1162 – Functional genetics of solid tumours), is coordinating the liver cancer project, which is looking into hepatocellular carcinoma (HCC) in particular. HCC is the second most common cause of death from cancer in the world and is linked to various pre-existing problems such as hepatitis B and C infections, excessive alcohol consumption, high iron levels and obesity-related chronic hepatitis.

Professor Zucman-Rossi and her colleagues have used high-throughput sequencing techniques to study cancer linked to excessive alcohol consumption and obesity in particular, seeking to identify the mutations and rearrangements implicated in tumour genesis and the progression and resistance of the disease.

The team's research, published in the journal *Nature Genetics* on 30 March 2015, demonstrates:

- that there is a link between individuals' exposure to risk factors during their lives (alcohol, tobacco, food toxins) and the DNA mutations found in their tumours;

- that each tumour is the product of a unique combination of genetic changes, involving around 40 genes on average. The complexity of this genetic diversity explains in large part the problem of resistance to current treatments. However, using this new gene catalogue, for almost 1 in 3 cases a genetic change can be identified that could be targeted by an anticancer drug. The efficacy of drugs prescribed in this way on the basis of genome alterations will need to be demonstrated in next generation 'genome-based clinical trials', which will form the basis for the forthcoming ICGC2 project;

- lastly, these studies have identified the initial mutations behind the malignant changes in liver cells[1]. This finding should help to improve early diagnosis and to detect which patients are most at risk of developing liver cancer.

[1] Mutations in the TERT promoter gene, which codes for telomerase, were found to be the initial events in the malignant transformation of the cells.

The research was coordinated and funded by the National Cancer Institute (INCa) and was carried out in close collaboration with Inserm. It also benefited from:

- scientific collaboration with Prof. Josep Llovet's team in Barcelona and Prof. Mike Stratton's team in Cambridge;

- support from Paris Descartes, Paris Diderot and Paris 13 Universities and Paris Saint-Louis Haematology Institute;

- support from the French Cancer Research Association (ARC), through the PAIR CHC project, funded jointly with INCa, and support from the EU HEPTROMIC project (FP7);

- collaboration with the National Liver Tumour Biobank (CRB), coordinated by Bruno Clément with clinicians and histopathologists from Bordeaux University Hospital (Paulette Bioulac-Sage, Jean-Frédéric Blanc, Charles Balabaud) and Créteil University Hospital (Julien Calderaro, Alexis Laurent);

- all the high throughput sequencing was carried out by IntegraGen (Evry, France);

- the support of the National Cancer League (Ligue contre le Cancer-labelled team).

ICGC France project publications:

Schulze K*, Imbeaud S*, Letouzé E*, Alexandrov LB, Calderaro J, Rebouissou S, Couchy G, Meiller C, Shinde J, Soysouvanh F, Calatayud AL, Pinyol R, Pelletier L, Balabaud C, Laurent A, Blanc JF, Mazzaferro V, Calvo F, Villanueva A, Nault JC, Bioulac-Sage P, Stratton MR, Llovet JM, Zucman-Rossi J. Exome sequencing of hepatocellular carcinomas identifies new mutational signatures and potential therapeutic targets. ***Nature Genetics***, in press. *contribution égale

Pilati C, Letouzé E, Nault JC, Imbeaud S, Boulai A, Calderaro J, Poussin K, Franconi A, Couchy G, Morcrette G, Mallet M, Taouji S, Balabaud C, Terris B, Canal F, Paradis V, Scoazec JY, de Muret A, Guettier C, Bioulac-Sage P, Chevet E, Calvo F, Zucman-Rossi J* Integrative genomic profiling of hepatocellular adenomas reveals recurrent FRK activating mutations and mutational processes of malignant transformation, ***Cancer Cell***, 25(4):428-41, 2014

Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, Bignell GR, Bolli N, Borg A, Børresen-Dale AL, Boyault S, Burkhardt B, Butler AP, Caldas C, Davies HR, Desmedt C, Eils R, Eyfjörd JE, Foekens JA, Greaves M, Hosoda F, Hutter B, Ilicic T, Imbeaud S, Imielinsk M, Jäger N, Jones DT, Jones D, Knappskog S, Kool M, Lakhani SR, López-Otín C, Martin S, Munshi NC, Nakamura H, Northcott PA, Pajic M, Papaemmanuil E, Paradiso A, Pearson JV, Puente XS, Raine K, Ramakrishna M, Richardson AL, Richter J, Rosenstiel P, Schlesner M, Schumacher TN, Span PN, Teague JW, Totoki Y, Tutt AN, Valdés-Mas R, van Buuren MM, van 't Veer L, Vincent-Salomon A, Waddell N, Yates LR; Australian Pancreatic Cancer Genome Initiative; ICGC Breast Cancer Consortium; ICGC MMML-Seq Consortium; ICGC PedBrain, Zucman-Rossi J, Andrew Futreal P, McDermott U, Lichter P, Meyerson M, Grimmond SM, Siebert R, Campo E, Shibata T, Pfister SM, Campbell PJ, Stratton MR. Signatures of mutational processes in human cancer. ***Nature.*** 2013, 500(7463):415-21

Nault JC, Mallet M, Pilati C, Calderaro J, Bioulac-Sage P, Laurent C, Laurent A, Cherqui D, Balabaud C, Zucman-Rossi J*. High frequency of telomerase reverse transcriptase promoter somatic mutations in hepatocellular carcinoma and pre-neoplastic lesions. ***Nature Communications***, 2013, 26;4:2218.

Guichard C**, Amaddeo G**, Imbeaud S**, Ladeiro Y, Pelletier L, Ben Maad I, Calderaro J, Bioulac-Sage P, Letextier M, Degos F, Clément B, Balabaud C, Chevet E, Laurent A, Couchy G, Letouzé E, Calvo F, Zucman-Rossi J*. Integrated analysis of somatic mutations and focal copy number changes identifies key genes and pathways in hepatocellular carcinoma. ***Nature Genetics***, 44, 694–698,

2012. **equally contributed.

International Cancer Genome Consortium. International network of cancer genome projects. ***Nature***. 2010 Apr 15;464(7291):993-8.

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Read Professor Zucman-Rossi's article

Watch the video by Professor Zucman-Rossi, winner of the 2012 research award here