Uncovering a Map of Human Cancer Signaling

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Scientists from the National Research Council, Biotechnology Research Institute (NRC-BRI) in Montreal recently released a map of human cancer signaling that provides a framework for discovering preferred combinations of signaling cascades used by cancer cells.

The study provides a more comprehensive picture about the protein communications in cells that drive cancer development. The human cancer signaling map contains around 300 proteins and nearly 900 signaling relationships among their respective genes, which are mutated or methylated in cancer cells.

The investigators found that as little as 10% of the signaling relationships account for the majority of signaling interactions that are the most frequently used by many kinds of tumors. These can be regarded as signaling communication superhighways for cancer development and progression.

To generate such map, the investigators first manually construct a network diagram of human cellular signaling that encapsulates the accumulated cellular signaling knowledge produced in the past 60 years.

The nodes in the network are then annotated based on a list of a few hundred cancer causally mutated genes, which were identified by large-scale sequencing of tumor genomes. From this emerges the human cancer signaling map.

"Enormous efforts have been made over the past few decades to illustrate cancer signaling. However, it has been a struggle to get clues of how the cancer signaling is structurally and functionally organized," says Maureen O'Connor-McCourt, a co-author of the work and the scientific leader of NRC-BRI Cancer Genomics project.

"This offers the first glimpse of a more global view of the architecture of cancer signaling, which provides a blueprint for tumorigenesis. Well-known cancer signaling events can be seen in the map as well as suggestions of many new cancer signaling events, generating a number of testable hypotheses."

Based on the signaling relationships among these proteins, the human cancer signaling map can be divided into 12 signaling communication network modules.

"Traditionally, scientists treat cellular signaling as linear pathways, like avenues and roads of a city. We see the signaling map as a network or a 'wiring diagram'. A signaling communication network module is like an area of the city such as downtown area, which is a region of intersection of many different avenues and roads. In biology, genes in a module are expected to perform similar biological functions," explains Edwin Wang, the corresponding author of the study and an NRC-BRI bioinformatics scientist, trained in both molecular biology and computer science.

"Although gene mutations are tremendously complex in tumors, they can be classified into a few signaling modules, thus uncovering the underlying logic of cancer signaling," says Maria Jaramillo, a tumor cell biologist at NRC-BRI and co-author of the study. "A very interesting aspect of this work is the demonstration that different tumor types appear to achieve tumorigenesis via distinct mechanisms, i.e., through collaboration between different signaling modules."

In the process of uncovering where the oncogenic stimuli are embedded in the human signaling network the putative regulation mechanisms of these stimuli are revealed. For example, activating mutations are enriched in positive signaling regulatory loops, whereas methylated genes and inactivating mutations of tumor suppressors are enriched in negative signaling regulatory loops.

Taking a systems-biology approach, the researchers present a network view of molecular mechanisms of cancer signaling that will shape our understanding of fundamental tumor cell biology. This knowledge can assist in guiding the rational selection of combination drug therapy in particular tumor types, and in forming new strategies for the early diagnosis of cancer.

Some researchers have criticized the utility of genome-wide sequencing of tumors. They argue that it is time- and resource-consuming with unclear results. This work, however, is a counterexample to such a view.

"With proper bioinformatics analysis, important and meaningful biological insights can be extracted from large-scale cancer genome sequencing efforts," says Enrico Purisima, a co-author of the study and a computational biophysicist at NRC-BRI.

This work will be published online on Tuesday 18 December by Molecular Systems Biology. The team's members are from the National Research Council Canada, China's Tianjin Normal University, and Tianjin University.