PRESS RELEASE
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New perspective on tumour genome evolution

An interdisciplinary team of scientists at the Centre for Genomic Regulation (CRG) in Barcelona, Spain, deepens understanding of tumour genome evolution and suggests negative selection acting on cancer-essential genes plays a more important role than previously anticipated. Their work, published in *Genome Biology*, also provides new insights for improving cancer immunotherapies in the future.

Natural selection shapes genomes to evolve and to adapt but, are the rules of natural selection also applying to cancer genome evolution? An interdisciplinary team of scientists at the Centre for Genomic Regulation (CRG) in Barcelona, Spain, developed a method to detect genes under selection and showed that the effect of negative selection, which is a type of natural selection acting towards preventing the accumulation of mutations that would decrease the fitness of a cell, has a major role in cancer evolution. Their results challenge the most extended paradigm of an exclusive role of positive selection in cancer evolution.

In the past, many researchers worldwide aimed at identifying cancer-causing genes, meaning those genes that are relevant for tumour progression and cell malignancy, where a mutation in a particular gene makes the difference in cancer. So, most of the cancer genomics research has been focused in the role of positive selection, which is the evolutionary mechanism promoting mutations in those cancer driver genes. On the other hand, the existence of detectable levels of negative selection in cancer genomes is being questioned by several studies. Negative selection is the opposite type of natural selection promoting stability and preventing the accumulation of harmful mutations. Even though it is a major force in species evolution, experimental and computational methods attributed only a limited role to negative selection in cancer.

Now, CRG researchers led by Martin Schaefer, staff scientist at the Design of Biological Systems laboratory and Stephan Ossowski, former CRG group leader and currently at the Institute of Medical Genetics and Applied Genomics in Tübingen, in collaboration with other CRG alumni researchers, have developed a new method to identify genes under negative selection. “We found that negative selection plays an important role in cancer evolution, which is quite controversial because it has been historically neglected in most studies and, ultimately, challenges the current paradigm of an exclusive role of positive selection in cancer,” explains Dr. Schaefer.

Researchers analysed more than 7,500 individual functional genomes (exomes) from 26 tumor types from *The Cancer Genome Atlas* (TCGA) data and identified essential cancer genes and immune-exposed protein regions under significant negative selection. “This is the first large scale study with a solid method to detect a substantial impact of negative selection in shaping cancer genomes. We demonstrate that negative selection is underestimated and acts stronger on certain regions, which are related to essential cellular functions and to immune response,” adds Schaefer. “Our work could be interpreted as a proof of concept; it may shed light upon mechanisms underlying immune evasion and may provide insights for improving cancer therapies in the future by revealing cancer vulnerabilities”.

Interdisciplinarity and collaboration are the key success factors

This work, which has been published in *Genome Biology*, shows how interdisciplinary research pushes the boundaries of knowledge and contributes to finding new insights for improving health. In this case, it gathered together experts in population genetics and evolution (Fyodor Kondrashov, former CRG group leader and currently at the Austria Institute of Science and Technology – IST; and Oriol Pich, former CRG researcher and currently at IRB Barcelona), medical genomics (Luis Zapata, former CRG researcher and currently at the Institute of Cancer Research, ICR in UK; and Stephan Ossowski), and in computational and systems biology (Martin Schaefer and Luis Serrano).

This is a new example on how interdisciplinarity may lead to new insights in cancer genomics and provides new tools for cancer research.

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NOTES TO THE EDITORS

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