COMPUTATIONAL CANCER GENOMICS JUNIOR GROUP

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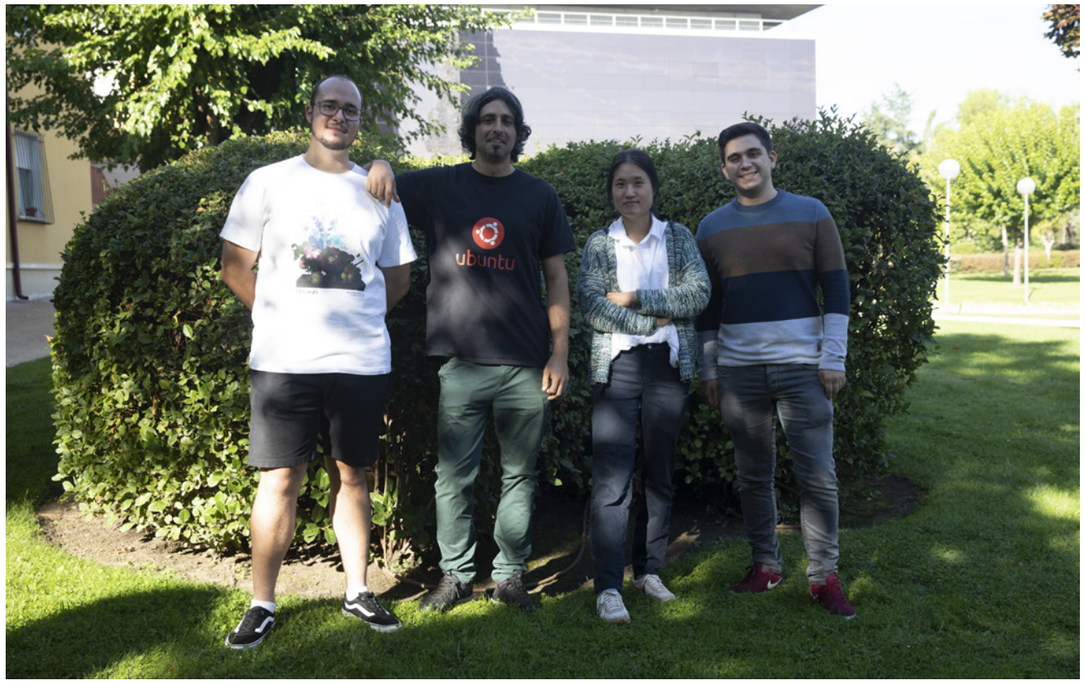

OVERVIEW

Cancer is one of the most complex human diseases, involving genetic, environmental, and even unknown factors. Over the past several decades, our knowledge of cancer has rapidly accumulated thanks to different omics technologies, including genomics and proteomics. However, we still lack a complete understanding of the cancer fitness landscape across conditions. For example, how do cancer genes change their working models of tumour progression depending on cancer types or contexts? What kind of trans-interactions exist between 2 genes or many genes beyond single-gene level alterations? How can protein complexes or interactions be perturbed depending on different mutation positions? Based on large-scale genomics and proteomics analyses, we aim to pursue these questions.

"High-order interactions identify mutations that change the dominance and dosage sensitivity of cancer genes. These high-order interactions in the same pathway can be alternative evolutionary paths."

Visiting Master's Student
Manuel Moradiellos (since September) (*Universidad Autónoma de Madrid*, Spain)

Visiting Scientist
Lee Heetak (July-September) (IMBA - Institute of Molecular Biotechnology, Vienna, Austria)

RESEARCH HIGHLIGHTS

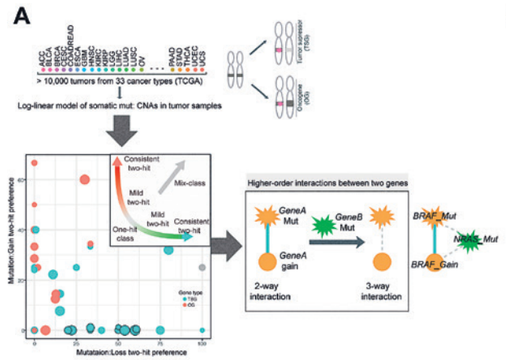

FIGURE Context-specific cancer fitness landscape. (**A**) The optimum model of cancer fitness is diverse across tissues. The third-order interaction refers to the phenomenon of the optimal path for cancer fitness landscape. (**B**) Mutation-specific protein interaction network with the TP53 model.

High-order genetic interactions between two genes

To better understand the dominance and dosage sensitivity of cancer genes, we systematically quantified the interactions between mutations and copy number changes. We found that many cancer genes do not behave like consistent models, but have activity-fitness functions that change across cancer types. To gain a better understanding of this switch, we identified one cause of these changes to be mutations in trans, as higher-order interactions. Most trans interactions were found to be in the same cancer signaling pathways and to share their functions. Our manuscript (in revision) will report the first analysis of high-order interactions in cancer genomics, based on studies conducted in collaboration with F. Supek (*IRB* Barcelona, Spain) and B. Lehner (*CRG*, Barcelona, Spain). Furthermore, we expand this concept to 2 different aspects: (1) time-dependent high-order interaction with germline variants, and (2) condition-specific high-order interactions with cancer-causing factors.

Looking beyond genomics to see cancer using TP53 and KRAS model

Over several years, more than 1,000 somatic drivers have been discovered by analising huge amounts of genomics data. However, we need a next-level analysis to obtain a complete view of their working model in cancer. To overcome this missing link, we proposed to map position-specific protein interaction networks by integrating genomics and large-scale Y2H screening. Specifically, we focused on the 2 most important cancer genes, *TP53* and the *RAS* family. In 2021, we created clones for > 10 *TP53* hotspot variants and > 50 *RAS* family variants and conducted large-scale Y2H screening with a complete human library. Our screening results will provide the systematic protein-interaction networks to show how protein interactions can be differentially changed depending on mutations. This will point the way to identifying new precision treatments based on differential protein interaction networks across patients. These studies were carried out in collaboration with Yang's Lab (*CRAG*, Barcelona, Spain). ■

PUBLICATIONS

- Kwon HY, Kumar Das R, Jung GT, Lee HG, Lee SH, Berry SN, Tan JKS, Park S, Yang JS, Park S, Baek K, Park KM, Lee JW, Choi YK, Kim KH, Kim S, Kim KP, Kang NY, Kim K, Chang YT (2021). Lipid-oriented live-cell distinction of B and T lymphocytes. *J Am Chem Soc* 143, 5836-5844.
- Park S, Supek F, Lehner B (2021). Higher order genetic interactions switch cancer genes from two-hit to one-hit drivers. *Nat Commun* 12, 7051.
- Herranz-Montoya I, Park S, Djouder N (2021). A comprehensive analysis of pre-foldins and their implication in cancer. *iScience* 24, 103273.