Istituto di Analisi dei Sistemi ed Informatica "Antonio Ruberti"
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"La mente è come un paracadute.
Funziona solo se si apre"
A. Einstein

Evolution of the cancer genome: mathematical and computational approaches

Prof. **Franziska Michor**
Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute and
Department of Biostatistics, Harvard School of Public Health

Abstract

Human cancer is caused by the accumulation of genetic alterations in cells. This talk will introduce two approaches designed to better understand the evolution of the cancer genome. (1) Of special importance for cancer evolution are changes that occur early during malignant transformation because they represent promising targets for therapeutic intervention. We have described a mathematical modeling approach, called Retracing the Evolutionary Steps in Cancer (RESIC), to deduce the temporal sequence of genetic events during tumorigenesis from cross-sectional genomic data of tumors at their fully transformed stage. RESIC represents the first evolutionary mathematical approach to identify the temporal sequence of mutations driving tumorigenesis and may be useful to guide the validation of candidate genes emerging from cancer genome surveys. (2) An unstable genome is a hallmark of many cancers. It is unclear, however, whether some mutagenic features driving somatic alterations in cancer are encoded in the genome sequence and whether they can operate in a tissue-specific manner. We performed a genome-wide analysis of 663,446 DNA breakpoints associated with somatic copy-number alterations (SCNAs) from 2,792 cancer samples classified into 26 cancer types. Many SCNA breakpoints are spatially clustered in cancer genomes. We observed a significant enrichment for G-quadruplex sequences (G4s) in the vicinity of SCNA breakpoints and established that SCNAs show a strand bias consistent with G4-mediated structural alterations. Notably, abnormal hypomethylation near G4s-rich regions is a common signature for many SCNA breakpoint hotspots. We propose a mechanistic hypothesis that abnormal hypomethylation in genomic regions enriched for G4s acts as a mutagenic factor driving tissue-specific mutational landscapes in cancer.