Research - System biology and individual cancer therapy

By integrating computer sciences and mathematics into molecular bioscience, 'system biology' developed. An example is provided of how system biology is used in the research to enhance cancer therapy.

Research in molecular bioscience predominantly is taken place in the laboratory. Formerly, mathematics and statistics were not very much in use in the discipline. That changed around the year 2000 when computer science and sophisticated statistical methods found their way into biology termed ‘systems biology’ (1). The science of biology, as one learns at high school, studies live and living organisms. That includes medicine, microbiology, molecular biology, genetics, and physiology, among others. Tremendous advancements in research methodology and the subsequent accumulation of discoveries made it almost impossible to keep an overview of the significance of all the overwhelming knowledge gained. Highly specified research topics were distributed among various research groups existing side by side. The saying was that one knows 'more and more about less and less'.

The reductionist method

Throughout the preceding 50 years, ' hot' research topics comprised of immunology and genetics. The aim to study molecules was to find out how they function, but less how they are integrated into a whole system. The standard approach is to break down a complex structure into parts. That is easier to investigate the chemical constituents and functions. This paradigm is known as reductionist method. It is a bottom-up approach starting on a lower level, hopefully allowing to move upwards to understand the whole. For instance, bacteria have a particular signaling system to initiate cellular reactions, which has been studied for Salmonella bacteria (2). Another example given here is the study of how small peptides and proteins react in nanotechnology (3).

A Nobel price and system biology

'System biology' was thought to be a paradigm shift. The idea to look into 'genetic circuits' was pursued already around the 1960th (4). In 1965, two French scientists, François Jacob and Jacques Monod got the Nobel Prize in Physiology or Medicine for demonstrating that gene networks in bacteria, here E. coli, 'alter the production of certain enzymes depending on the type of food available (5). However, only at the beginning of the present decennium 'system biology' was pushed forward and heavily supported. Due to advanced computer technology and computer scientists' cooperation with researchers in molecular biology, the "dynamic interaction" of whole systems within the molecular biosciences was addressed (6). In genetics, one no longer was satisfied to talk about genes, but about ‘genomics,’ mRNA issues became ‘transcriptomics,’ proteins ‘proteomics,’ and metabolites ‘metabolomics,’ and the whole was termed the ‘omic’ technologies (7). Microbiology became the 'heaven of system biology,' and research in the area of 'omics' favored the 'top-down' approach (6).

The top-down approach

Top-down-systems are based on extensive datasets derived from various experiments. A given organism is exposed to many challenges. In genetics, this might be due to mutations, gene overexpression, and RNA interferences. Environmental factors such as changes in

nutrients or drugs may play a role as well. Data analysis reveals correlations between molecular behavior and facilitates the formulation of new hypotheses, usually described in models such as stoichiometric-, regulatory-, or kinetic models. The ultimate aim of the exercise is to discover new molecular mechanisms.

A fundamental problem of system biology explained through an example faced in public health

Unfortunately, 'system biology' didn't live up to expectations. One of the main problems is that an organism's genome reflects the biology of that system but might not elucidate the individual components' role, resulting in the system's particular functions (6). In public health, this phenomenon is well known. For example, to explain the problem, set the 'genome' as 'human behavior.' For studies of human behavior, results from well-thought questionnaires, containing numerous entries, are adjusted to different models, and the results finally are given as scores. In attempts to change behavior, the success or failure of such an intervention is explained by pointing towards the scores' variation. Finally, it is difficult to see which particular behavior has a specific influence on the scores' overall change. Of course, because of the difficulties in explaining the investigations' results, behavioral sciences will not be abandoned.

Mutations and cancer

Likewise, system biology comes up with beneficial research attempts too. An example is the link between system biology to cancer therapy (4). One major problem in cancer therapy is that particular drugs work for some patients inhibiting the spread of the disease, and others fail to do so. This is because mutations for the same type of cancer might differ from one individual patient to another. Mutations, as such, might interfere with the normal cell turnover. Genes, which normally control cellular growth and death, might fail to do so after mutation. They no longer control cell division and cell death.

Cell death is called apoptosis. Apoptosis is necessary to maintain health, enable immune functions and embryogenesis. In case the programmed cell death is deregulated, besides neurodegeneration and autoimmunity also cancer occurs. The cancer genome of one patient might consist out of multiple mutations (8). It is said that there are 'more potential combinations of cancerous mutations than atoms in the universe' (4). That might be an exaggeration. Yet, to focus on one particular patient's cancer, identifying a drug that is suitable to work against the mutations just for this patient would be an enormous task. 'Tens of thousands of drugs might be needed to treat cancer patients all over.'

Cancer, miRNA and ceRNA and system biology

The new approach of interest is to identify description factors acting as master regulators of the cancer genome. MicroRNA (miRNA) normally is noncoding but regulates and stabilizes mRNA translation (9). In case of a 'dysregulation' cancer might occur (10). MicroRNA activity on the target gene can also be influenced by the presence or absence of other competing endogenous RNA (ceRNA). To interfere with drugs on the network of miRNA and ceRNA might decrease the spread of cancer cells for a given patient. Like mutations, the candidates of miRNA targets are abundant, and the regulatory mechanism is quite specific. That is where system biology comes in. Using complex algorithms, the targets of miRNA and ceRNA for each different tumor is assessed. By this, appropriate drugs could be individually

identified and used to interfere in the process. In the relevant paper, this reads as 'sequence-based evidence and functional clues derived from RNA and miRNA expression analysis'…were applied…' predicting candidate miRNA binding sites and associated target genes using ensemble machine learning classifier that are trained on validated interactions' (11). In effect, that means that gene interaction is identified by complex equation patterns, and the transcription factor with the largest influence is distinguished (4). It is not feasible to develop drugs for each of the countless numbers of mutations. Instead, one might find some 'master regulators,' and from available and suitable drugs identify the most promising to target the regulators and try to inhibit cancer progression.

Andrea Califano and the VIPER algorithm

At Columbia University, New York, under the guidance of Andrea Califano, he and his colleagues used an algorithm, called VIPER, to look at RNA sequence data from more than 10.000 individual tumor samples derived from the Cancer Genome Atlas. From 407 transcription factor genes, acting as suspected mainstays, only 20 to 25 of them related to any given cancer (unpublished data (4)). That means various cancers join a limited number of transcription factors. Not numerous transcription factors might have to be addressed, but only some knots within the system.

The algorithm defining the transcription factors is linked to a database about drugs affecting multiple genes. The information about suitable drugs is derived from reviews of the literature and other pharmaceutical sources. An ongoing process automatically samples tumor cells and investigate how promising drugs alters the cells' RNA sequence profile.

Will the system work?

No clinical trials were conducted yet. But at the laboratory of Califano, RNA sequence data from 100 cancer patients had been tested for master regulators, and drugs were suggested commonly not be used for the cancer type the patient was suffering from. Testing was done in connection with ‘DarwinHealth,’ a commercial company founded by Califano and companion. For 1600 USD, an 'Onco-target reading' is provided. For a few dozen cases, the suggested drug was tested in mice to determine whether the patient's tumor responds to the master regulators as predicted. For five patients in the late stage of the cancer disease, who did no longer respond to available treatment, doctors dared to try the drug suggested by the algorithms. Four of the patients responded to the drug at least for some time.

One of the patients was suffering from meningioma, a tumor in the brain. These patients usually die because of the pressure on the brain. In this case, the algorism results pointed towards a drug called etoposide, usually utilized for lung or ovarian cancer. The brain tumor did not grow for over a year but started to enlarge slightly after that. The patient was put on a different clinical trial, but his cancer started then to grow fast again.

Skepticism about the method is voiced from various sources. For instance, Morgan Craig, who uses a computational approach to find new drugs, judges the DarwinHealth system a step forward in a systematic way. But he doubts that the method will soon be integrated into clinical practice. Gordon Mills, director of precision oncology for the Knight Cancer Institute at Oregon Health and Science Institute, sees a long way ahead before the method will be successful.

But some promising results can be accounted for. In a recently completed clinical trial at the Icahn School of Medicine and Mount Sinai, the combination of the drugs dexamethasone and selinexor was applied to treat multiple myeloma (12). The combination only worked in about one-quarter of the patients. In retrospect, with the method of DarwinHealth, an attempt was made to predict who of the patients respond and who didn't. From 12 patients, four of five patients were correctly identified, who benefited from the drugs, and correctly pointed out six of seven patients, who's cancer failed to respond (4).

Outlook

Columbia University allocated 15 Million USD for testing 3.000 cancer patients for the next three years. The DarwinHealth algorism will analyze each patient's cancer and recommend treatment. By this, the methodology will be tested on a large scale, and hopefully, in the end, it can be decided whether the method works or not. Presently, this project is a telling example of how systematic biology can be integrated into medical research, based on the cooperation of formerly far apart scientific fields.

References

1. Tavassoly I, Goldfarb J, Iyengar R. Systems biology primer: the basic methods and approaches. Essays Biochem. 2018;62(4):487-500.
2. Solano C, Garcia B, Latasa C, Toledo-Arana A, Zorraquino V, Valle J, et al. Genetic reductionist approach for dissecting individual roles of GGDEF proteins within the c-di-GMP signaling network in Salmonella. Proc Natl Acad Sci U S A. 2009;106(19):7997-8002.
3. Gazit E. Reductionist Approach in Peptide-Based Nanotechnology. Annu Rev Biochem. 2018;87:533-53.
4. Khamsi R. Computing cancer's weak spots. Science. 2020;368(6496):1174-7.
5. Jacob FM, J. Genetic regulatory mechanisms in the synthesis of proteins. Journal of Molecular Biology. 1961;3(3):38.
6. Bruggeman FJ, Westerhoff HV. The nature of systems biology. Trends Microbiol. 2007;15(1):45-50.
7. Horgan RPK, L.C.' Omic' technologies: genomics, transcriptomics, proteomics and metabolomics. The Obstetrician and Gynaecologist. 2011;13(3):7.
8. Stratton MR, Campbell PJ, Futreal PA. The cancer genome. Nature. 2009;458(7239):719-24.
9. Filipowicz W, Bhattacharyya SN, Sonenberg N. Mechanisms of post-transcriptional regulation by microRNAs: are the answers in sight? Nat Rev Genet. 2008;9(2):102-14.
10. Garzon R, Calin GA, Croce CM. MicroRNAs in Cancer. Annu Rev Med. 2009;60:167-79.
11. Chiu HS, Llobet-Navas D, Yang X, Chung WJ, Ambesi-Impiombato A, Iyer A, et al. Cupid: simultaneous reconstruction of microRNA-target and ceRNA networks. Genome Res. 2015;25(2):257-67.
12. Chari A, Vogl DT, Gavriatopoulou M, Nooka AK, Yee AJ, Huff CA, et al. Oral Selinexor-Dexamethasone for Triple-Class Refractory Multiple Myeloma. N Engl J Med. 2019;381(8):727-38.

The manuscript was written by Frank P. Schelp. Points of views expressed are those from the author and might not reflect the stance and policy of the Faculty of Public Health, Khon Kaen University, Thailand.