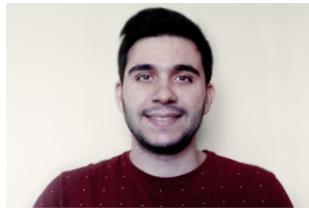


COMPUTATIONAL CANCER GENOMICS JUNIOR GROUP

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OVERVIEW

According to the conventional point of view of the 1980s, cancer drivers were classified into tumour suppressor genes (TSGs) and oncogenes (OGs) based on their functional roles in cancer. Mutations in TSGs were considered recessive while mutations in OGs were expected to be dominant gain-of-function mutations. However, importantly, the success of large-scale cancer genomics has led to debate around the dogma in cancer genetics that all cancer genes should behave according to the same model, even in different contexts (e.g., cancer types).

By analysing large-scale cancer genomics data, many exceptions have been observed, including haploinsufficiency in TSGs or amplification-linked mutation in OGs and even in dual-functional genes. It is clear that activity levels of genomic alterations in cancer genes are disparate across cancer types, and

“By analysing large-scale cancer genomics data, we aim to further pursue novel questions about cancer-type and context-specific tumour progression to understand tumour heterogeneity.”

optimal models for tumour progression may also vary depending on contexts or cancer types. The pioneering cancer genomics studies referenced above have triggered many interesting questions about how cancer genes change their models of tumour progression depending on cancer types or contexts.

RESEARCH HIGHLIGHTS

Cancer fitness landscape: from within a gene (cis) to between genes (trans)

The classic 2-hit model postulates that both alleles of a tumour suppressor gene must be inactivated by a combination of 2 different alterations for tumour progression. However, some cancer genes increase tumour fitness after only a single hit and, in some cases, a second hit may actually be detrimental. To comprehensively understand the cancer fitness landscape, we analysed > 10,000 tumours and classified cancer genes as 2 hits, 1 hit, or having optimal activity levels, which is a dangerous approximation because the activity-fitness functions of individual cancer genes are often diverse depending on the context. Specifically, mutations in other cancer genes frequently switch individual drivers from requiring 2 hits to 1 hit being sufficient to promote tumour progression. These results will provide the correct genetic model for a cancer gene, depending on their contexts, and emphasise a frequent redundancy between a second hit occurring in the same gene or in a second gene in a pathway during tumour progression. These studies were conducted in collaboration with Fran Supek (*IRB*, Barcelona) and Ben Lehner (*CRG*, Barcelona).

Inherited variants of Mendelian disease-associated genes in cancer genomics

Hereditary diseases are caused by pernicious mutations in certain genes or chromosomes. Usually, the abnormalities appear in newborns or during infancy, but sometimes they also occur in adults, such as is the case with Huntington's disease. In cases of late onset, it is reported that not only does it cause a single disease, but it also changes the concomitant pathways or affects cancer development if the stress from toxicity is sustained. The occurrence of cancer is apparent when there is an accumulation of additional variations. Using large-scale cancer genomics data, we identified the contribution of Mendelian disease-associated genes to cancer risk across more than 30 cancer types. These results will enable cancer prevention through genetic testing aimed at reflecting individual disease susceptibility to various diseases. These studies were carried out in collaboration with Young-il Goh (Seoul National University, South Korea). ■

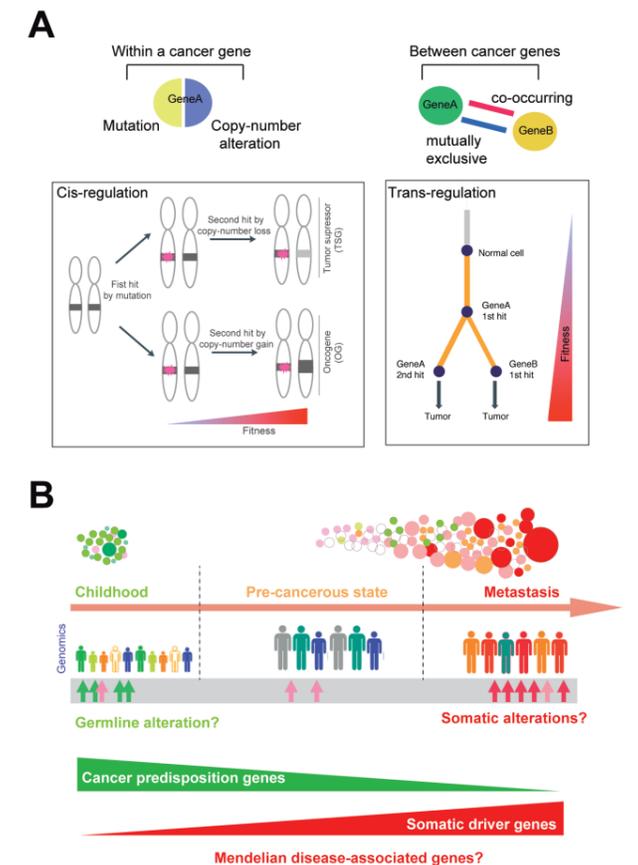


FIGURE A systematic understanding of tumour progression depending on the context from cis-regulation to trans-regulation. (B) Novel insight into the increment of cancer risk by Mendelian disease-associated genes.